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Faculty of Medicine, Universitas Airlangga
Jl. Prof. Dr. Moestopo 47 Surabaya 60132
Phone: 62-31-5020251,
E-mail: fmi@journal.unair.ac.id

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Original Research Report

BACTERIAL AND ANTIBIOGRAM PROFILE OF URINARY TRACT INFECTION PATIENTS IN A TERTIARY HOSPITAL, SURABAYA

Mahrumi Dewi Tri Utami[1], Manik Retno Wahyunitisari[2,3], Nunuk Mardiana[4], Rebekah Juniati Setiabudi[2,3]

[1]Medical Program, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia
[2]Department of Medical Microbiology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia
[3]Clinical Microbiology Specialist Program, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia
[4]Department of Internal Medicine, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia

ABSTRACT

Urinary tract infection (UTI) is one of the most common bacterial infections. Inappropriate antibiotic use for UTI treatment may lead to antibiotic resistance. This study aimed to provide an updated bacterial and antibiogram profile from urine specimens of patients diagnosed with UTI. This study was a retrospective study using urine culture and antibiotic susceptibility test results obtained from Clinical Microbiology Laboratory in a tertiary general hospital in Surabaya, Indonesia for a two-month period between June to July 2019. There were 215 patients with significant urine culture results of 54.4% from Escherichia coli female patients. Most aged more than and/or equal to 59 years, in both sexes. Gram-negative bacteria, particularly , was being the most common bacteria that caused UTI, followed by K. pneumoniae. Some antibiotics with the highest susceptibility to gram-negative bacteria were carbapenem antibiotics and amikacin, while teicoplanin and vancomycin were some antibiotics susceptible to gram-positive bacteria. This study result indicated that there was an urge to conduct local antibiogram profile investigation due to the low susceptibilities shown in recent empirical therapy recommendations, such as trimethoprim-sulfamethoxazole, fluoroquinolone, nitrofurantoin, and fosfomycin.

Keywords: *Antibiotic resistance; Escherichia coli; microbial susceptibility test; public health; urinary tract infection*

Correspondence: Manik Retno Wahyunitisari, Department of Medical Microbiology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia. Email: manik-r-w@fk.unair.ac.id

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Highlights:

1. Most urinary tract infections are caused by Gram-negative bacteria with E. coli being the most common bacteria.
2. Antibiotics with the highest susceptibility for Gram-negative bacteria were ertapenem, meropenem, amikacin, and imipenem.
3. Antibiotics with the highest susceptibility for Gram-positive bacteria mainly were susceptible to colstreptomycin, vancomycin, rifampin, tigecycline, teicoplanin, and ampicillin.

INTRODUCTION

Urinary tract infection (UTI) is one of the leading causes of both community-acquired and hospital-acquired infections (Najar et al. 2009). Both Gram-negative and Gram-positive bacteria can cause UTI. The most common etiology of UTI is *E. coli* (Flores-Mireles et al 2015). It is estimated that there were 150 million UTI cases occur annually worldwide. As one of the most common bacterial infections (Flores-Mireles et al. 2015), UTI could greatly contribute to inappropriate use of antibiotics which leads to resistance occurrence.

A local antibiogram or bacterial resistance profile is one consideration in choosing appropriate empiric antibiotic therapy. Initial therapy for infection is needed immediately, especially for patients with severe infection, as the microbiological result is not usually available in the first 24 to 72 hours (Leekha et al. 2011). UTI can contribute to urosepsis. In adults, urosepsis counted in about 25% of all sepsis cases. In this setting, providing adequate initial antibiotic therapy is a critical step in improving patient outcomes (Wagenlehner et al. 2013). Therefore, updating the bacterial resistance profile is an important way to increase the success rate of therapy.

Moreover, antibiotic resistance is a critical public health issue, specifically in developing countries with poor hygiene practices, poverty, and drug abuse (Seifu & Gebissa 2018). Until now, Indonesia does not have a formal estimation of the antibiotic resistance burden. However, the rate is considered high and is still rising (Parathon et al. 2017). Studies concerning antibiotic resistance rate and its susceptibility are needed to provide local data for clinical use of antibiotics, to lower the risk of inappropriate antibiotic use. In

addition, Indonesia is one of the developing countries where the empirical use of antibiotics is frequently still used due to the expensiveness of antibiotic susceptibility tests and much time is needed to conduct the procedure (Rosana et al. 2020). This study aimed to provide an updated bacterial and antibiogram profile from urine specimens retrieved from UTI patients in Clinical Microbiology Laboratory at tertiary general hospital in Surabaya, Indonesia for two-month period between June to July 2019. From this setting, the associated laboratory had a large sample volume so that two-month period of data had reached quite a lot of samples.

MATERIALS AND METHODS

The study was a descriptive retrospective study of 215 bacterial UTI patients from both in- and out-patients. The patients' age was limited above 18 years. Results indicating fungal and parasitic infections were excluded from this study. Data were obtained consecutively from a urine culture, bacterial identification, and antibiotic susceptibility test data conducted in the Clinical Microbiology Laboratory, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia for a two-month period between June to July 2019. Additional data regarding the patients' profiles were taken from medical records. All data were descriptively analyzed using IBM SPSS Statistics for Windows, Version 21.0 (Armonk, NY: IBM Corp.).

Urine specimens were previously collected from the patients by either clean-catch midstream or indwelling catheter urine, according to indication and the patients' condition. The uncentrifuged, homogenized urine specimen was streaked on an agar plate with Mayo's technique and then incubated for 24 hours at 35±2ºC in aerobic conditions. UTI was diagnosed when the bacterial count was greater than or equal to 10^5 CFU/m. Any urine samples with three or more different bacterial colonies were not considered for further investigation. Bacterial identification was done using VITEK 2 system based on fluorescence technology. Antibiotic susceptibility testing was carried out automatically by broth microdilution system of VITEK 2 according to Clinical Laboratory Standards Institute (CLSI) guidelines.

The study was approved by the Health Research Ethics Committee, Dr. Soetomo General Academic Hospital with reference number: 0222/LOE/301.4.2/XI/2020. Data were collected and analyzed retrospectively, therefore patient's consent was not obtained.

RESULTS

Patients' characteristics

Out of 215 patients in total, 117 (54.4%) patients were females. Most patients aged more than equal to 59 years, in both genders. The summary of the patients' age and sex distribution is available in Table 1.

Most of the patients had at least one associated underlying disease (N; %: 212; 98.6%), with the most common comorbidities were malignancy (N; %: 57; 26.5%), chronic kidney disease (N; %: 44; 20.5%), and diabetes mellitus (N; %: 41; 19.1%).

Table 1. Patients' characteristics

Age (years)	Sex				Total (n)	
	Male		Female			
	n	%	n	%	n	%
19-28	7	3.26%	12	5.58%	19	8.84%
29-30	6	2.79%	10	4.65%	16	7.44%
39-48	5	2.33%	17	7.91%	22	10.23%
49-58	31	14.42%	38	17.67%	69	32.09%
≥59	49	22.79%	40	18.60%	89	41.40%
Total (n; %)	98	45.58%	117	54.42%	215	100%

Bacteriological investigations

Most UTI-causing bacteria were Gram-negative bacteria (N; %: 181; 84.19%). *E. coli* was the most common bacteria in the current study (N; %: 91; 42.33%), with 67 out of 91 *E. coli* isolates were ESBL-producing strains.

Table 2. Distribution of UTI-causing bacteria

Bacteria	Gram	Total (n)	%
Escherichia coli	Negative	91	42.33
Klebsiella pneumoniae	Negative	25	11.63
Enterococcus faecalis	Positive	20	9.30
Pseudomonas aeruginosa	Negative	19	8.84
Acinetobacter baumanii	Negative	9	4.19
Enterobacter cloacae	Negative	7	3.26
Proteus mirabilis	Negative	5	2.33
Citrobacter freundii	Negative	5	2.33
Burkholderia cepacia	Negative	4	1.86
Morganella morganii	Negative	3	1.40
Streptococcus agalactiae	Positive	3	1.40
Kluyvera ascorbata	Negative	2	0.93
Enterococcus faecium	Positive	2	0.93
Staphylococcus aereus	Positive	2	0.93
Corynebacterium urealyticum	Positive	2	0.93
Escherichia fergusonii	Negative	1	0.47
Klebsiella ozaenae	Negative	1	0.47
Klebsiella oxytoca	Negative	1	0.47
Pseudomonas spp. (species not classified)	Negative	1	0.47
Moraxella spp. (species not classified)	Negative	1	0.47
Citrobacter werkmanii	Negative	1	0.47
Citrobacter koseri	Negative	1	0.47
Stenotrophomonas maltophilia	Negative	1	0.47
Enterobacter aerogenes	Negative	1	0.47
Salmonella enterica	Negative	1	0.47
Providencia rettgeri	Negative	1	0.47
Streptococcus gallolyticus	Positive	1	0.47
Pediococcus pentosaceus	Positive	1	0.47
Corynebacterium amylocatum	Positive	1	0.47
Corynebacterium matruchotii	Positive	1	0.47
Bacillus pumilus	Positive	1	0.47
Total		215	100

K. pneumoniae, *P. aeruginosa*, *A. baumanii*, and *E. cloacae* were other Gram-negative bacteria that followed *E. coli* in number to cause UTI. Similar to *E. coli*, there were ESBL and non-ESBL-producing *K. pneumoniae* strains, with 12 out of 25 total isolates were ESBL-producing strains. Meanwhile, *E. faecalis* was the most common Gram-positive bacteria causing UTI (N; %: 20; 9.30%). The order of UTI-causing Gram-positive bacteria prevalence following *E. faecalis* were *S. agalactiae*, *E. faecium*, *S. aereus*, and *C. urealyticum*. The bacterial distribution is summarized in Table 2.

Antibiotics susceptibility

Gram-negative bacteria tended to have high resistance level to amoxicillin (100%), cefotetan (100%), cefoxitin (100%), trimethoprim (100%), ampicillin (96.05%), cefazolin (95.33%), and colistin (92.31%), while gram-positive bacteria were mostly resistant to fusidic acid (100%), trimethoprim (100%), streptomycin (100%), tobramycin (95.45%), cefoxitin (94.12%), trimethoprim-sulfamethoxazole (90%), gentamicin (85.29%), quinupristin-dalfopristin (85.71%), amikacin (87.5%), ceftriaxone (82.61%), and clindamycin (81.82%).

Antibiotics with the highest susceptibility for Gram-negative bacteria were ertapenem (100%), meropenem (92.18%), amikacin (90%), and imipenem (85.63%). Meanwhile, chloramphenicol (100%), rifampin (100%), tigecycline (100%), streptomycin (100%), vancomycin (90.63%), teicoplanin (90.00%), and ampicillin (82.61%) were some antibiotics with susceptibility for Gram-positive bacteria. Despite linezolid only having a 51.52% in sensitivity level, 42.42% of the Gram-positive isolates showed intermediate results. It is implicated in the resistance level of linezolid for Gram-positive bacteria which was only 6.06%. Full data are available in Tables 3 and 4.

Specifically, each bacteria had different susceptibilities to diverse antibiotics. The result of antibiotic susceptibility tests from specific bacteria isolates has already been summarized in Table 5 and 6.

DISCUSSION

Patient's characteristics

Women have a greater risk of developing UTIs as their urethra is shorter compared to men, therefore allowing more vulnerability of women's urinary tract to be exposed. The current result showed that UTIs were more common in women (54.4%) and this result was supported by another research that have been conducted previously. Pratista *et al* stated that 52% of their patient who experienced UTIs were women, while a study mentioned that 87.4% of the population were women (Pratistha et al. 2018, Ren et al. 2016).

Table 3. Gram-negative UTI-causing bacteria susceptibilities to antibiotics

Antibiotics	Gram-negative bacteria		
	R (%)	I (%)	S (%)
Amikacin	7.78	2.22	90.00
Amoxicillin	100.00	0.00	0.00
Amoxicillin-clavulanate	78.21	5.59	16.20
Ampicillin	96.05	0.56	3.39
Ampicillin-sulbactam	69.32	7.95	22.73
Aztreonam	64.25	0.56	35.20
Cefazolin	95.33	0.00	4.67
Cefepime	61.63	1.16	37.21
Colistin	92.31	0.00	7.69
Cefotaxime	68.33	1.11	30.56
Cefotetan	100.00	0.00	0.00
Gentamycin	38.67	1.66	59.67
Cefoxitin	100.00	0.00	0.00
Ceftazidime	55.80	2.21	41.99
Ceftriaxone	67.84	4.09	28.07
Chloramphenicol	78.95	0.00	21.05
Ciprofloxacin	64.00	2.86	33.14
Ertapenem	0.00	0.00	100.00
Fosfomycin	37.21	0.00	62.79
Imipenem	9.38	5.00	85.63
Levofloxacin	59.78	3.91	36.31
Meropenem	7.26	0.56	92.18
Moxifloxacin	63.31	2.88	33.81
Nitrofurantoin	45.98	6.90	47.13
Piperacillin	74.85	4.29	20.86
Piperacillin-tazobactam	18.18	11.36	70.45
Tetracycline	71.08	2.41	26.51
Tigecycline	19.43	9.71	70.86
Trimethoprim	100.00	0.00	0.00
Trimethoprim-sulfamethoxazole	62.50	0.00	37.50
Cefoperazone-sulbactam	8.47	24.29	67.23

I: intermediate; R: resistant; S: sensitive

Table 4. Gram-positive UTI-causing bacteria susceptibilities to antibiotics

Antibiotics	Gram-positive bacteria		
	R (%)	I (%)	S (%)
Amikacin	87.5	0.00	12.5
Amoxicillin-clavulanate	50.00	0.00	50.00
Ampicillin	17.39	0.00	82.61
Cefotaxime	78.57	7.14	14.29
Gentamycin	85.29	0.00	14.71
Cefoxitin	94.12	0.00	5.88
Ceftriaxone	82.61	4.35	13.04
Chloramphenicol	0.00	0.00	100.00
Ciprofloxacin	50.00	10.00	40.00
Clindamycin	81.82	3.03	15.15
Erythromycin	62.96	11.11	25.93
Fosfomycin	25.00	0.00	75.00
Fusidic Acid	100.00	0.00	0.00
Levofloxacin	62.07	13.79	24.14
Linezolid	6.06	42.42	51.52
Meropenem	100	0.00	0.00
Moxifloxacin	50.00	0.00	50.00
Nitrofurantoin	35.48	0.00	64.52
Oxacillin	75.00	0.00	25.00
Penicillin	74.19	0.00	25.81
Rifampin	0.00	0.00	100.00
Quinupristin-dalfopristin	85.71	0.00	14.29
Teicoplanin	10.00	0.00	90.00
Tetracycline	62.50	0.00	37.50
Tigecycline	0.00	0.00	100.00
Tobramycin	95.45	0.00	4.55
Trimethoprim	100.00	0.00	0.00
Trimethoprim-sulfamethoxazole	90.00	0.00	10.00
Streptomycin	100.00	0.00	0.00
Vancomycin	9.38	0.00	90.63

I: intermediate; R: resistant; S: sensitive

Table 5. Specific Gram-negative bacteria susceptibility to antibiotics

Antibiotics	*E. coli* (n=91)		*K. pneumoniae* (n=25)		*P. aeruginosa* (n=19) (%)	*A. baumanii* (n=9) (%)
	Non ESBL (%)	ESBL producing strain (%)	Non ESBL (%)	ESBL producing strain (%)		
Amikacin	100	98.48	100	83.33	94.74	33.33
Amoxicillin	NA	0	0	NA	R	R
Amoxicillin-clavulanate	52.17	0	61.54	9.09	R	R
Ampicillin	16.67	0	R	R	R	R
Ampicillin-sulbactam	50	2.99	69.23	10	R	44.44
Aztreonam	95.83	0	84.62	8.33	52.63	R
Cefazoline	20	0	33.33	0	0	0
Cefepime	95.83	0	75	8.33	72.22	0
Colistin	NA	NA	NA	100	NA	NA
Cefotaxime	95.83	0	84.62	0	0	0
Cefotetan	NA	NA	NA	NA	0	NA
Gentamycin	87.50	56.72	69.23	41.67	73.68	0
Cefoxitin	NA	NA	NA	NA	NA	NA
Ceftazidime	100	1.49	84.62	8.33	68.42	0
Ceftriaxone	85.71	0	84.62	8.33	R	0
Chloramphenicol	100	50	NA	NA	R	R
Ciprofloxacin	66.67	10.61	41.67	16.67	61.11	0
Ertapenem	NA	100	100	NA	R	R
Fosfomycin	50	88.89	100	50	33.33	R
Imipenem	100	95.16	90.91	100	82.35	44.44
Levofloxacin	70.83	11.94	53.85	33.33	57.89	0
Meropenem	95.83	98.51	92.31	100	89.47	44.44
Moxifloxacin	66.67	9.68	45.45	25	NA	NA
Nitrofurantoin	75	72.31	23.08	8.33	0	0
Piperacillin	26.09	0	50	0	76.47	0
Piperacillin-tazobactam	95.65	73.13	100	66.67	72.22	0
Tetracycline	29.17	33.87	36.36	16.67	R	0
Tigecycline	91.30	90.77	81.82	58.33	R	44.44
Trimethoprim-sulfamethoxazole	47.83	33.33	50	16.67	R	55.56
Cefoperazone sulbactam	78.26	64.62	92.31	50	57.89	50

NA: not available, specific test was not conducted; R: intrinsically resistant.

Table 6. Specific Gram-positive bacteria susceptibility to antibiotics

Antibiotics	*E. faecalis* (n=20) (%)
Ampicillin	100
Ciprofloxacin	33.33
Erythromycin	12.50
Fosfomycin	100
Levofloxacin	15.79
Linezolid	15.79
Meropenem	0
Moxifloxacin	0
Nitrofurantoin	80
Oxacillin	0
Penicillin	17.65
Quinupristin-dalfopristin	5.26
Teicoplanin	88.89
Tetracycline	27.78
Vancomycin	84.21

Urinary tract infection comprises several clinical syndromes including asymptomatic bacteriuria, acute pyelonephritis, acute cystitis,and severe urosepsis. Urinary tract infection prevalence is determined by sex and age. In this study, patients over 59 years old were the most population experiencing UTI about 41.40% of all the population. Several factors are associated with the vulnerability of elder patients to

experience UTI. The factors are, for example, high rates of catheter use in this population, urinary retention, and the prevalence of comorbid diseases in elderly patient, such as stroke and dementia. UTIs are also commonly diagnosed in sexually active young women (Rowe & Juthani-Mehta 2013). However, in this study there was no peak of UTI incidence in the sexually active women age. Recent study was done in a tertiary hospital in which the patients tended to have many complications. On the other hand, UTI which is experienced by a sexually active young woman is usually the uncomplicated one, so it might already have been well treated by a previous primary health care provider (Lema & Lema 2018). This result was consistent with a study that no UTI incidence peaks in sexually active women age (Gidamudi et al. 2015).

Microbiological investigation

Most of the uropathogens identified in this study were gram-negative. *E. coli* was the most common bacteria. This result was supported by other previous studies in Indonesia and other countries as well (Ren et al. 2016, Pratistha et al. 2018, Setyorini et al. 2019). Fimbriae, flagella, toxins, pili, curli, and iron acquisition systems are some virulence factors that help *E. coli* cause infection (Terlizzi et al. 2017).

Nearly 74% of *the E. coli* strain in this study was an ESBL-producing strain. Another study in the same area that used data in the year 2018 mentioned that only 34.78% of the *E. coli* strain produces ESBL in hospitalized patients (Setyorini et al. 2019). The data indicated that there was a rapid spreading of the ESBL gene in the clinical environment as Indonesia is a country where there is the emersion and transmission of ESBL genes harbored inside the bacterial strains (Severin et al. 2010).

Antibiotics susceptibility

Gram-negative and positive bacteria were resistant to several penicillin class antibiotics, cephalosporins, and trimethoprim. Particularly for gram-negative bacteria, the resistance of beta-lactam antibiotics (penicillin and cephalosporin) can evolve along with the emergence of the ESBL strain of uropathogen. In this study, *E. coli* and *K. pneumoniae* that produce ESBL had higher resistance to related antibiotics compared to the ones which not produce ESBL. It could happen because ESBL is an enzyme that will hydrolyze beta-lactam rings, causing loss of beta-lactam antibiotic activities (Trevor et al. 2015). However, the higher resistance rate of ESBL-producing strain presented in this study was not limited to beta-lactam antibiotics. These data were supported by another study which found that ESBL-producing strain of *E. coli* was more resistant to antibiotics tested except amikacin, imipenem, meropenem, and nitrofurantoin which had a similar result in this study (Gharavi et al. 2021). The high susceptibility of amikacin, meropenem, and imipenem toward *E.coli* that produced ESBL was also mentioned in other studies (Rajabnia et al. 2019, Yadav & Prakash 2017).

In this study, *K. pneumoniae* that produced ESBL had a higher resistance rate to ceftazidime, cefotaxime, ceftriaxone, and trimethoprim-sulfamethoxazole. The result was consistent with Gharavi et al. study (2021). Some antibiotics with a high level of sensitivity for ESBL-producing *K. pneumoniae* shown in this study were carbapenem antibiotics (imipenem and meropenem), amikacin, and colistin. In many isolates, the sensitivity of imipenem and meropenem toward ESBL-producing *K. pneumoniae* was high (Mansury et al. 2016). Another study by Singh et al. (2015) discussed that 76% of ESBL-producing *K. pneumoniae* was still sensitive to amikacin.

Most gram-negative bacteria were susceptible especially to carbapenems (ertapenem, meropenem, imipenem) and aminoglycosides (amikacin). Carbapenems are antibiotics that have low susceptibility to beta-lactamase. They are commonly used intravenously for bacteria that are resistant to other antibiotics. This antibiotic has a broad spectrum of activity for gram-negative rods, gram-positive cocci, and anaerobic bacteria. Meanwhile, amikacin is one of the aminoglycoside antibiotics with the lowest resistance profile (Trevor et al. 2015). However, it should be noted that aminoglycosides are one of the well-known nephrotoxic agents (Morales-Alvarez 2020).

In complicated UTI patients, especially with underlying kidney disease, prescribing nephrotoxic antibiotics should be done carefully and under closed monitoring. Moreover, chronic kidney disease was one of the most common comorbidities found in patients in this study.

The majority of gram-positive-related UTIs were caused by *E. faecalis* in this study. Unfortunately, this bacterium was resistant to many antibiotics including meropenem, moxifloxacin, and oxacillin. *E. faecalis* had a high intermediate level for linezolid in this study. Linezolid and vancomycin were two antibiotics with very good susceptibility for *Enterococcus* bacteria (Gajdács et al. 2020). This indicated that the use of linezolid for *E. faecalis* needs to be given in a higher dose to achieve an effective effect (Gajdács et al. 2020).

Chloramphenicol, rifampin, tigecycline, streptomycin, vancomycin, teicoplanin, ampicillin, and fosfomycin were some antibiotics that gram-positive bacteria were

mostly susceptible to. For specific bacteria, linezolid was also one of the most susceptible antibiotics for Gram-positive bacteria (seen as low resistance percentage for Gram-positive bacteria).

Linezolid is an oxazolidinone antibiotic which active in overcoming resistant Gram-positive bacterial infections, such as MRSA (Methicillin-Resistant *Staphylococcus aereus*), PRSP (Penicillin Resistant *Streptococcus pneumoniae*), and VRE (Vancomycin-Resistant Enterococcus) (Trevor et al. 2015). In another study, Gram-positive bacteria had good susceptibility to vancomycin as well. Mechal et al. (2021) mentioned that 88.9% of Gram-positive bacteria were sensitive to vancomycin (Mechal et al. 2021).

Recent clinical antibiotic preference for UTI

Antibiotic prescriptions might be different around the world. Yet, it should be noted that according to Infectious Disease Society of America guidelines, trimethoprim-sulfamethoxazole is a therapy of choice in treating women experiencing uncomplicated UTI. Inside the guidelines, it is stated that trimethoprim-sulfamethoxazole can only be used for uncomplicated UTI if local uropathogens resistance does not exceed 20% (Gupta et al. 2011). In this study, uropathogens (both Gram-negative and -positive) had a high resistance rate exceeding 20%. This should be taken into consideration in prescribing trimethoprim-sulfamethoxazole as empirical therapy for UTI patients. However, as the most common Gram-positive bacteria, Enterococci could greatly contribute to the high resistance rate of Gram-positive bacteria to trimethoprim-sulfamethoxazole due to its characteristic that intrinsically resistant to trimethoprim-sulfamethoxazole.

In Indonesia, the current empirical first drug choice in overcoming both lower and upper UTIs is a fluoroquinolone (especially levofloxacin) as it is affordable and broadly available in Indonesia (Sugianli et al. 2017). However, from this study, the susceptibility result of both Gram-negative and Gram-positive bacteria to levofloxacin was not satisfying enough, with a sensitivity rate of only 36.31% and 24.14%, respectively. Other fluoroquinolones tested in this study were ciprofloxacin and moxifloxacin. Both of them also had low sensitivity levels, in percentage 33.14% and 33.81% for gram-negative, and 40% and 50% for gram-positive bacteria, respectively.

In primary care background, nitrofurantoin is one choice in managing uncomplicated UTI due to its affordable price, acceptable previous resistance prevalence, and mild toxicity (Huttner et al. 2015, Sugianli et al. 2017). Fosfomycin is another choice for managing lower uncomplicated UTIs (Sugianli et al. 2017).

The result of the current study showed that the sensitivity for fosfomycin and nitrofurantoin were 62.79% and 47.13% for gram negative-bacteria, 75% and 64.52% for gram-positive bacteria, respectively. However, Regulation of the Ministry of Health, Republic of Indonesia number 8 the year 2015 stated that antibiotic has good susceptibility if the sensitivity is exceeding 80%. This showed that even though fosfomycin and nitrofurantoin were acceptable in managing UTI, it was not considered a good antibiotic in this study setting based on the mentioned regulation. This highlights, even more, the importance to update the local antibiotic-resistant profile.

Continuous study regarding this topic should be done to monitor the rise of resistance levels to provide proper empirical therapy for UTI patients. The limitation of this study was that the secondary data used as a data source made the authors unable to control the intervention carried out directly on the research.

Strength and limitation

This work provides the latest findings on the bacterial and antibiogram profiles of urine specimens from UTI patients. Clinicians may be informed regarding the most appropriate administration of antibiotics to treat an illness according to the profile. Ongoing research on this topic are needed to monitor the increasing resistance levels and offer appropriate empirical therapy for UTI. The limitation of this study was that the authors were unable to carry out the intervention directly due to the use of secondary data as a data source.

CONCLUSION

Most UTIs were caused by gram-negative bacteria, with *E. coli* as the most common etiology. This result was consistent with other studies that showed The predominant microorganism found in UTI was Escherichia coli. The possible reason Escherichia coli was a causative agent of UTI is that this bacterium can occupy and reproduce within uroepithelial cells that supply a survival advantage to escape recognition and apoptosis by both innate and adaptive immune defense mechanisms. Gram-negative bacteria were susceptible to ertapenem, meropenem, amikacin, and imipenem, while teicoplanin and vancomycin were some antibiotics with high sensitivity levels for gram-positive bacteria. A high level of drug resistance for recent antibiotic preferences was seen in this study. It urges the need of updating empirical therapy recommendations based on local antibiograms for ensuring the success of the patient's therapy. Furthermore, definitive therapy of UTI should be based on antibiotic susceptibilities test.

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Conflict of interest

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Author contribution

MDTU, WM and RJS conceived the idea of the study. MRW prepared the draft of the manuscript. MDTU was in charge of the manuscript arrangement. All authors were involved in the revision of the manuscript and have agreed to the final content.

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Original Research Report

VASCULAR DEMENTIA PATIENTS CHARACTERISTICS WITH A HISTORY OF STROKE IN A NATIONAL BRAIN CENTER HOSPITAL JAKARTA, INDONESIA

Afifah Kusuma Hanifah[1], Riezky Valentina Astari[1,2], Hikmah Muktamiroh[1], Arman Yurisaldi Saleh[1]
[1]Universitas Pembangunan Nasional Veteran, Jakarta, Indonesia
[2]Jantung Diagram Hospital, Depok, Indonesia

ABSTRACT

Stroke patients increase each year. Stroke is a cerebrovascular disorder caused by disruption of cerebral blood flow, which could reason vascular lesions within the mind parenchyma to be a threat to significant disorders. One of them is vascular dementia. Each affected person is prone to growing dementia after a stroke in three to five instances. This study aimed to decide the traits of patients with vascular dementia with a record of stroke. This study used a descriptive retrospective approach with a cross-sectional method. The samples were obtained from the total sampling technique. The sample of the study was vascular dementia patients with a stroke record at the National Brain Center Hospital Prof. Dr. dr. Mahar Mardjono,Jakarta, in the period of 2020 through the inclusion standards with 191 samples. This study found that the majority of patients were males as many as 129 (67.5%), age group of 55-64 were 67 patients (35.1%), post-ischemic strokes were 164 patients (85.9%), grade 1 hypertension as many as 70 patients (36.6%), and basal ganglia as many as 76 patients (29.23%). Characteristics of vascular dementia patients with the maximum stroke records in men, aged 55-64 years, post-ischemic stroke, grade 1 hypertension, and a majority of the lesions within the basal ganglia.

Keywords: *Vascular dementia; history of stroke; characteristics; cardiovascular disease*

Correspondence: Afifah Kusuma Hanifah, Universitas Pembangunan Nasional Veteran Jakarta, Jakarta, Indonesia. Email: afifahkusumah@upnvj.ac.id

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Highlights:

1. Characteristics of vascular dementia patients with a history of stroke was aimed.
2. The most characteristics of vascular dementia patients with stroke history are men, post-ischemic stroke, hypertension grade 1, and lesions in the basal ganglia.

INTRODUCTION

Stroke is a public health issue that keeps increasing each year. Stroke remains the third-leading cause of death, the second-main motive of demise motive and disability combined in the world (Feigin et al. 2022). Globally, one-third of 15 million human beings die because of stroke every year; and the rest experience permanent disability (Stroke Forum 2015). Based on the data, a wide variety of human population who have gotten stroke is around 713,783 people. Every affected person who has stroke record can get better or be proned to experiencing significant issues from slight to severe symptomps (Basic Health Research 2018).

Many people continue to stay with their long-time period motor and exist after stroke, cognitive and touchy effects because of advances in intervention strategies (Donkor 2018). It regularly results in cognitive decline, even in stroke patients who underwent revascularization therapies (Lattanzi et al. 2020), starting from subjective cognitive decline to dementia (del Ser et al. 2005, van der Flier et al. 2018).

Stroke is harmful for the brain that looks sudden, progressive, and hasty because of non-traumatic cerebral blood circulation disorders. Stroke is divided into two, specifically ischemic stroke which is a result of a loss of blood deliveryy to a place in brain tissue because of blockage withinside the brain's arteries. In contrast, hemorrhage stroke which is a result of cerebral hemorrhage or subarachnoid hemorrhage caused by cerebral blood vessels rupture (Munir 2017).

The threat elements that affect the occurrence of stroke are divided into two, modifiable threat elements and non-modifiable threat elements. The threat elements that cannot be modified are heredity (genetic), race, age, and gender. Meanwhile, the threat elements that may be modified are diabetes mellitus, high blood pressure, hypercholesterolemia, and stress (Harsono 2015). However, some of the numerous elements that affect the occurrence of stroke such as the handiest high blood pressure, notably influence in the occurrence of stroke, when lipid degrees and smoking behavior were not notably related to the occurrence of stroke (Puspitasari 2020).

Vascular dementia (VaD) is a different cerebrovascular disease or subclinical or clinical cerebrovascular damage induced by a hemorrhagic or ischemic stroke (Li et al. 2021). VaD is the second most common cause of dementia in the elderly (Bir et al. 2021). Dementia can be caused by stroke. Some studies have proved stroke can cause loads of pathologies, along with the ones related to subcortical vascular dementia, multi-infarct dementia, and infarct dementia. Each affected person with a stroke record can be more susceptible to grow dementia in 3-5 instances than sufferers without a preceding stroke. Dementia that happens after a stroke is assessed as vascular dementia. After six months of stroke, the occurrence of vascular dementia is 20%, and signs grow with the dimensions of the lesions produced after stroke (Lastri 2017). In fact, within the first 12 months after stroke, there is as much as a nine-fold extra danger of dementia, and the occurrence grows more thereafter (Desmond et al. 2002).

Vascular dementia is intently associated with numerous vascular mechanisms and adjustments withinside the brain. Vascular lesions within the brain parenchyma arise through ischemic, hemorrhagic, or an aggregate of those factors. Damage to the lesion within the brain manifests as signs of reminiscence impairment and impaired cognitive function (Emdin et al. 2016).

This study was conducted as an observation on the characteristics of patients with vascular dementia with a stroke history. This study was expected to benefit the health sector as a consideration in preventive interventions in stroke patients to reduce the incidence of vascular dementia and maintain or improve health status and quality of life in post-stroke patients. In addition, it could provide information about the characteristics of vascular dementia patients in patients with a history of stroke.

MATERIALS AND METHODS

This study used a cross-sectional method conducted at the National Brain Center Hospital Prof. Dr. dr. Mahar Mardjono, Jakarta, Indonesia. A cross-sectional study design is an observational study, where the exposures of the study participants and the investigator measure the results at the same time (Setia 2016). This study used medical records to be more adequate, and relevant but not excessive and uncollected to respond to the existing study. Secondary data analyses are not usually replicable (Border et al. 2019), robust to analytic choices (Botvinik-Nezer et al. 2020), or reproducible (Seibold et al. 2021). It is consequently essential for medical and societal progress (Baldwin et al. 2022). In this study, the data had been evaluated for certain criteria (Tripathy 2013).

The study was carried out from November to December 2021. The population in the study was patients with vascular dementia recorded in the medical records from January to December 2020. The sampling used was total sampling technique.

This study utilized inclusion criteria and exclusion criteria, following the research criteria. The variables in this study were history of stroke as the independent variable and vascular dementia as the dependent variable. The instruments in this study were medical record data and CT scans along with the analysis results as a tool to see the location of lesions in patients with vascular dementia.

RESULTS

The research was conducted at the Neuro Medical Record Polyclinic of Prof. Dr. dr. Mahar Mardjono National Brain Center Hospital, Jakarta, Indonesia, from November 2021 to December 2021. Based on medical record data, vascular dementia patients with a history of stroke were 191 patients.

Table 1. Distribution of vascular dementia patients by age

Age (years)	Total	
	(n)	(%)
< 45 years	14	7.3
45-54 years	37	19.4
55-64 years	67	35.1
65-74 years	45	23.6
75-84 years	23	12.0
> 85 years	5	2.6
Total	191	100.0

Based on the table, there were 67 patients (35.1%) aged 55-64 years, 45 patients (23.6%) aged 65-74 years, 37 patients (19.4%) aged 45-54 years, 23 patients (12.0%) aged 75-84 years, 14 patients (7.3%) aged <45 years, and 5 patients (2.6%) aged >85 years.

Table 2. Distribution of vascular dementia patients by gender

Gender	Total	
	(n)	(%)
Male	129	67.5
Female	62	32.5
Total	191	100.0

The table above shows that the number of male patients was 129 patients (67.5%) and women were 62 patients (32.5%).

Table 3. Distribution of vascular dementia samples based on a history of hypertension

Hypertension	Total	
	(n)	(%)
Normal	14	7.3
Prehypertension	45	23.6
Hypertension Grade 1	70	36.6
Hypertension Grade 2	62	32.5
Total	191	100.0

History of hypertension in DVA patients with a history of stroke in the form of hypertension grade 1 was 70 patients (36.6%), hypertension grade 2 were 62 patients (32.5%), prehypertension was 45 patients (23.6%), and average (not hypertension) were 14 patients (7.3%).

Table 4. Distribution of vascular dementia samples by type of stroke

Types of stroke	Total	
	(n)	(%)
Post-Ischemic stroke	164	85.9
Post-Hemorrhagic stroke	27	14.1
Total	191	100.0

The history of stroke showed that there were 164 patients (85.9%) after ischemic stroke and 27 patients (14.1%) in post-hemorrhagic stroke.

Table 5. Distribution of samples of vascular dementia based on the location of the lesion

Lesions Location	Total	
	(n)	(%)
Frontal lobe	53	11.4
Parietal lobe	29	6.3
Occipital lobe	6	1.3
Temporal lobe	13	2.8
Basal Ganglia	76	16.4
Cerebellum	17	3.7
Thalamus	39	8.4
Pons	30	6.5
Frontotemporalis	3	.6
Frontoparietal	7	1.5
Parietotemporalis	3	.6
Parietooccipitalis	14	3.0
Temporooccipitalis	6	1.3
Interna Capsule	29	6.3
External Capsule	26	5.6
Insula lobe	31	6.7
Corona Radiata	31	6.7
Periventricular Lateral	23	5.0
Temporoparietal lobe	6	1.3
Frontotemporoparietal lobe	6	1.3
Temporoparietooksipital lobe	1	.2
Occipitalis lobe	3	.6
Mesencephalon	1	.2
Perivencular	5	1.1
Nucleus caudatus	5	1.1
Total	463	100.0

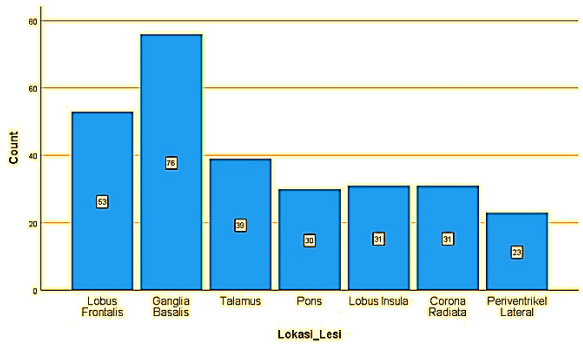

Figure 1. Distribution of samples of vascular dementia Basef on the location of the lesions.

Based on the table, it can be concluded that the 5 most locations of lesions in vascular dementia patients with a history of stroke are as follows.

Based on the location of the lesion, it was concluded that there were five most significant groups of lesion locations, namely the location of the most lesions in the basal ganglia in 76 locations (29.23%), frontal lobes in 53 locations (20.38%), thalamus in 39 locations (15 0.00%), insula lobes in 31 locations (11.92%), corona radiata in 31 locations (11.92%), and pons in 30 locations (11.54%).

DISCUSSION

Based on the results in Table 1, it is recognized that most samples of vascular dementia with the aid of using age have been within the 55-64 years age group as many as 67 patients (35.1%), while the least at > 85 years were 5 patients (2.6%). The increase in age will result in impaired blood flow caused by degenerative processes and atherosclerosis in blood vessels in the brain (Tumeleng et al. 2015).

In Table 2, it can be seen that the distribution of vascular dementia samples by gender is the highest in males as many as 129 patients (67,5%), while in women only 62 patients (32.5%). This study's results are in line with research by Riyanto and Brahmahdi (2017), with 38 samples of vascular dementia found that 21 patients (57.9%) were male. This situation is related to smoking conduct in most men, which can cause atherosclerosis of blood vessels (Tumeleng et al. 2015).

In Table 3, the distribution of vascular dementia patients based on hypertension mainly is in grade 1 hypertension as many as 70 patients (36.6%). However, the least on average (non-hypertensive) were 14 patients (7.3%). Research performed on the elderly in the Integrated Healthcare Center (Posyandu) Dauh Puri Kelod Village found no statistically significant relationship between the degree of hypertension and impaired cognitive function.

Out of 70 samples, elderly with grade 1 hypertension there were as many as 40 people (57.1%), while there were those who with grade 2 hypertension with as many as 19 people (27.1%) and the remaining were 11 people (15.7%) with grade 3 hypertension. This study also found that from 47 people (67.1%) who experienced cognitive function disorders, 42 people had a history of hypertension for more than 5 years. Five people had a hypertension history for less than 5 years (Indrayani & Purnawati 2020). Based on a study, there were 46 people who had hypertension for ≥ 5 years; among them, 16 people (34.8%) had moderate dementia, 13 people (28.3%) did not experience cognitive impairment, and 17 people (37.0%) had

severe dementia (Rahmayanti 2018). This damage was due to the history of hypertensive patients which takes more than 5 years with lacunar infarctions in certain parts of the brain (Nurimah 2018).

However, there were several weaknesses: the sample of dementia vascular patients with a history of stroke, unknown history of treatment for hypertensive, the type of drug that might affect the results study and other factors that could affect dementia vascular in hypertensive patients. For future researchers, it is suggested to pay attention in describing the research results accurately in history of hypertension treatment, history of stroke, types of drugs that can affect research results, and other factors that can affect vascular dementia in hypertensive patients is recommended.

Based on Table 4, the distribution of patients with vascular dementia was most common in patients after ischemic stroke, 164 patients (85.8%) compared to 27 patients (14.1%) after a hemorrhagic stroke. This result was in line with the research of Tini and Surya (2021) which found that 42 people (68.8%) had ischemic stroke and 19 people (31.2%) had a hemorrhagic stroke. Twelve of the 31 patients with possible dementiahad dementia, and 18 patients had no cognitive impairment.

However, another study conducted by Riyanto and Brahmahdi (2017) also found that the number of dementia patients was higher in a sample of post-hemorrhagic stroke patients than in a sample of post-ischemic stroke patients. From 35 samples of patients with post-hemorrhagic stroke, 29 patients (41.23%) had dementia and 6 patients (8.57%) did not have dementia. The difference in the results of this study was associated with the dominant factors in the occurrence of post-stroke cognitive function disorders in the form of multiple stroke onset lesions and lesions location (Pinzon et al. 2018). Based on Figure 1, the lesion location in patients with vascular dementia mainly occurred in the basal ganglia with 76 locations (29.23%), the frontal lobe with 53 locations (20.38%) and thalamus with 39 locations (15.00%).

A research that found that patients with lesions in the white matter of the frontal gyrus, basal ganglia, and thalamus could affect impaired cognitive function strengthens the argument in this study. Basal ganglia has a dominant role in knowledge, perceptual decision making, and absent motor pathways such as fluency, cognition, and behavior (Zhao et al. 2018). In addition, the results of this study were supported by Wang et al. (2016) study which found that the presence of infarcts in the white matter in the frontal lobe, basal ganglia, and thalamus were associated with the appearance of impaired cognitive function.

Strength and limitation

This study provides characteristics of patients with vascular dementia that can be used to prevent the prevalence of the disease. This study had several limitations, including a lack of vascular dementia patients with a history of stroke, an unknown history of hypertensive treatment, various types of medications that could have an impact on the results of this study, and other factors not investigated that could otherwise have an impact on the patients.

CONCLUSIONS

Of the 191 samples who were screened for vascular dementia patients with a history of stroke, it was found that the highest number of patients was male as many as 129 patients (67.5%), post-ischemic stroke as many as 164 patients (85.9%), grade 1 hypertension as many as 70 patients (36.6%), 55-64 year-old groupas many as 67 patients (35.1%), and basal ganglia as many as 76 patients (29.23%).

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Conflict of interest

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Author contribution

AKH and RVA writed and analyzed of the manuscript. HM was revised of the manuscript. AYS was involved in the revision of the manuscript and have agreed to the final content.

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Original Research Report

RISK FACTORS OF URINARY TRACT INFECTION CAUSED BY EXTENDED-SPECTRUM β-LACTAMASE-PRODUCING *Escherichia Coli* IN INPATIENTS AT A TERTIARY HOSPITAL IN SURABAYA, INDONESIA

Ishak S Wuwuti[1], Kuntaman[2,3] , Eddy Bagus Wasito[2]

[1]Department of Clinical Microbiology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia
[2]Department of Microbiology, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia
[3]Indonesian Society for Clinical Microbiology, Indonesia

ABSTRAK

The incidence of urinary tract infections (UTIs) caused by extended-spectrum beta-lactamase (ESBL) producing Escherichia coli (E. coli) bacteria has become a global problem and has increased in recent years. The purpose of this study was to analyze the risk factors for the incidence of UTI in inpatients at Dr. Soetomo General Academic Hospital, Surabaya. This research was an analytic descriptive study. Specimens were sent to the Clinical Microbiology Laboratory using sterile containers and processed according to standard laboratory procedures. It resulted in ESBL-producing E. coli that were used as a case group and non ESBL-producing E. coli as a control group. The identification and testing of antibiotic susceptibility were carried out using the BD Phoenix™ Automated Microbiology System. Ninety-four bacterial isolates were collected, consisting of 54 (57.4%) ESBL-producing E. coli bacteria and 40 (42.6%) non ESBL-producing E. coli bacteria. Recurrent UTIs (OR = 4.31; ρ =0.002; 95% CI = 1.68-11.04) and catheter use (ρ = 0.049; OR = 4.250; 95% CI = 1.050-17.210) were used as independent risk factors caused by ESBL-producing E. coli bacteria. Recurrent UTIs and catheter use were dependent risk factors caused by ESBL-producing E. coli bacteria.

Keywords: *E.coli; extended-spectrum beta-lactamase ; urinary tract infections; risk factors; disease*

Correspondence: Ishak Samuel Wuwuti. Clinical Microbiology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia. Email: graciawuwuti@gmail.com

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Highlights:

1. ESBL frequency in women was higher than in men.
2. Catheter use in patients with urinary tract infections and recurrent urinary tract infections has four times the risk of ESBL caused by Escherichia coli bacteria
3. ESBL-producing E.coli bacteria are resistant to amoxicillin-clavulanic, ceftazidime, aztreonam, and ceftriaxone.

INTRODUCTION

Urinary tract infections (UTIs) represent microbial colonization and infection of urinary tract structures and are classified according to the site of infection into the kidney, bladder, and urethra (Sheerin 2011). UTI is one of the most common microbial diseases in a clinic, affecting all age groups (Kunin 1994). Globally, the prevalence of UTI is estimated at approximately 150 million people per year (Gupta et al. 2001). UTI is also one of the most common nosocomial infections, accounting for approximately 40% of all nosocomial bacterial infections worldwide (Mahamat et al. 2006). In Indonesia the incidence of UTIs is approximately 180,000 new cases annually (Sugianli et al. 2020). *Escherichia coli* (*E. coli*) is the most prevalent nosocomial pathogen (Ejrnæs 2011). Beta-lactamase risk factors were 83.3% in UTI isolates, 72.7% in urinary catheter use, and 65.3% before admission to ICU and use of antibiotics within 3 months (Sheik et al. 2016). Appropriate UTI management should be implemented to avoid recurrence and possible complications, also to prevent persistent bacteriuria, bacteremia, and urosepsis. Recurrent UTIs can lead to acute necrotizing renal infections. The presence of bacterial mutations that cause UTIs at different times and places allows for the presence of antimicrobial-resistance (AMR) bacteria Vranicianu (Tonolini 2018).

E. coli is responsible for 70-95% of UTI cases (Behzadi, P et al. 2010). Over 90% of ESBL-producing *E. coli* are susceptible to antibiotics such as tigecycline, amikacin, meropenem, ertapenem, and doripenem (Dahesihdewi et al. 2019). Several risk factors for infection with ESBL-producing bacteria have been identified, such as aginal infections, HIV/AIDS, immune system disorders, etc. (Uswanas et al. 2022; McLellan 2016).

Over the past two decades, there has been a significant number of infections caused by bacteria expressing extended-spectrum β-lactamases (ESBLs) and carbapenemases (Logan and Weinstein, 2017). In particular, ESBL isolates have been found in humans (Ashiboe-Mensah 2016), animals, the environment (water and soil) (Runcharoen et al., 2017), meat, and even vegetables (Yang et al., 2019). Increase of ESBL is becoming more common as use and exposure to β-lactamase, especially cephalosporins, are selected for this phenotype. This has led to a vicious cycle of drug resistance and diminishing therapeutic efficacy. Increased use of cephalosporins has been associated with *E. coli* infections in swine (Hammerum et al., 2014) and the high frequency of ESBL-producing *E. coli* was directly associated with high consumption of the third or fourth cephalosporins (Andersen et al., 2015; Chen et al., 2019). The increasing prevalence of ESBLs and multidrug resistance caused by multiple classes of antibiotics in UTIs has led the authors to conduct a research on risk factors for UTIs caused by ESBL-producing bacteria at a tertiary hospital of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.

MATERIALS AND METHODS

A cross-sectional study was conducted at Dr. Soetomo Hospital in Surabaya, Indonesia to investigate the characteristics and risk factors of patients diagnosed with ESBL-producing *E. coli* in the medical and surgery ward. Ninety-four *E. coli* isolates from hospitalized patients with UTIs were phenotypically assessed for ESBL production using semi-automatic Phoenix BD. Its automated susceptibility and identification testing system provides rapid, reliable, and accurate detection of known and emerging antimicrobial resistance.

Data collected from both electronic, questionnaire, and paper-based medical records included patients demographics (birth date, sex, admission ward), culture and susceptibility results, antibiotic therapy for 3 months, hospitalization during 12 months, transfer from another healthcare facility, urinary catheterization during 30 days, and comorbidities based on Charlson Comorbidity Score. These study subjects were patients aged ≥ 18 years with suspected UTIs treated at the medical and surgery ward, Dr. Soetomo Hospital for more than 48 hours. The study was conducted at the Clinical Microbiology Unit from March to July 2019. The first isolate culture results were used in this study. The ethics committee had approved this study as outlined in the ethics eligibility statement number 1095 / KEPK / IV / 2019.

Samples from urine specimens were identified and tested for antibiotic susceptibility using a semi-automatic BD Phoenix system that met the inclusion and exclusion criteria. Urine isolates of 1 µL are taken to be inoculated on MacConkey and blood agar mayo is streaked using a calibrated loop and incubated for 18-48 hours at 37°C with the growth of 10≥5 CFU/ml (colony forming units/mL) is considered positive Samples from urine specimens were identified and tested for antibiotic susceptibility using a semi-automatic BD Phoenix system that met the inclusion and exclusion criteria. Urine isolates of 1 µL are taken to be inoculated on MacConkey and blood agar mayo is streaked using a calibrated loop and incubated for 18-48 hours at 37°C with the growth of 10≥5 CFU/ml (colony forming units/mL) is considered positive culture as the result (Versalovic et al. 2011).

Data were analyzed using Statistical Package for the Social Sciences (SPSS), version 25 (IBM Co., Armonk, NY, USA). Risk factors for ESBL-producing *E. coli* UTI were identified by univariate analysis. The final model included confounding variables significant at a two-tailed P-value of <0.05. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the strength of association.

RESULTS

In this study, ninety-four *E. coli* were collected from patients' urine samples at the Clinical Microbiology Laboratory of Dr. Soetomo General Academic Hospital that consisted of 54 (57.4%) ESBL isolates and 40 (42.6%) non ESBL-producing isolates. The identification was done by using the semi-automatic BD Phoenix system. The BD Phoenix is a bacterial growth-based automated system for determining antibiotic resistance characteristics in various test panels (Jonas, D et al. 2021). Based on age, the youngest patient was 25 years old and the oldest was 86 years old, while the average age of 56.60 was identified as the producer of ESBL and the average age of 57.00 was not the producer of ESBL. Out of the 55-64 years, ESBL was identified in as many as 20 (21.27%) isolates, while non ESBL-producing were 13 (13.82%) isolates, with a total of 33 isolates. The frequency of *E. coli* isolates by sex consisted of 67 women (71.3%) isolates and 27 men (28.7%) isolates. ESBL-producing bacteria were 36 (38.29%) isolates in women and 18 (19.14%) isolates in men. Urine specimens in this study according to ward origin consisted of 68 from medical ward (72.3%) and 26 from surgical ward (27.7%) (Table 1).

Table 1. Frequency of ESBL-producing and non-ESBL-producing *E. coli* bacteria

Room	*E. coli* ESBL n(%)	*E. coli* non ESBL n(%)	Total n (%)
Wards Medical	40 (42.5)	28 (29.8)	68 (72.3)
Surgical	14 (14.9)	12 (12.8)	26 (27.7)
Total	54 (57.4)	40 (42.6)	94 (100)

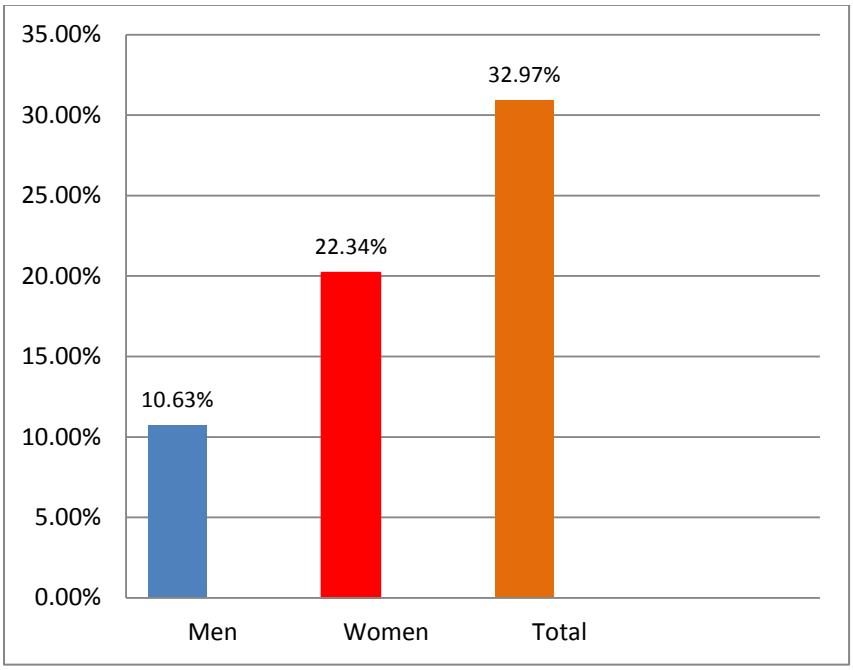

Figure 1. Frequency of UTI inpatients

Table 2. Antibiotic susceptibility to *E. coli* bacteria

	***E.coli* ESBL**			***E.coli* non ESBL**		
Antibiotic	S(%)	I(%)	R(%)	S(%)	I(%)	R(%)
Amikasin	54(57.4)			39(41.5)		1(1.1)
Gentamicin	38(40.4)		16(17)	36(38.3)		4(4.3)
Astreonam			54(57.4)	38(40.4)	1(1.1)	1(1.1)
Ampicillin Sulbactam			54(57.4)	15(16)	15(16)	10(10.6)
Amoxicillin clavulanate acid			54(57.4)	28(29.8)	10(10.6)	2(2.1)
Ampicillin			54(57.4)	11(11.7)		29(30.9)
Cefepime	3(3.2)		51(54.3)	36(38.3)	3(3.2)	1(1.1)
Piperacillin tazobactam	35 (37.2)	9(9.6)	10(10.6)	37(39.4)	2(2.1)	1(1.1)
Ceftazidim			54(57.4)	38(40.4)		2(2.1)
Cefotaxime			54(57.4)	38(40.4)		2(2.1)
Ceftriaxone	1(1.1)		53(56.4)	37(39.4)	1(1.1)	2(2.1)
Cefoperazon sulbactam	32(34)	14(14.9)	8(8.5)	36(38.3)	4(4.3)	
Trimethropin sulfametasol	16(17)		38(40.4)	19(20.2)	2(2.1)	19(20.2)
Tetracyclin	9(9.6)		45(47.9)	12(12.8)	1(1.1)	27(28.7)
Tigecycline	15(16)	1(1.1)	38(40.4)	33(35.1)	1(1.1)	6(6.4)
Ciprofloxacin	2(2.1)		52(55.3)	30(31.9)		10(10.6
Levofloxacin	3(3.2)		51(54.3)	30(31.9)		10(10.6)
Moxifloxacin	2(2.1)	1(1.1)	51(54.3)	30(31.9)		10(10.6)
Fosfomycin	44(46.8)	1(1.1)	9(9.6)	35(37.2)		5(5.30)
Nitrofurantoin	29(30.9)	13(13.8)	12(12.8)	37(39.4)	1(1.1)	2(2.1)
Meropenem	51(54.3)		3(3.2)	39(41.5)		1(1.1)
Imipenem	48(51.1)	3(3.2)	3(3.2)	36(38.3)	1(1.1)	3(3.2)

Table 3. Univariate risk factors for UTIs of ESBL-producing *E.coli* bacteria and non-ESBL-producing *E. coli*

Risk factors	ESBL n (%)	Non-ESBL n (%)	ρ-value	OR; (CI 95%)
Sex				
Male	18(33.3)	9 (22.5)	0.359	1.722; 0.677-4.379
Female	36(66.7)	31(77.5)		
Age	57.48 ±13.2	55.40 ±15.2	0.467	1.011; 0.981-1.041
Hospitalization			0.167	2.571; 0.762-8.675
Yes	12(22.2)	4(10)		
No	42(77.8)	36(90)		
Catheter use			0.049	4.250; 1.050-17.210
Yes	51(94.4)	32(80)		
No	3(5.6)	8(20)		
Transfer from			0.637	1.325; 0.512-3.431
another healthcare	15(27.8)	9(22.5)		
Yes	39(72.2)	31(77.5)		
No				
Recurrent UTI			0.002	4.308;1.681- 11.037
Yes	28(51.9)	8(20)		
No	26(48.1)	32(80)		
Surgical procedure			0.157	0.475; 0.188-1.201
Yes	11(20.4)	14(35)		
No	43(79.6)	26(65)		
Malignancy			0.014	0.277; 0.099-0.772
Yes	7(13)	14(35)		
No	47(87)	26(65)		
Chemotherapy			0.454	0.529; 0.112-2.511
Yes	3(5.6)	4(10)		
No	51(94.4)	36(90)		
Chronic disease			0.458	1.467; 0.544-3.954
Yes	44(81.5)	30(75)		
No	10(18.5)	10(25)		

The frequency of *E. eoli* isolates based on patients diagnosed with UTI in this study was 31 (32.97%) isolates, consisting of 21 (22.34%) isolates from women and 10 (10.63%) isolates from men (Figure 1).

From the susceptibility test results (Table 2), there was antibiotic sensitivity of piperacillin-tazobactam, cefoperazone sulbactam, nitrofurontoin, amikacin, gentamicin, meropenem, imipenem, and phosphomycin between 30%-57% in the ESBL-producing *E. coli* bacteria, while in non ESBL-producing *E. coli* bacteria the sensitivity was ≤ 40%.

Based on demographic data and characteristics of *E. coli* bacterial isolates, univariate analysis, variables such as sex, age, previous hospitalization, transfer from other healthcare, catheter use, recurrent UTI, antibiotic use, surgical procedures, malignancies, and comorbidities showed that independent risk factors of ESBL in this study was the use of a catheter with ρ = 0.049 and recurrent UTIs ρ = 0.002 (Table 3).

DISCUSSION

Extended-spectrum β-lactamases are enzymes that mediate resistance to the newer β-lactam antibiotics. In 1980s, ESBL-producing organisms were first reported, shortly after the introduction of the oxyimino β-lactam agents, and have now become widespread all over the world.

These enzymes are produced by the members of the *Enterobacteriaceae* family, mainly *Escherichia coli*, *Klebsiella pneumoniae*, and *Klebsiella oxytoca*.

UTIs are a common infectious diseases around the world. However, the diagnosis and treatment of UTI by clinicians tend to be based on their experiences. In developing countries, guidelines for UTI treatment cannot always be referenced. Despite this situation, studies to utilize UTI guidelines and to properly manage UTI in developing countries have not been fully investigated.

UTI caused by resistant bacteria is becoming more prevalent. Few studies are available regarding community-onset UTIs caused by extended-spectrum β-lactamase (ESBL)-producing bacteria. Research on risk factors associated with UTIs caused by ESBL-producing bacteria, especially Gram-negative bacteria, has been widely validated in European countries (Colodner et al., 2004; Ena et al., 2006). The ninety-four *E.coli* isolates meeting the inclusion and exclusion criteria were 67 (71.3%) isolates from women and 27 (28.7%) isolates from men. As reported by Joseph et al. (2014), the number of *E. coli* isolates identified by

Tamegnon et al. (2016) was 74.7% in women and 25.3% in men, slightly lower than those in this study.

Prevalence of ESBL was 54 (57.44%) isolates and non-ESBL was 40 (42.55%) isolates. The total number of ESBL in women was 36 (38.29%) isolates and 18 (19.14%) isolates in men. The number of ESBL-producing *E. coli* isolates was up to 56%, the same as the study conducted in Pakistan by Kausar et al. (2014).

This study was identical to a previous study by Ben-Ami et al. (2009) which found that catheter use was a risk factor for infection with ESBL-producing *E. coli* (rate 3.3). The frequency of recurrent UTI in this study was 28 (51.9%) isolates, consisting of 26 (48.1%) isolates from women and 10 (10.63%) isolates from men. The number of ESBL-producing *E. coli* bacteria was identified in 10 (10.63%) female and 6 (6.38%) male patients with $\rho = 0.002$; OR 4,308; CI 1.681-11.037. Al Yousef et al. (2016) showed that there were four risk factors for ESBL-producing bacteria, one of which was recurrent UTI infection (Odds 2.93). Meanwhile, Al-Jamei et al. (2018) in Jordan studied about the prevalence and risk factors for ESBL (Odd 2.83).

The independent risk factor in this study was the use of indwelling urine catheters that increased the risk of ESBL caused by *E. coli* by 4 times with $\rho = 0.049$; OR 4.250; CI 1.050-17.210. Pitout et al. (2005) stated that the use of catheters increases the risk of UTIs caused by improper sterilization techniques and minimal expertise during installation which causes contamination. Brill et al. (2021) stated the use of certain catheters such as foley catheters plays an important role as a risk factor for ESBL through biofilm formation between the catheter and urethral mucosa.

Antibiotic sensitivity of piperacillin-tazobactam, cefoperazone sulbactam, nitrofurantoin, amikacin, gentamicin, meropenem, imipenem, and phosphomycin is between 30%-57% in ESBL-producing *E. coli* bacteria, while in non ESBL-producing *E. coli* the sensitivity is ≤40%.

This study showed that ESBL-producing *E. coli* bacteria were resistant to amoxicillin-clavulanic and third-generation cephalosporins, such as ceftazidime, aztreonam, and ceftriaxone. These results were similar to those obtained by Taneja et al. (2008) and Bourjilat et al. (2011). High antibiotic sensitivity in this study included amikacin at 57.4%, phosphomycin at 46.8%, meropenem at 54.3%, and imipenem at 51.1%, which had similarities to antibiotics in a study in Pakistan by Kausar et al. (2014).

Strength and limitation

This study can contribute to research on urinary tract infections by adding more evidence of the risk factors for the disease. However, as a hospital-based research, this study might have a limited sample size.

CONCLUSION

The prevalence of ESBL was 54 (57.44%) isolates and 40 (42.55%) isolates for non-ESBL. ESBL frequency was 36 (38.29%) isolates in women and 18 (19.14%) isolates in men. The frequency of UTI in this study was 31 (32.97%) isolates, consisting of 21 (22.34%) isolates from women and 10 (10.63%) isolates from men. Catheter use in patients with UTIs and recurrent UTIs has four times the risk of ESBL caused by *E. coli* bacteria. ESBL-producing *E. coli* bacteria are resistant to amoxicillin-clavulanic and third-generation cephalosporin, such as ceftazidime, aztreonam, and ceftriaxone.

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Conflict of interest

None.

Funding disclosure

None.

Author contribution

ISW and K was responsible for conceptualization, data collection, and providing analysis. EBW was responsible for investigation of the data, data collection, manuscript revision, and grammatical checks. K was responsible as the supervisor, corresponding author, and also involved in manuscript preparation and validation.

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Original Research Report

KNOWLEDGE ON THE RISK OF THE ISCHEMIC HEART DISEASE ESTIMATION BY WHO CHARTS IN CEMPAKA BARU, INDONESIA

Hasna Luthfiah Fitriani, Karina Ajeng DA Ridwan
Faculty of Medicine, Universitas Yarsi, Jakarta, Indonesia

ABSTRACT

In 2018, Indonesia became the country with the second-highest number of deaths and disabilities (DALYs) due to ischemic heart disease. Based on Riskesdas data in 2018, Jakarta is one of the provinces with a high percentage (1.9%) of ischemic heart disease. Risk factors for ischemic heart disease that are not treated quickly will increase the severity of ischemic heart disease in the future. Therefore, this study was to provide education regarding the assessment of risk estimation for ischemic heart disease with WHO/ISH charts among participants in Cempaka Baru sub-district. This study used pre-test and post-test questionnaires. After the seminars, the interview and examination results were carried out as well as calculating the estimated risk of ischemic heart disease using the WHO chart. These charts were divided into low risk (<10%), moderate (10-20%), and severe (>20%). The evaluation was conducted by comparing the pre-test and post-test results, which indicated that the knowledge level increased significantly from the Paired T-Test with a p-value = 0.000 (p<0.05). The significant estimation of high risk of ischemic heart disease for high blood pressure was 72.7% (p=0.023) and total cholesterol level was 66.7% (p=0.049). The increasing knowledge of the stratification risk of ischemic heart disease with the WHO chart was expected to reduce the risk of ischemic heart disease in the future.

Keywords: *Ischemic heart diseases; knowledge; screening; WHO charts; cardiovascular disease*

Correspondence: Hasna Luthfiah Fitriani, Faculty of Medicine, Universitas Yarsi, Jakarta, Indonesia. Email: hasna160297@gmail.com

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Highlights:

1. The risk estimation of ischemic heart disease.
2. High blood pressure and cholesterol levels affect Ischemic heart disease.

INTRODUCTION

Globally, cardiovascular disease is the leading cause of death worldwide. One of them is ischemic heart disease (IHD) which is caused by the narrowing of the coronary arteries. The narrowing occurs due to the formation of atherosclerotic plaques in the lumen of blood vessels, resulting in an imbalance in the flow of nutrients and oxygen to the myocardium (Shahjehan & Bhutta 2022). In 2018, Indonesia became the country with the second-highest number of deaths and disabilities (DALYs) due to ischemic heart disease (Uli et al. 2020). Data from the Ministry of Health in 2018 showed that three provinces in Indonesia had a high prevalence of heart disease: North Kalimantan (2.2%), Central Sulawesi (2%), and Jakarta (1.9%). This is also supported by the area of residence, the urban population suffers more from heart disease with a prevalence of 1.6% compared to the rural population which is only 1.3% (Ministry of Health 2018). Even though IHD treatment in Indonesia has developed, the prevalence of IHD in Indonesia's working-age population is still relatively high for the young and the old at 1.45% (1.3% in men and 1.6% in women), equivalent to almost 2.0 million people (865,855 men and 1.08 million women) aged between 15 and 55 years (Uli et al. 2020).

The recent lifestyle of the Indonesians is still classified as unhealthy and increases the risk factors for IHD (Suryati & Suyitno 2020), therefore a nationally representative health survey showed that the prevalence of diagnosed stroke among people aged 15 years and above increased by 56% (from 0.7 to 1.1%) during 2013–2018. The prevalence of hypertension among people aged >18 years also increased by 32% (from 26 to 34%), and that of obesity increased by 47% (from 15 to 22%) from 2013 to 2018 (Adisasmito et al. 2020). Also, the lifestyle of urban communities plays a role in increasing cases of IHD (i.e., hypertension, high cholesterol levels, smoking, diabetes, overweight/obesity, lack of physical activity, and unhealthy food patterns). In addition, factors that cannot be controlled are age (getting older increases the risk of IHD), gender (males have a greater prevalence of IHD incidence), family history of the disease, and ethnicity/race (Hajar 2017). This condition will increase mortality and morbidity in Indonesia.

Based on information from the representative participants, the people in Cempaka Baru sub-district do not yet fully understand the risk factors and prevention of IHD. This is illustrated by the fact that there are still many people who consume processed foods, high calories and fat, and lack exercise, which are trigger factors for the occurrence of IHD in the future. For this reason, it is important to increase the knowledge of allies or the community to be able to recognize the risk of IHD from the aspect of age, gender, smoking habits, increased blood pressure, total cholesterol, and a history of diabetes.

The risk for IHD can be detected simply through early detection with WHO/ISH cardiovascular risk prediction charts, which are the simplest and most helpful tools in identifying someone at high risk of cardiovascular disease and motivating them to change their lifestyle, administer antihypertensives, cholesterol/lipid-lowering drugs and aspirin if needed. In addition, the results of this tool can determine what percentage of an individual's risk of ischemic heart disease in the next 10 years, so individuals can prevent these events earlier. However, if the findings are severe, allies and the community can quickly consult with health workers at the nearest health facilities or hospitals. This study aimed to provide education regarding the assessment of risk estimation for ischemic heart disease with WHO/ISH charts among participants in Cempaka Baru sub-district.

MATERIALS AND METHODS

This study used a one-group pre-test and post-test design, namely an initial test (pre-test) before being given education and a final test (post-test) after being given education on IHD risk factors. The population was the representatives of Cempaka Baru sub-district community by using a purposive sampling technique with inclusion and exclusion criteria. The inclusion criteria were the residents of Cempaka Baru sub-district, Central Jakarta, Indonesia, who became representative participants in the area. Meanwhile, the exclusion criteria included non-citizens of Cempaka Baru sub-district, Central Jakarta, Indonesia, and not representative participants in that area. The collection of participants was done using online sounding to the representative participants of the Cempaka Baru sub-district to get residents included in the inclusion criteria. Due to the Covid-19 pandemic, we had limited the number of participants to only 30 participants.

The participants were asked to fill out a pre-test that had been provided by the organizing committee 10 minutes before the speaker explained the learning materials, by including identity in the form of the name, age, gender, and residential address. The pre-test contained 10 questions. The deadline for filling out the pre-test was before the activity started. The symposium activity consisted of conveying learning materials by the speaker on the ischemic heart disease risk factor estimation knowledge using WHO/ISH prediction charts.

During the presentation, participants were also taught how to use the WHO chart and an example case was given to use as a screening exercise. In addition, participants were also given a small guidebook, so participants could see the steps for assessing IHD risk with the WHO chart. After the symposium was finished, participants were required to fill out a post-test that will be given by the organizing committee. After that, the event was continued by conducting a screening examination for ischemic heart disease using the WHO chart.

The examination consisted of interviewing participant history, smoking status (all active smokers or smoking cessation <1 year), past medical history, physical activity (physical activity <600 MET minutes/weeks), followed by examination of blood pressure, current blood glucose levels, and total blood cholesterol using a simple blood check. After obtaining the results of the examination, the estimated risk of ischemic heart disease for individuals using the WHO chart is divided into low risk (<10%), moderate risk (10-20%), and severe risk (>20%). This examination and calculation of the estimated risk of IHD is a form of application from the previous symposium.

The data that had been obtained is then processed computerized using Microsoft Excel and SPSS 23 version software. The data from the seminar activities will be analyzed to see the frequency distribution of the characteristics of the participants, which is carried out using a non-parametric numerical test. The results of the pre-test and post-test were also analyzed to see if there was an increase in participants' knowledge about early detection of ischemic heart disease with the WHO chart after providing education.

On the results of the examination of IHD risk factors, a Chi-Square test was performed to find the relationship of risk factors (age, gender, smoking status, past medical history, physical activity, blood pressure, current blood glucose, and total blood cholesterol) to the risk of IHD. Besides, the odds ratio was calculated with a 95% confidence interval.

RESULTS

Characteristics of participants

The symposium was attended by representative participants in the Cempaka Baru sub-district, Central Jakarta, Indonesia. Cempaka sub-district is only 1.2 km

from Universitas Yarsi and has become a frequent target area for health education activities. The Covid-19 pandemic has limited the number of symposium participants so that 30 participants are set to attend the symposium.

The participants consisted of various ages with the most participants in old adults or >50 years (67%). Participants were divided into 3 groups, namely young adults (aged 15-30 years) as many as 1 person (3%), middle-aged adults (aged 31-50 years) as many as 9 people (30%) and older adults (age >50 years) as many as 20 people (67 %). Most of the participants were female namely 23 people (77%) and 7 male (23%).

Table 1. Characteristics of participants

Characteristics	Frequency	Percentage (%)	Std. Deviation
Gender			
Male	7	23	± 11.31
Female	23	77	
Age			
Young Adults (15 – 30 years old)	1	3	± 9.53
Middle-aged Adults (31 – 50 years old)	9	30	
Old Adults (>50 years old)	20	67	

Knowledge

After the pre-test and post-test data were obtained, the data were processed using Microsoft Excel and the SPSS.23 version software. Based on the results of the normality test, it was found that the significance value was 0.170 which showed p>0.05, then the data distribution was normal. Then because the data distribution is normal, it is continued with Paired T-Test on pre-test and post-test data and the results showed that there was a significant difference if the p-value <0.05.

Table 2. The differences in mean, median, and modus in pre-test & post-test

	Pre-test	Post-test	p-value
Mean	81.67	89.67	
Median	85	90	
Mode	90	100	0.00
Minimum	50	50	
Maximum	100	100	

Table 3. The comparison of knowledge scores in pre-test and post-test

	Frequency	Percentage (%)
Post-test < Pre-test score	1	3
Post-test > Pre-test score	18	60
Post-test = Pre-test score	11	37
Total	30	100

After the symposium, there was a significant increase in participants' knowledge (Table 3). There was an increase in the value of the mode (the majority value of the participants) from the pre-test, which was 90 to 100 in the post-test. Then, there was an increase in the average score of the participants from 81.67 in the pre-test to 89.67 in the post-test (p = 0.00). Based on Table 3 the results of the post-test scores increased from the pre-test scores for 18 participants (60%), and there were also participants whose post-test scores did not change from the pre-test scores which were 11 participants (37%). There was also one participant who experienced a decrease in their post-test scores compared to their pre-test scores (3%).

Estimation of ischemic heart diseases with WHO/ISH risk prediction chart

After the symposium, the participant's interview and measurement of metabolic parameters were carried out, namely, age, gender, smoking status, past medical history, physical activity, blood pressure, current blood glucose, and total blood cholesterol. It was found that the high risk (high risk: >20%) for ischemic heart disease was found in women (90.9%), aged over 50 years (90.9%), with less physical activity (72.7%), history of diabetes (27.3%) and hypertension (27.3%). In addition, the results of the examination showed that a high risk of IHD (high risk: >20%) was found in systolic blood pressure 140/90 in 8 people (72.7%) and total cholesterol ≥ 200 mg/dL in 10 people (90.9%). In contrast, a low risk of IHD (low risk <10%) was found in blood glucose <200 mg/dL in 10 people (90.9%), systolic blood pressure <140/90 mmHg in 9 people (81.8%) and total cholesterol <200 mg/dL as many as 6 people (54.5%).

Table 4. Distribution of variables with category of ischemic heart disease risk level

No.	Variable	Low risk n=11 N (%)	Moderate risk n=8 N (%)	High risk n=11 N (%)	Total n=30 N (%)
	Gender				
1	Male	4 (36.4%)	2 (25%)	1 (9.1%)	7 (23.3%)
	Female	7 (63.6%)	6 (75%)	10 (90.9%)	23 (76.7%)
	Age				
2	< 50	6 (54.5%)	2 (25%)	1 (9.1%)	9 (30%)
	≥ 50	5 (45.5%)	6 (75%)	10 (90.9%)	21 (70%)
	Smoker				
3	Yes	4 (36.4%)	2 (25%)	1 (9.1%)	7 (23.3%)
	No	7 (63.6%)	6 (75%)	10 (90.9%)	23 (76.7%)
	Physical activity				
4	Sufficient	1 (9.1%)	1 (12.5%)	3 (27.3%)	5 (16.7%)
	Insufficient	10 (90.9%)	7 (87.5%)	8 (72.7%)	25 (83.3%)
	Medical history				
	None	8 (72.7%)	3 (37.5%)	3 (27.3%)	14 (46.7%)
	Diabetes	1 (9.1%)	1 (12.5%)	3 (27.3%)	5 (16.7%)
5	Hypertension	1 (9.1%)	2 (25%)	3 (27.3%)	6 (20%)
	Diabetes and hypertension	0	0	2 (18.2%)	2 (6.7%)
	Heart failure and hypertension	0	1 (12.5%)	0	1 (3.3%)
	Cancer	1 (9.1%)	0	0	1 (3.3%)
	Osteoarthritis	0	1 (12.5%)	0	1 (3.3%)
	Systolic blood pressure				
6	< 140/90	9 (81.8%)	5 (62.5%)	3 (27.3%)	17 (56.7%)
	≥ 140/90	2 (18.2%)	3 (37.5%)	8 (72.7%)	13 (43.3%)
	Blood glucose				
7	< 200 mg/dL	10 (90.9%)	7 (87.5%)	7 (63.6%)	24 (80%)
	≥ 200 mg/dL	1 (9.1%)	1 (12.5%)	4 (36.4%)	6 (20%)
	Total cholesterol				
8	< 200 mg/dL	6 (54.5%)	3 (37.5%)	1 (9.1%)	10 (33.3%)
	≥ 200 mg/dL	5 (45.5%)	5 (62.5%)	10 (90.9%)	20 (66.7%)

*****Low risk: <10%, moderate risk: 10% - 20%, high risk: >20%

Table 5. Ischemic heart disease risk variable with risk levels < 20% and > 20%

No.	Variables	IHD risk <20% n= 19 N (%)	IHD risk >20% n= 11 N (%)	Total	p-value	OR (95% CI)
1	Systolic blood pressure					
	< 140/90	14 (73.7%)	3 (27.3%)	17 (56.7%)	0.023	7.467 (1.4 - 39.836)
	≥ 140/90	5 (26.3%)	8 (72.7%)	13 (43.3%)		
2	Total cholesterol					
	< 200 mg/dL	9 (47.4%)	1 (9.1%)	10 (33.3%)	0.049	9 (0.954 - 84.899)
	≥ 200 mg/dL	10 (52.6%)	10 (90.9%)	20 (66.7%)		
3	Age					
	< 50	8 (42.1%)	1 (9.1%)	9 (30%)	0.1	7.273 (0.768 - 68.887)
	≥ 50	11 (57.9%)	10 (90.0%)	17 (70%)		
4	Gender					
	Male	6 (31.6%)	1 (9.1%)	7 (23.3%)	0.215	4.615 (0.476 - 44.757)
	Female	13 (68.4%)	10 (90.9%)	23 (76.7%)		
5	Smoker					
	No	13 (68.4%)	10 (90.9%)	23 (76.7%)	0.215	0.217 (0.022 - 2.101)
	Yes	6 (31.6%)	1 (9.1%)	7 (23.3%)		
6	Physical activity					
	Sufficient	2 (10.5%)	3 (27.3%)	5 (16.7%)	0.327	0.314 (0.043 - 2.265)
	Insufficient	17 (89.5%)	8 (72.7%)	25 (83.3%)		
7	Blood glucose					
	< 200 mg/dL	17 (89.5%)	7 (63.6%)	24 (80%)	0.156	4.857 (0.718 - 32.867)
	≥ 200 mg/dL	2 (10.5%)	4 (36.4%)	6 (20%)		

Based on Table 5, the systolic blood pressure variable had a significant relationship with the risk of developing an IHD of 0.023 with a p-value <0.05. The OR (odds ratio) value was 7,467, which meant that people with a blood pressure of 140/90 were at risk of developing ischemic heart disease by 7.47 times,

compared to people who have systolic blood pressure <140/90. The confidence interval (95% CI) showed a value of 1.4-39.836 which the lowest risk of IHD was 1.4 times and the highest was 39.8 times. There was also a significant relationship between the variable total cholesterol and the risk of developing IHD, with a significance value of 0.049. Then, the odds ratio showed that people who had total cholesterol ≥ 200 mg/dL were at risk of developing IHD by 9 times when compared to people who have total cholesterol < 200 mg/dL. The confidence interval (CI 95%) of 0.954-84,899, showed that the lowest risk opportunity was 0.95 times and the highest was 84.90 times. In addition, the variables of age, sex, smoking status, physical activity, and blood sugar levels did not have a significant relationship with the risk of coronary heart disease.

DISCUSSION

The results of the analysis of knowledge on the estimation of ischemic heart disease with the WHO chart by considering the results of the pre-test and post-test showed the majority of post-test results were increasing and it could be interpreted that the provision of knowledge in this symposium could significantly increase participants' knowledge. As a result of the knowledge of the risk factors for ischemic heart disease, people are becoming aware of their health and taking various disease prevention measures. Knowledge has a relationship with the severity of ischemic heart disease. It is stated in some literature that a low level of education has a higher prevalence of risk behaviors (smoking, obesity, lack of physical activity, unhealthy eating patterns, etc.), more likely to have a poor polluted environment, lack of medical information awareness of the impact of lifestyle behaviors, poor adherence/wrong medication, ignorance of medical examinations), and have a higher prevalence of depression (Dégano et al. 2017, Khaing et al. 2020). In addition, good knowledge will increase good body responses such as an increase in HDL due to individual awareness of the importance of exercise and increased medical care (Hamad et al. 2019).

According to 2014 WHO/ISH risk prediction charts guidelines, it is stated that the use of this guide greatly facilitates people in an area that has limited health facilities and can estimate the percentage of IHD in the next 10 years, so the public can find out the appropriate forms of prevention and management. In addition, according to the AHA/ACC guidelines, it is recommended to calculate the estimated risk of IHD in the next 10 years, by assessing several risk factors, such as age, gender, blood pressure, blood glucose levels, cholesterol, and smoking status, and disease history. Some people who do not have previous heart disease are advised to calculate the estimated IHD risk every 4-6 years and for individuals aged 20-59 years with low risk, the outcomes (<7.5%) are assessed for 30 years or for life (Hajar 2017). The accomplishment of the participants was known based on the comparison between the knowledge test scores before and after the provision of material and also from the activeness of participants in asking and answering questions related to the material presented. This is supported by Tiksnadi et al. (2018) who stated that the basis for the formation of health representatives was a special community group that actively participates in health development.

On the results of the examination of the risk of IHD, it was found that more women had a higher risk (90.9%) than men. This is also influenced by the unequal number of participants between men and women. However, according to research by (Gheisari et al. 2020), there was a high prevalence of IHD risk in American women aged between 20-70 years. Contributing factors (i.e., hypertension, increased cholesterol levels, smoking, overweight, and lack of physical activity) were the most common problems in the female population. Hormonal factors, particularly decreasing estrogen levels in menopause conditions can increase the risk of heart disease. Increasing age will increase the risk of IHD and the highest incidence is in the age group 45 years. According to research by Mora et al. (2021), the incidence of IHD was 10-fold higher at the age of 75 years compared to the age of 55 years. Getting older causes a greater incidence of plaque that is stuck to the wall and caused disruption of blood flow through it (Gheisari et al. 2020). Novriyanti et al. (2014) conducted a study on the effect of long hypertension on IHD at the Cardiology Polyclinic of Dr. Mohammad Hoesin Palembang Hospital and resulted that most IHD cases occurred in the 45–64-year age group (75.0%).

Based on WHO data, low physical activity was recorded as a cause of diabetes by 27% and 30% of ischemic heart disease (Cleven et al. 2020). In their study, two of 11 studies reported an increased risk of diabetes incidence (179 and 145%, respectively) for participants who engaged in minimal leisure-time physical activity compared with the highly active group. Patients with diabetes had a 10% greater risk of IHD, 53% of myocardial infarction, and 58% of stroke. This is corresponding to the results of research showing an increase in the occurrence of IHD due to a person's low physical activity. In contrast, physical activity that is carried out regularly produces beneficial results in the form of prevention and therapy of IHD (Chomistek et al. 2016). This is corresponding with the

results of a 1-year multifactorial intervention study that included 3 hours of exercise per week which induced a 3.1% regression in coronary stenosis which was associated with a reduction in the incidence of cardiovascular disease (Winzer et al. 2018). In addition, one effective way is to reduce and control glucose levels in the blood so that it can protect the microvasculature from damage that will cause IHD (Einarson et al. 2018). Research by Suryati and Suyitno (2020) states that diabetes and hypertension are two risk factors for ischemic heart disease with a very strong relationship with the occurrence of myocardial infarction. Increasing systolic blood pressure by 20 mm Hg and diastolic blood pressure by 10 mm Hg more, has a 2-fold higher risk of CVD (Fuchs & Whelton 2020). A literature states that treatment of hypertension significantly reduces the risk of cardiovascular disease and death in various patient populations (Suryati & Suyitno 2020). According to (Ettehad et al. 2016), a 10 mm Hg reduction in systolic blood pressure reduced the risk of major cardiovascular disease events by 20%, ischemic heart disease by 17%, stroke by 27%, heart failure by 28%, and all-cause mortality by 13%.

A study conducted by Jeong et al. (2018) showed that increased cholesterol levels were associated with a higher risk of IHD compared to the group with low cholesterol. In addition, higher total cholesterol levels were associated with 11% higher mortality from CVD (95% CI, 4%-18%), 16% for IHD (4%-31%), and 19% for AMI (5% –36%) especially in the elderly (Kwon et al. 2019). LDL is one of the blood cholesterols associated with plaque formation in coronary arteries, in one study stated that the risk of IHD with LDL-cholesterol >190 mg/dL is more dangerous than LDL-cholesterol <130 mg/dL (Ueda et al. 2018). One of the reasons is that dyslipidemia is one of the factors that can accelerate atherosclerotic changes in blood vessels. In contrast, it has been demonstrated that the benefit of reducing serum cholesterol for IHD risk is related to age, i.e., a 10% reduction in serum cholesterol results in a 50% reduction in CHD risk at age 40, 40% at age 50, 30% at age 60, and 20 years. 20% at the age of 70 years. There are two risk factors that have a significant relationship with the development of IHD, namely hypertension, and hypercholesterolemia. These two risk factors form a circle of problems that can lead to other risk factors developed.

A recent study reported that among individuals with high blood pressure almost 60% cause type 2 diabetes. In addition, dyslipidemia causes endothelial damage resulting in loss of vasomotor activity, which can lead to hypertension (Ajabnoor et al. 2021). As an effective preventive measure, it is possible to control risk factors quickly and precisely, such as lowering total cholesterol (24%), systolic blood pressure (20%), smoking (12%), and lack of physical activity (5%) to reduce mortality from IHD by half (Sanchis-Gomar et al. 2016).

Strength and limitation

Based on several explanations and the results that have been described previously, our research still has some limitations. Estimates were collected from the limited number of participants due to the Covid-19 pandemic which made it impossible to collect many participants, as well as the results of the pre-test, post-test, and examination results which are a sequence of the symposium have a high level of heterogeneity both in terms of the level of education, income, environment and some disruptive factors during the event which we cannot strictly monitor. This research still needs further review, both in terms of the number of respondents and the variables studied to be able to estimate IHD estimates with risk factors that are more specific and comprehensive and reduce biased results.

CONCLUSION

The results of the assessment illustrate that the knowledge of participants after being given education in the form of a symposium, shows an increase in knowledge with significant results, with a p-value = 0.00 ($p < 0.05$). Increased knowledge in the community has a positive impact on the prevention of IHD in the future. However, in old-age, females, the results of blood pressure and cholesterol examinations which are a sequence of the symposium, there is a significant increase in the high risk for the occurrence of IHD. Rising several risk factors for IHD are due to the majority of people living in densely populated urban areas accompanied by an unhealthy lifestyle.

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Conflict of interest

None.

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None.

Author contribution

HLK was conceptualization, data collection, analysis data,and revise the manuscript. KADER was grammatical checks, methods design, and final validation

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Original Research Report

FERNING AND SCHIRMER TEST 1 FOR THE DETECTION OF GRADING SEVERITY OF DRY EYE SYNDROME IN POST PHACOEMULSIFICATION PATIENTS

Tengku Siti Harilza Zubaidah[1], Rodiah Rahmawaty Lubis[1], Lita Feriyawati[2]
[1]Department of Ophthalmology, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia
[2]Department of Anatomy, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia

ABSTRACT

Dry eye syndrome is a multifactorial disease on the surface of the eyeball characterized by loss of tear film homeostasis, which is associated with eye symptoms, where there is tear instability and hyperosmolarity, inflammation, and damage to the surface of the eye, as well as neurosensory disorders that act as the cause of this syndrome. The aim of this study was to identify relationship between the Ferning pattern and the Schirmer test 1 in post-phacoemulsification patients. The design of this study was an analytical observational study with a cross-sectional data collection method where the Ferning and Schirmer test 1 were examined to determine the severity of dry eye syndrome in post-phacoemulsification patients. The Ferning test was assessed according to Rolando's classification. In this study, it was found that the gender who suffer from dry eye syndrome are women. The most considerable age is age ≥ 60 years (56,7%). The results showed that the majority of patients experienced dry eyes measured with the Ferning test, and these results were following the previous Schirmer Test 1 examination. The Ferning and Schirmer tests were found to be abnormal in most of the subjects. It was found that there was a significant relationship between the Ferning pattern and the Schirmer test with the calculation of the t-value of 7.345 with a p-value of 0.001. There was a statistically significant difference between the results of Ferning and the Schirmer test in post-phacoemulsification patients.

Keywords: *Ferning test; Schirmer test; dry eye syndrome; phacoemulsification; illness*

Correspondence: Tengku Siti Harilza Zubaidah. Department of Ophthalmology, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia. Email: ct_ab2204@yahoo.co.uk

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Highlights:

1. Females were the most gender who suffer from dry eye syndrome than males.
2. Undergone phacoemulsification patients had frequent dry eye syndrome.
3. Post-phacoemulsification patients were not statistically significant between the Ferning and the Schirmer test.

INTRODUCTION

Based on Tear Film Ocular Surface Dry Eye Workshop II (TFOS DEWS II) in 2017, dry eye syndrome is a multifactorial ocular surface disease characterized by loss of tear film homeostasis and is accompanied by symptoms of tear instability and hyperosmolarity, inflammation, and damage to the ocular surface, and neurosensory abnormalities. Symptoms that often appear are a scratchy or gritty sensation. Other symptoms are itching, secretions of excess mucus, inability to produce tears, burning sensation, photosensitivity, redness, pain, and difficulty moving the eyelids. Dry eye syndrome increases with age and occurs when the tear film is disrupted due to decreased production of excess water and evaporation of tears (Galor et al. 2011, Cantor et al. 2014).

The prevalence of dry eye syndrome varies from 4.3% to 75% in some populations. The prevalence of dry eye syndrome in Asia varies from 21% to 73.5% using a questionnaire (Chia et al. 2003, Schaumberg et al. 2003, Stapleton et al. 2017). The prevalence of dry eye syndrome is higher in the elderly because of inadequate tear production due to lacrimal gland dysfunction, impaired secretory reflexes, or inflammation of the lacrimal gland. Dry eye syndrome can be assessed with several examinations, such as Schirmer and Ferning test.

Schirmer test is a tear volume assessment test. Schirmer test is performed by placing a paper strip in the lateral third of the lower eyelid after drying the inferior fornix and then measuring the length of the moistened portion of the strip after 5 minutes. The Schirmer I test is performed without anesthesia that measures basic and reflex tearing. The Schirmer II test is done following nasal stimulation that measures reflex tearing only. Ferning test is a tear quality assessment test by examining the tear pattern under a microscope. The pattern of the tear depends on the composition of the tear sample. The Ferning test may be a simple test to assess tear quality (Masmali et al. 2014, Alanazi et al. 2019, Tribowo et al. 2021).

Cataracts are the opacity of the lens and the leading cause of blindness worldwide, which is 35.15%.

Cataracts are divided into metabolic cataracts, congenital cataracts, and age-related cataracts. Older people are also at risk of developing lens opacification and cataracts. The prevalence of cataracts at the age of more than 74 years is 38.3% for men and 45.89% for women (Jick 2019). The procedure of cataract extraction is definitive therapy to resolve blindness due to cataracts, where the technique 'phacoemulsification' is a popular cataract extraction surgical technique at this time (Zhang & Li 2010, Jick 2019, Shi et al. 2022)**.**

Phacoemulsification describes the patient who lies on his back on the operating table, with the patient's head flattened and pointed at an overhead microscope. In 1967, Dr. Charles D. Kelman revolutionized cataract surgery with the introduction of phacoemulsification which is now the safest and most preferred technique for cataract surgery to ensure high volume, high quality, and affordable medical care (Hunter 1995), while in 1993, Nagahara introduced a number of modifications to this technique, including the stop-and-chop (Koch & Katzen 1994), drill-chop (Kim & Jang 2012), nucleofractis (Gimbel 1991), pocket-chop (Braga-Mele & Mednick 2016), crater-and-split (Aslan et al. 2012), cross-chop (Kim 2009), crater-and-chop (Vanathi et al. 2001), multilevel chop (Vasavada & Raj 2011), lift and crack (Cakir & Utine 2010), and retrochop techniques (Falabella et al. 2013, Joshi 2022).

The phacoemulsification technique uses ultrasonic technology and a vacuum to emulsify and aspirate the crystalline lens through a very small corneal incision reducing the risk of serious complications associated with wound and vitreous leak**.** This routine technique can be a challenge in medical conditions such as orthopnea, scoliosis, Meniere's disease, kyphosis, and CNS abnormality (Zhang & Li 2010, Jick 2019, Brayan et al. 2022)**.**

MATERIALS AND METHODS

The design of this study was an analytical observation method for cross-section data collection. This test was performed at Chevani Tebing Tinggi General Hospital. The sample of the study consisted of 30 patients who had undergone phacoemulsification at Chevani Tebing Tinggi General Hospital. The sample selection criteria for this study were patients less than a year old who had undergone phacoemulsification and patients aged 18 or older who were willing to become study samples. The exclusion criteria were patients with eye infections, patients with a history of previous eye trauma, patients with a history of previous eye surgery, and patients with systemic diseases, such as diabetes mellitus. Before conducting the research, we gave written informed consent to the research subjects after conducting an explanation beforehand. The stages of sample taking from the Ferning test are (a) the patients are requested to look up, (b) tears are obtained by sweeping Schirmer's paper over the inferior conjunctival fornix and placed on a slide, allowed to dry for a few minutes, and (c) examined under a microscope.

Ferning's pattern is examined with a microscope using 10x and 40x magnification. The classification of tear Ferning patterns consist of 4 types and it relies on assessing the spacing between the branches in the ferns. In Type I, the ferns are closely packed with no spaces between the branches. In Type II, the ferns are smaller and have gaps between the branches. In Type III, the ferns are small and incompletely formed with rare or no branching and the gaps become larger and wider, and in Type IV the Ferning phenomenon is absent.

Stages of sampling in Schirmer I test determination is performed by putting Schirmer paper folded end first in the inferior conjunctival fornix lateral 1/3 for 5 minutes then measuring. The Schirmer I values taken as the study sample were >5 mm and <10 mm. All data are analyzed using the Statistical Product and Service Solution (SPSS version 23 with a 95% confidence level. All categorical data are presented in percentage form. A Chi-square test is performed to determine the relationship between the results of the Ferning test and Schirmer test in dry eye syndrome. The T-test is performed to determine the difference between the results of the Ferning test and the Schirmer test. The p-value <0.05 are considered significant.

RESULTS

Samples of 30 patients who had undergone phacoemulsification have been obtained and have been examined with Schirmer I test and Ferning test on the eyes that had been operated on. As an initial measure, visual acuity was examined in the patient's eyes, then a Schirmer I test was performed, followed by a Ferning test.

In Table 1, the frequency distribution of patients based on age is greatest at the age of 60 years, consisting of 17 patients (56.7%), and at age 50 – 59 years of 13 subjects (43.3%). Most of the patients were female with a total of 17 subjects (56.7%) and male 13 subjects (43.3%). In this study, the frequency distribution of the eye that received phacoemulsification in the right eye and left eye was the same, with 15 subjects each (50.0%). The distribution of the frequency of greatest visual

acuity from the patients was > 6/60 in 26 subjects (86.7%), 1/60 – 6/60 in three subjects (10.0%), and 1/300 in one subject (3.3 %) respectively.

Table 1. Characteristics of research subjects

Characteristics	n	%
Age (years)		
50 – 59	13	43.3
≥ 60	17	56.7
Gender		
Male	13	43.3
Female	17	56.7
Phacoemulsification action		
Right eye	15	50.0
Left eye	15	50.0
Visual acuity		
> 6/60	26	86.7
1/60 - 6/60	3	10.0
1/300	1	3.3
Total	30	100.0

Table 2. Frequency distribution of Ferning test results

Ferning test results	n	%
Type 1	8	26.7
Type 2	4	13.3
Type 3	11	36.7
Type 4	7	23.3
Total	30	100.0

Table 2 shows that most of the groups belonged to type 3, comprising 11 patients (36.7%), type 1 eight patients (26.7%), type 4 seven patients (23.3%), and type 2 four patients (13.3%) respectively.

Table 3. Frequency distribution of Schirmer test results

Schirmer test results	n	%
< 10 mm	23	76.7
> 10 mm	7	23.3
Total	30	100.0

Table 3 shows the results of the Schirmer test. Most of the patients had results <10 mm in 23 patients (76.7%), followed by > 10 mm in seven patients (23.3%).

Table 4. Incidence of dry eye syndrome

Dry eye syndrome	n	%
Yes	18	60.0
No	12	40.0
Total	30	100.0

As many as 18 patients (60%) of this study sample had dry eye syndrome and 12 patients (40%) did not have dry eye syndrome.

Table 5. Relationship between Ferning test results and dry eye syndroame

Ferning test results	Dry eye syndrome				Total		p value
	Yes		No				
	n	%	n	%	n	%	
Type 1	0	0.0	8	100.0	8	100.0	
Type 2	0	0.0	4	100.0	4	100.0	0.00
Type 3	11	100.0	0	0.0	11	100.0	1
Type 4	7	100.0	0	0.0	7	100.0	
Total	18	60.0	12	40.0	30	100.0	

It is known that all types 1 and 2 did not have dry eye syndrome, and all types 3 and 4 had dry eye syndrome. The p-value was obtained at 0.001 (< 0.05), which means that there was a significant relationship between the results of the Ferning test and dry eye syndrome in post-phacoemulsification patients.

Table 6. Relationship between Schirmer test results and dry eye syndrome

Schirmer test results	Dry eye syndrome				Total		p value
	Yes		No				
	n	%	n	%	n	%	
< 10 mm	11	47.8	12	52.2	23	100.0	
> 10 mm	7	100.0	0	0.0	7	100.0	0.024
Total	18	60.0	12	40.0	30	100.0	

The results of the Schirmer test < 10 mm who had dry eye syndrome were 11 subjects (47.8%). The p-value was obtained at 0.024 (< 0.05), indicating a significant relationship between the results of the Schirmer test and dry eye syndrome in post-phacoemulsification patients.

Table 7. The difference in the results of the Ferning test Schirmer test

Ferning test - Schirmer test	t	Sig.
	7.345	0.001

The calculated t-value was 7.345 with a p-value of 0.001, which could be concluded that statistically there was a significant difference between the results of the Ferning test and the Schirmer's test in post-phacoemulsification patients.

DISCUSSION

In this study, females were more likely than males to experience dry eye syndrome. This was in line with result obtained by Noor et al. (2020) at the Jakarta Eye Center. Meanwhile, the highest age was found to be

61.3 years (50-70 years). This was in accordance with a study conducted by Bobrow (2011), where the incidence of cataracts increased to about 50% in individuals aged 65-74 years and 70% in individuals aged over 75 years.

This study found that the frequency distribution of the Ferning test results was greatest in type 3, which consisted of 11 subjects (36.7%), and the frequency distribution of the Schirmer test results <10 mm in 23 subjects (76.7%). There was a significant difference between the results of the Ferning test and the Schirmer test, where the t-value was 7.345, and the p-value was 0.001. Besides, the Schirmer test technique is easier to apply than the Ferning test in detecting dry eye syndrome.

The Ferning test is an examination carried out to assess the mucus layer of the conjunctiva. Sampling is done by collecting tear fluid through a micropipette from the inferior meniscus and dripping it on the slide and allowed to dry through the evaporation process. To determine the diagnostic results of this examination, the picture of a microscope is classified into 4 types according to the classification of Rolando with type 1 and 2 are normal pictures, and type 3 and 4 as a picture of patients who had dry eye syndrome (Tsubota 2017).

This study found a significant relationship between the results of the Ferning test and dry eye syndrome in post-phacoemulsification patients. This indicates tear film disruption due to tear deficiency or excessive tear evaporation which causes damage to the interpalpebral surface of the eye and is associated with symptoms of eye discomfort. In conventional cataract surgery, a large incision is made at the limbus, denervating nearly half of the superior cornea. As a result, corneal desensitization occurs with various symptoms coupled with the presence of multiple sutures to close the wound, the need for longer antibiotics and steroids is required, exacerbating dry eye symptoms. In the current phacoemulsification operation, when many procedures are performed, the incision in the cornea is much smaller, resulting in less corneal denervation, thereby minimizing tear film disruption. In addition, the shorter duration of phacoemulsification surgery makes the ultrasound device exposure shorter and the visual rehabilitation faster making the tapering of topical drugs faster. However, both with conventional cataract surgery and phacoemulsification, there are still dry eye symptoms after surgery. Previous studies reported that both conventional cataract surgery and phacoemulsification caused or exacerbated dry eye and affected dry eye test scores up to three months postoperatively (Sinha et al. 2018).

The incidence of dry eye in postoperative phacoemulsification patients is associated with corneal denervation, which results from an incision in the clear cornea. The cornea is innervated by the long ciliary nerve which is a branch of the ophthalmic nerve (nervus V1). This nerve reaches the cornea via the limbus and travels radially forward in the stroma before branching off. Loss of innervation or denervation of the cornea results in reduced blink reflex and decreased tear production, leading to increased epithelial permeability, decreased metabolic activity of the epithelium, and inhibited wound healing. Other factors that influence the incidence of post phacoemulsification dry eye include topical anesthetics and eye drops containing preservatives such as benzalkonium chloride (BAC) which are known to affect the corneal epithelium.

Topical antibiotics containing preservatives are associated with inflammation of the ocular surface characterized by increased proinflammatory cytokines. Preservatives such as BAC have detergent-like properties that can damage the LAM fat layer, resulting in a decrease in surface tension with a consequent decrease in break-up time. This causes evaporation from the aqueous layer and in the long term facilitates superficial punctate epithelial erosion. In addition, preservatives can also damage the microvilli and tight junctions on the surface layer of the corneal epithelium, making it easier for epithelial erosion and increasing the risk of corneal ulcers. In the conjunctiva, besides damaging the conjunctival epithelium, BAC can also reduce goblet cells so that mucin production is also reduced which in turn causes the stability of LAM to be disturbed, causing dry eye symptoms. Thus the decrease in the number of tears in post-cataract surgery patients can be influenced by the use of topical drugs (Kaur et al. 2009, Chao & Lim-Bon-Siong 2017).

A previous study examining the degree of dry eye after phacoemulsification in cataract patients showed results on day 7 to day 30. There were 7 patients (14%) experiencing worsening dry eye symptoms 1 week after surgery which was marked by an increase in the degree of dry eye of the patient. A total of 16 (32%) patients had no change 1 week after phacoemulsification surgery. This previous study also found that the relationship between pre-phacoemulsification dry eye and dry eye 1 month after phacoemulsification had a p-value of 0.000, and indicated a significant relationship (Tarigan 2020). The 24th European Society of Cataract and refractive surgeons (ESCRS) congress also gave the same explanation regarding the pathogenesis of dry eye symptoms post phacoemulsification. Modern cataract surgery with the phacoemulsification technique involves an incision in the cornea, which cuts the corneal sensory nerves. This has the potential to

interfere with the sensory feedback mechanisms required for tear film stability and tear basal production. Disruption of this mechanism is thought to cause dry eye symptoms, and may even contribute to more complex conditions such as neurotrophic keratitis (Korb 2018).

However, a prospective study of the impact of surgery on phacoemulsification of dry eye symptoms performed at Harold Wood Hospital, Romford, Essex, UK, reported that there was no significant change in tear production six to eight weeks after cataract surgery in 50 eyes examined. However, a number of patients reported an increase in dry eye symptoms after surgery but this increase was not statistically significant (Naderi et al. 2020).

Exposure to light from operating lamps is also thought to be associated with postoperative dry eye. In addition, the use of ultrasound in cataract surgery can damage corneal structures, such as the epithelium, stroma, keratocytes, endothelium, and nerve plexuses. However, when compared with conventional cataract surgery, ocular surface complications are less common in phacoemulsification surgery (Ernawati et al. 2020).

Another study evaluated 23 patients with dry eye who underwent phacoemulsification. Although all patients reported sensations of discomfort and irritation that were more severe than before surgery even persisting 3-4 weeks after surgery, as well as minimal changes in Schirmer's test and TBUT, it was concluded that phacoemulsification was safe and there were only minimal complications in dry eye patients related to surgery. with age, with or without systemic disease**.** Changes in corneal sensitivity and tear film physiology in postoperative phacoemulsification patients. There was a decrease in corneal sensitivity and tear film immediately after phacoemulsification surgery. Although there is a trend toward full recovery, corneal sensitivity does not return to its preoperative state until 3 months postoperatively. However, tear film function improved within 1 month postoperatively (Eah et al. 2021).

A study had previously stated that dry eye can develop or worsen dramatically after cataract surgery if not treated promptly (Sahu et al. 2015), and this can occur one week after surgery and peak in about one month. In addition, misuse of eye drops is one of the main pathogenic factors that cause dry eye after cataract surgery (Zaidi 2013). However, the role of eye drops in the postoperative dry eye has not been confirmed in other studies.

Strength and limitation

This study can contribute to existing studies by providing more experiments utilizing Ferning and Schirmer tests. It strengthens the evidence for the validity of both tests in assessing dry eye syndrome among post-phacoemulsification patients. However, the limitation of this study was that it only had a small study population.

CONCLUSION

It was found that there was a significant relationship between the Ferning pattern and the Schirmer test with the calculation of the t-value of 7.345 with a p-value of 0.001. This study concluded that in post-phacoemulsification patients, there was a statistically significant difference between the outcomes of the Ferning and the Schirmer test.

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Conflict of interest

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Author contribution

TSH and RRL contributed in the conceptualization, design of the research, data analysis, and interpretation of the obtained results and collected the specimens and wrote the manuscript. TSH and LP were final check the manuscript.

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Original Research Report

THE RISK FACTORS OF CENTRAL OBESITY IN INDONESIAN MEN: A CROSS-SECTIONAL DATA STUDY OF THE INDONESIA FAMILY LIFE SURVEY 5 (IFLS 5)

Dahlia[1], Gracia Satyawestri Pribadi[2], Santi Martini[3], Chung Yi-Li[4]

[1]Faculty of Public Health, Universitas Airlangga, Surabaya, Indonesia
[2]District Health Office of Sidoarjo, Sidoarjo, Indonesia
[3]Department of Epidemiology, Biostatistics, Population, and Health Promotion, Faculty of Public Health, Universitas Airlangga, Surabaya, Indonesia
[4]Department of Public Health, College of Medicine, National Cheng Kung University, Tainan, Taiwan

ABSTRACT

Obesity is one of the leading health problems in both developed and developing countries. Central obesity can be defined as a condition where excess fat has accumulated in the abdominal area. There are several risk factors that may cause central obesity in men such as smoking habits, physical activity, and dietary habits. This study aimed to analyse the risk factors of central obesity in Indonesian men. This was an analytical observational study using a cross-sectional design. It used secondary data from the Indonesia Family Life Survey (IFLS 5) with a sample size of 4,648 respondents. The variables studied here were smoking status, type of smoker, type of cigarette, physical activity, and meat consumption frequency. Logistic regression analysis was used. The results of this study showed that the mean age of the respondents was 51 years old. There was a relationship between smoking status (p=0.000), type of smoker (p=0.002), type of cigarette (p=0.000), physical activity (p=0.000), and meat consumption frequency (p=0.024) and the incidence of central obesity. The conclusion of the study was that there was a relationship between smoking status, type of smoker, type of cigarette, physical activity, meat consumption frequency, and the incidence of central obesity, all of which were risk factors of central obesity in Indonesian men. A low level of physical activity was the most prominent risk factor associated with central obesity among Indonesian men. From this study, we suggested controlling the risk factors of central obesity by providing education on the dangers of smoking and the importance of physical activity and a balanced nutritional diet.

***Keywords**: Central obesity; cigarette smoking; physical activity; indonesia family life survey; obesity*

Correspondence: Santi Martini, Department of Epidemiology, Biostatistics, Population, and Health Promotion, Faculty of Public Health, Universitas Airlangga, Surabaya Indonesia. Email: santi-m@fkm.unair.ac.id

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Highlights:

1. Low levels o physical activity are the major risk factor of central obesity among Indonesian men.
2. There was a relationship between smoking status, smoker type, cigarette type, physical activity, and meat consumption frequency and the incidence of central obesity.

INTRODUCTION

Obesity is one of the leading health problems in both developed and developing countries (Ng et al. 2014). This is also the case in Indonesia. Obesity happens due to an excess fat accumulation in the adipose tissue. It might happen due to interactions between genetic, environmental, and behavioral factors (Flores-Dorantes et al. 2020). Meanwhile, central obesity is a health condition caused by fat accumulation in the abdominal area, specifically in the visceral adipose tissue. In men, it is characterized by a waist circumference of more than 90 cm. It is also referred to as the apple body shape due to the excess fat accumulation in the abdominal area. The number of people with central obesity is increasing, especially in developing countries (Owolabi et al. 2017).

In Indonesia, the incidence of diabetes has increased in obese people (18.0%-20.1%). Most of the increase has led to the rise of obesity prevalence (Johan et al. 2022). On the other hand, the prevalence of obesity has increased based on the data from the 2018 Riskesdas where obesity cases for those aged over 18 years old have reached 21.8%. This number was much higher than the 2013 Riskesdas data, which was 15.4%. Central obesity cases in Indonesia in 2018 had exceeded the number of cases of total obesity, which was 31%. Based on age, central obesity was mostly observed in the population aged 45-54 years old. Untreated central obesity can also cause various other health problems, such as type II diabetes mellitus, cardiovascular disease, hypertension, cancer, sleep apnoea, and metabolic syndrome (Tehernof & Després 2013). Several behavioral factors cause central obesity, including low levels of physical activity, unhealthy dietary habits, and smoking habits. This study aimed to analyze the risk factors for central obesity in Indonesian men.

MATERIALS AND METHODS

This was an analytical observational study using a cross-sectional design. It was conducted from June to October 2019. A cross-sectional study design is an observational study type in which the researcher measures the outcome and exposure of the study participants at the same time. It is used to assess the disease prevalence using population-based surveys in clinic-based samples (Setia 2016). The study used secondary data from the Indonesia Family Life Survey (IFLS 5).

The Indonesia Family Life Survey is a general-purpose survey designed to provide data for the purpose of studying many different behaviors and outcomes. IFLS collects a rich set of information on health outcomes through self-reporting and including both biomarkers such as the wealth of information collected at the individual and household levels, including indicators of economic and non-economic well-being: migration, consumption, assets, income, education, labour market outcomes, fertility, marriage, processes underlying household decision-making, contraceptive use, use of health care and health insurance, relationships among co-resident and non-resident family members, transfers among family members, and participation in community activities (Witoelar et al. 2012). It had been approved by the Institutional Review Board of RAND Corporation (USA) and the Ethics Committee of Universitas Gajah Mada, Indonesia. The population in this study followed the population in the Indonesia Family Live Survey 5 (IFLS5) in 2014-2015. The case population was all 16,430 male respondents. Based on this population, the sample in this study was 4648 respondents. Sampling was based on the inclusion criteria, that the respondents had complete data on the required variables in this study and the respondents were men aged over 40 years old (middle-aged).

The data analysis was performed in a univariate, bivariate, and multivariate manner. The univariate analysis was performed to identify the frequency (number of proportions) of each study variable, namely the smoking status, type of smokers, type of cigarette, physical activity, and meat consumption frequency. The bivariate analysis in this study used logistic regression to determine the relationship between the dependent variable and the independent variable which in this case was the relationship between smoking status, type of smoker, type of cigarette, physical activity, meat consumption frequency, and central obesity. The multivariate analysis was performed to determine the relationship between several variables (more than one) and one or more dependent variables.

RESULTS

The results of this study were presented descriptively and in the form of a logistic regression. The descriptive presentation was used to describe the characteristics of the respondents according to each variable in the study by presenting the frequency and percentage. Logistic regression tests were performed to account for the relationship between smoking status, type of smoker, type of cigarette, physical activity, meat consumption frequency, and central obesity. Multivariate tests were performed to determine the variables that were the significant risk factors for central obesity. The results of this study were presented in succession with a description of the respondent characteristics, logistic regression tests, and multivariate tests.

The characteristics of the respondents based on smoking status, type of smoker, type of cigarette, physical activity, and meat consumption frequency are presented in Table 1. Table 1 shows that the sample size studied was 4,648 respondents. Based on the inclusion criteria, the respondents studied were men aged 40 years and over, and based on the results of the study, the youngest respondent's age was 40 years and the oldest was 89 years old. The average age of the respondents studied was 51 years old with a standard deviation of 9.41. There were more smoking respondents than non-smoking ones; 72.87% or 3387 respondents were smokers while 27.13% of them were non-smokers. The most prominent type of smokers was moderate smokers, totalling 1,620 respondents or 34.85%. The most prominent type of cigarettes smoked were unfiltered cigarettes (*kretek*) with 2,803 respondents or 60.31%. Most of the respondents (1929 [41.50%]) had a high level of physical activity. Most respondents (92.45%) consumed meat at a low frequency which was less than 4 days a week.

The next results were from the logistic regression tests to account for the relationship between smoking status, type of smoker, type of cigarette, physical activity, meat consumption frequency, and the incidence of central obesity. The results are presented in Table 2.

Table 1. Respondents' characteristics

Variable	n	Mean	Standard deviation	Min	Max
Age	4,648	51.48236	9.41171	40	89

Smoking status	Frequency	Percentage (%)
Non-smoker	1261	27.13
Smoker	3387	72.87
Total	4648	100

Type of smoker	Frequency	Percentage (%)
Heavy smoker	414	8.91
Moderate smoker	1620	34.85
Light smoker	1353	29.11
Non-smoker	1261	27.13
Total	4648	100

Type of cigarette	Frequency	Percentage (%)
White cigarette	584	12.56
Unfiltered cigarette	2803	60.31
Non-smoker	1261	27.13
Total	4648	100

Physical activity	Frequency	Percentage (%)
Low (<300 MET)	1264	27.19
Moderate (300-2999 MET)	1455	31.30
High (>3000 MET)	1929	41.50
Total	4648	100

Meat consumption	Frequency	Percentage (%)
High	351	7.55
Low	4297	92.45
Total	4648	100

Table 2. Logistic regression tests

Variable	Central obesity		Non-central obesity		Total		p-value
	n	%	n	%	n	%	
Smoking status							
Non-smoker	859	68.12	402	31.88	1261	100	0.000
Smoker	1965	58.02	1422	41.98	3387	100	

Variable	Central obesity		Non-central obesity		Total		p-value
	n	%	n	%	n	%	
Smoking respondents (3387 people)							
Type of smoker							
Heavy smoker	259	62.56	155	37.44	414	100	0.002
Moderate smoker	969	59.81	651	40.19	1620	100	
Light smoker	737	54.47	616	45.53	1353	100	

Variable	Central obesity		Non-central obesity		Total		p-value
	n	%	n	%	n	%	
Smoking respondents (3387 people)							
Type of cigarette							
While cigarette	378	64.73	206	35.27	584	100	0.000
Unfiltered cigarette	1587	56.62	1216	43.38	2803	100	

Physical activity	Central obesity		Non-central obesity		Total		p-value
	n	%	N	%	n	%	
Low	809	64	455	36	1264	100	0.000
Moderate	923	63.43	532	36.57	1455	100	
High	1092	56.60	837	43.40	1929	100	

Meat consumption frequency	Central obesity		Non-central obesity		Total		p-value
	n	%	N	%	n	%	
High	233	66.38	118	33.62	351	100	0.024
Low	2591	60.30	1706	39.70	4297	100	

Table 2 shows that from the Chi-square test, we obtained the results for smoking status (p=0.000) which indicated a relationship between smoking status and the incidence of central obesity. For the smoking status variable, the analysis of the risk was carried out and yielded a Prevalence Ratio (PR) of 1.54 with 95% CI = 1.34 <PR <1.77. This meant that the non-smoking respondents were 1.54 times more at risk of central obesity than those who smoked.

The Chi-square test yielded a result for the type of smoker (p=0.000), meaning that there was a relationship between smoking status and the incidence of central obesity. On the type of smoker variable, between light smokers and moderate smokers, the Prevalence Ratio (PR) was 1.24 with 95% CI = 1.07<PR<1.44. The results indicated that moderate smokers were 1.24 times more likely to develop central obesity than light smokers.

The Chi-square test yielded a result for the type of cigarette (p=0.000) which meant that there was a relationship between smoking status and the incidence of central obesity. The analysis of the risk of the type of cigarette resulted in a Prevalence Ratio (PR) of 1.40 with 95% CI = 1.16 <PR < 1.69. That was, smokers who used white cigarettes were 1.40 times more likely to develop central obesity than smokers who used unfiltered cigarettes.

The Chi-square test yielded a result for physical activity (p=0.000) which meant that there was a relationship between smoking status and the incidence of central obesity. Based on the analysis of the risk between moderate levels of physical activity and high levels of physical activity, the Prevalence Ratio (PR) was 1.32 with 95% CI = 1.15 <PR <1.53. These results showed that people with moderate levels of physical activity were 1.32 times more likely to develop central obesity than people with high levels of physical activity. Based on the analysis of the risk between low and high levels of physical activity, the Prevalence Ratio (PR) was 1.36 with 95% CI = 1.17 <PR <1.58. These results showed that people with low levels of physical activity were 1.36 times more likely to develop central obesity than people with high levels of physical activity.

The Chi-square test yielded a result for meat consumption frequency (p=0.000) which meant that there was a relationship between smoking status and the incidence of central obesity. Based on the analysis of the risk, the Prevalence Ratio (PR) was 1.30 with 95% CI = 1.02<PR<1.65. These results showed that people who frequently consumed meat were 1.30 times more likely to develop central obesity than people who rarely consumed meat.

Table 3. Risk factors that influence central obesity in men

Variables	PR	95% Conf. interval	
		Lower	Upper
Type of smoker			
Heavy smoker	1.36	1.08	1.71
Moderate smoker	1.24	1.07	1.44
Light smoker (*reference*)	1.00		
Type of cigarette			
White cigarette	1.37	1.14	1.66
Unfiltered cigarette (*reference*)	1.00		
Physical activity			
Low	1.43	1.21	1.70
Moderate	1.32	1.12	1.56
High (*reference*)	1.00		
Meat consumption frequency			
High	1.25	0.95	1.67
Low (*reference*)	1.00		
Constant	0.93		

Table 3 shows that there are 3 variables that have become significant risk factors for central obesity in men aged above 40 years old. The constituent variables included the type of smoker (heavy smoker, moderate smoker), the type of cigarette (white cigarette), and physical activity (low, moderate). The variable presenting the highest risk was physical activity with a prevalence ratio = 1.43 (95% CI 1.21-1.70).

DISCUSSION

The results of the study showed that there was a relationship between smoking status and the incidence of central obesity with a p-value of 0.000. For the smoking status variable, non-smoking respondents were 1.54 times more likely to develop central obesity than smoking respondents. This was in line with several studies stating that smokers tend to lose weight due to the effect of nicotine that suppresses the appetite which in turn reduces their food intake and metabolism stimulation (Dare et al. 2015). Smokers involved in weight loss interventions will experience a weight loss comparable to non-smoking individuals where smoking can control diet and appetite (Murphy et al. 2018). Several epidemiological studies have shown that the cessation of smoking leads to weight gain (Oh 2019). The results of the study by Zhao in China in 2021 stated that smoking was negatively associated with the risk of central obesity in adult men (Zhao et al. 2021). However, several studies have reported that smoking status is not significantly associated with body mass index, despite an association with central obesity. Therefore, smokers tend to have a lower body mass index than non-smokers. Smoking can stimulate the accumulation of body fat in the stomach. Multiple mechanisms of action, such as cortisol, sex hormones,

insulin resistance, and chronic inflammation may explain the various effects of smoking status on central obesity (Kim et al. 2016).

The results of the study showed that there was a relationship between the type of smoker and the incidence of central obesity with a p-value of 0.002. It was found that among smokers, heavy smokers who smoke more than 20 cigarettes a day and moderate smokers who smoke around 11-20 cigarettes a day tend to have a waist-hip ratio greater than those of light smokers. The more cigarettes smoked in one day, the higher the risk of central obesity. These results were in line with the study by Zhao in 2021 stating that in China from 1991 to 2015, the prevalence of central obesity in adult men showed a significant increasing trend among non-smokers, light smokers, moderate smokers, and especially heavy smokers (Zhao et al. 2021). There are several explanations for the increased risk among heavy smokers. First, smoking stimulates the sympathetic nervous system which leads to an increase in cortisol, the stress hormone, and the deposition of belly fat (Direk et al. 2011). Smoking can have an anti-estrogenic effect. This can cause an imbalance of sex hormones in men, namely a decrease in the hormone testosterone. Smokers also tend to have unhealthy lifestyles, such as a low fruit and vegetable intake, a higher likelihood of depression, and sleep disturbances that can increase the risk of central obesity (Kim et al. 2016).

The results of this study showed that there was a relationship between the type of cigarette and the incidence of central obesity with a p-value of 0.000. It was known that smokers who used white cigarettes were 1.40 times more likely to develop central obesity than those who used unfiltered cigarettes. This is of particular interest because even though unfiltered cigarettes contain more tar and nicotine than white cigarettes, white cigarettes pose more of a risk of central obesity. White cigarettes are often called light cigarettes because of their low tar content and most light cigarette smokers believe that low-tar cigarettes are safer and provide substantial health benefits (Kiviniemi & Kozlowski 2015).

The results of this study showed that there was a relationship between physical activity and the incidence of central obesity with a p-value of 0.000. Based on the analysis of the risk, the lower the level of physical activity, the higher the risk of central obesity in men. Physical activity has a major effect on the total energy expenditure. Excessive energy without appropriate use or expenditure of energy, such as for basal metabolism, physical activity, disposal of food waste, and growth, will cause an increase in fat cell accumulation. Energy needs to be expended with a variety of high or low-volume and intensity physical activities because the amount of energy expended can reduce the risk of fat accumulation in the body (Banks 2011). A study in Korea revealed there to be a more significant relationship between physical activity and obesity measured using waist-to-height ratio rather than body mass index (Lee et al. 2016). Another study also echoed similar results, demonstrating the risk of central obesity and moderate or low levels of physical activity (PR=1.70–1.74) (de Costa et al. 2014).

The results of this study showed that there was a relationship between meat consumption frequency and the incidence of central obesity with a p-value of 0.024 and a PR of 1.30 and 95% CI = 1.02<PR<1.65. These results showed that people who frequently consumed meat were 1.30 times more likely to develop central obesity than those who rarely consumed meat. Meat contains fat which, if consumed in excess, can be a risk factor for central obesity. The results of this study were also in line with the study conducted by Wang et al. (2014) which stated that the consumption of large amounts of fatty red meat was significantly associated with a higher waist circumference and the risk of central obesity in adult men in China. Another study asserted that meat in modern dietary habits is just as bad as sugar since both cause obesity (You & Henneberg 2016).

Strength and limitation

This study contributes to recent studies by investigating the risk factors for central obesity, particularly in Indonesian men. As a low level of physical activity was the most prominent risk factor for central obesity, this study suggested the management of those risk factors by educating the community on the health hazards of smoking and the significance of physical activity and adequate nutrition.

CONCLUSION

There was a relationship between smoking status and the incidence of central obesity, between the type of smoker and the incidence of central obesity, between the type of cigarette and the incidence of central obesity, between physical activity and the incidence of central obesity, and between meat consumption frequency and the incidence of central obesity. Low levels of physical activity are the major risk factor of central obesity among Indonesian men.

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Conflict of interest

None.

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None.

Author contribution

D, GSP, and SM contributed to the conceptualization and review of the literature , study design and methodology, data collection, data analysis. SM and CYL were contributed to the final authorization of the completed work.

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Original Research Report

DURABILITY OF S-RBD IgG ANTIBODY LEVELS AFTER SINOVAC VACCINATION IN HEALTHCARE WORKERS

Jusak Nugraha[1], Cynthia Ayu Permatasari[2], Munawaroh Fitriah[1]

[1]Department of Clinical Pathology, Faculty of Medicine, Universitas Airlangga/ Dr. Soetomo General Academic Hospital, Surabaya, Indonesia
[2]Resident at Clinical Pathology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

ABSTRACT

Since it was declared a pandemic in early 2020, Coronavirus Disease 2019 (Covid-19) has caused high morbidity and mortality in the world. In view of the urgency of the situation, vaccination efforts are needed to break the chain of disease transmission. Various types of vaccines have been successfully developed and obtained approval for emergency use. However, the effectiveness of these vaccines, both in the short and long term, has not been fully known. This study aimed to examine the effectiveness of vaccination through the kinetics of the antibody response to the administration of the SARS-COV-2 vaccine by examining IgG S-RBD levels. This study was an observational analytic study with a prospective cohort approach carried out between January and November 2021 at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia. Fifty health workers who received Sinovac vaccination in as many as 2 doses underwent venous blood taking and measurement of quantitative S-RBD antibody level. Then, quantitative S-RBD IgG antibody levels were measured and recorded in each subject. The mean S-RBD IgG antibody was found to have fluctuation. The titer was found to significantly increase on day 14 and dropped significantly in month 3 ($p < 0.001$). There was a significant difference in S-RBD IgG levels 6 months after vaccination between Covid-19 uninfected groups and Covid-19 infected groups ($p < 0.001$). In a conclusion, two doses of the Sinovac vaccine formed antibodies, although humoral immunity obtained tended to decrease in 3rd month after vaccination to healthy individuals. The average level of S-RBD IgG antibody in the sixth month post-vaccination was found to be significantly different between groups without history and groups with a history of with infection COVID-19.

***Keywords**: Sinovac; vaccination; covid-19; IgG S-RBD; cinetics; virus; coronavirus*

Correspondence: Jusak Nugraha, Department of Clinical Pathology, Faculty of Medicine, Universitas Airlangga/ Dr. Soetomo General Academic Hospital, Surabaya, Indonesia. E-mail: jusak-n@fk.unair.ac.id

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Highlights:

1. The effectiveness of vaccination through the kinetics of the antibody response to the SARS-COV-2 vaccine administration by examining IgG S-RBD levels was aimed.
2. Two doses of the Sinovac vaccine formed antibodies in healthy individuals in the first 3rd month after vaccination.
3. An S-RBD IgG antibody in the 6th-month post-vaccination was significantly different between groups without a history and groups with a history of infection with COVID-19.

INTRODUCTION

Coronavirus disease (COVID-19) has spread to so many nations in such a short time that the World Health Organization (WHO) declared it a pandemic on March 11, 2020. Throughout the world, the ongoing COVID-19 infection has resulted in severe morbidity and mortality.On March 21, 2021, the WHO stated that 122,524,424 COVID-19 cases had been confirmed, with 2,703,620 patients died, or a Case Fatality Rate (CFR) of 2.20 percent (Jin et al. 2020, World Health Organization 2020). The Ministry of Health data on March 21, 2021, showed that 5,533,379 people had received vaccination (Ministry of Health 2020, Committee for COVID-19 Handling and National Economy Restoration 2021).

Given the severity of the situation, vaccination is absolutely important to break the disease transmission chain. In addition, vaccination is an effort to fulfill the Sustainable Development Goals (SDGs) to ensure a healthy life and promote prosperity for all. The keyword in the third point of the SDGs lies in the words 'healthy' and 'well-being'. The goal to be achieved is that all people will eventually have antibodies against the disease and the welfare of the people will be re-established when the pandemic has been overcome. Infections with SARS-COV-2 and vaccinations trigger an immunological response that includes the development of antibodies (binding antibodies) in the bloodstream. Vaccination-induced immunity is one of the options for reducing SARS-COV-2 disease morbidity and mortality. The Covid-19 vaccine is predicted to trigger a full immunological response, including cellular and humoral, as well as a high neutralizing antibody titer (Prekumar et al. 2020, Xia et al. 2020). NAbs are an antibody subset capable of blocking cellular infiltration and viral replication. The most essential target for neutralization is RBD in the S1 subunit. The COVID-19 vaccination is expected

to trigger an immunological response with a high neutralizing antibody titer. Several types of vaccinations have been successfully produced and approved for use in emergencies. However, the vaccines' usefulness in the short and long term has yet to be fully recognized (Amanat et al. 2020, Natarajan et al. 2021, Nile et al. 2020). Although COVID-19 serological diagnostic tests have been developed, antibody responses in vaccinated people, particularly those who received the Sinovac vaccination, remained largely unknown. This study aimed to determine the levels of anti-IgG S-RBD kinetics by taking samples on day 0 (before vaccination), day 14, day 28, 3 months, and 6 months following the second dose vaccination. By identifying the antibody response, the SARS-CoV-2 disease can be prevented and the time when the booster vaccine should be given can be determined.

MATERIALS AND METHODS

This prospective cohort observational study was carried out in January-November 2021 and involved fifty healthcare workers of Dr. Soetomo Hospital, Surabaya, Indonesia. This study had received ethics approval from the Health Research Ethics Committee, Dr. Soetomo General Academic Hospital, Surabaya, number: 0141/KEPK/II/2021. Participants who approved this study had received two doses of Sinovac vaccination between January 1 - March 31, 2021.

All subjects involved in this study had signed informed consent and were willing to participate in this study for blood taking before vaccination on day 0, after the second dose vaccination on day 14, day 28, after 3 months, and 6 months. Blood was taken from the cubital vein with a volume of 2.5 ml and collected in a serum separator tube (SST) and the plasma was stored at -80^{o}C until the measurement was carried out. The kit used was Abbott SARS-COV-2 IgG II Quantitative and run on the Architect I-1000 instrument.

The kinetics of the antibody response was obtained by observing the ups and downs or the pattern of S-RBD IgG antibodies depicted on the line diagram. The comparative test values of S-RBD IgG at each measurement time were analyzed using the non-parametric statistical test of the Friedman test followed by the Wilcoxon signed-rank test.

RESULTS

This study involved fifity health workers from Dr. Soetomo General Academic Hospital in Surabaya, Indonesia, who had received two doses of the SARS-CoV-2 vaccine (Sinovac). During the trial, 10 (20%) of the individuals were infected with COVID-19 after month 3 and before month 6 of sampling. The median CT-value of the infected patients was 10.58 (3.96 - 21.93). After booster vaccination, the median day of being confirmed or infected with COVID-19 was day 151. (144-164) (Table 1).

The sex of the patients receiving the Sinovac vaccine in the two sample groups (with and without a history of COVID-19 infection) revealed that females outnumbered males. Females made up a total of 25 patients (57.5%) in the group without a history of COVID-19 infection and 8 patients (80%) in the group with a history of COVID-19 infection. Among the male vaccine recipients, there were 17 patients (42.5%) in the group without a history of COVID-19 infection and 2 (80%) in the group with a history of COVID-19 infection.

The age range in both groups was 20-40 years, with 8 patients (80%) having a history of COVID-19 infection and 36 patients (90%) not having a history of COVID-19 infection. Comorbidities were discovered in 19 of the participants, with hypercholesterolemia being the most common, which was found in ten patients.

Table 2 shows the levels of S-RBD IgG antibodies in the two study groups before and after SARS-CoV-2 (Sinovac) vaccination. It is clear from Table 2 that the total median value has increased. In contrast to the fluctuation on day 0 (pre-vaccination), the median value of subjects who were not infected with COVID-19 during the study was 0.2 AU/mL (IQR 0.0-38.4), increased on day 14 to 655.4 AU/mL (IQR 154.1-5920.1), then started to decrease on day 28 to 606.2 AU/mL (IQR 94.4-4065.3), and then continued to decrease further.

Figures 1 and 2 illustrate the kinetics of the S-RBD IgG antibody response from before vaccination to 6 months after the second dose of vaccination. Figure 1 shows the kinetics of S-RBD IgG levels in patients without a history of COVID-19. The median level of IgG S-RBD continued to rise until observation day 14, which was the highest median. From observation day 28 onwards, this amount gradually decreased.

Figure 2 shows the fluctuation of IgG S-RBD levels for each group with a history of COVID-19 infection. The only alterations in the median peak point in many levels on day 14 and others on day 28 were the same as in the prior profile. The kinetics of S-RBD IgG values in patients with a history of COVID-19 infection revealed that the median of S-RBD IgG fluctuated, increasing and decreasing until month 3 of observation, and then increasing until a higher median value of more than 70,000 Au/mL was recorded starting from month 6.

Table 1. Sample profile

Groups	Profile	n (%)
Not infected with COVID-19 during the study	Sex	
	Male	17 (42.5)
	Female	23 (57.5)
	Age	
	2 0–30 years	7 (17.5)
	31–40 years	29 (72.5)
	> 40 years	4 (10.0)
	Comorbidity	
	None	25 (62.5)
	Present	15 (37.5)
	Hypercholesterolemia	5 (12.5)
	Hypertension	3 (7.5)
	Obesity	1 (2.5)
	DM & Hypertension	3 (7.5)
	Hypercholesterolemia & Obesity	1 (2.5)
	Hypercholesterolemia & Hypertension	2 (5.0)
Infected with COVID-19 after sampling in month 3 of the study	Sex	
	Male	2 (20.0)
	Female	8 (80.0)
	Age	
	20 – 30 years	4 (40.0)
	31 – 40 years	4 (40.0)
	> 40 years	2 (20.0)
	Comorbidity	
	None	6 (60.0)
	Present	4 (40.0)
	Hypercholesterolemia	1 (10.0)
	Hypertension	2 (20.0)
	Hypercholesterolemia & Obesity	1 (10.0)

Table 2. Pre- and post-vaccination S-RBD IgG antibody levels

Groups	Variables	n (%)	Range	Median	Mean	St. Dev
Not infected with COVID-19 during the study	S-RBD IgG	40 (80.0)				
	Day 0		0.0 – 38.4	0.2	3.1	7.2
	Day 14		154.1 – 5920.1	655.4	1194.4	1269.3
	Day 28		94.4 – 4065.3	606.2	888.7	795.0
	Month 3		32.6 – 2897.1	204.0	315.5	453.1
	Month 6		0.0 – 1607.5	104.5	182.6	285.1
Infected with COVID-19 after sampling in month 3 of the study	S-RBD IgG	10 (20.0)				
	Day 0		0.0 – 43.1	0.7	8.3	16.3
	Day 14		618.6 – 3319.5	1237.8	1401.8	768.3
	Day 28		433.3 – 2530.1	895.3	1085.6	656.1
	Month 3		98.0 – 610.9	257.6	286.7	185.7
	Month 6		1868.7 – 80000.0	77027.8	56552.7	30996.5

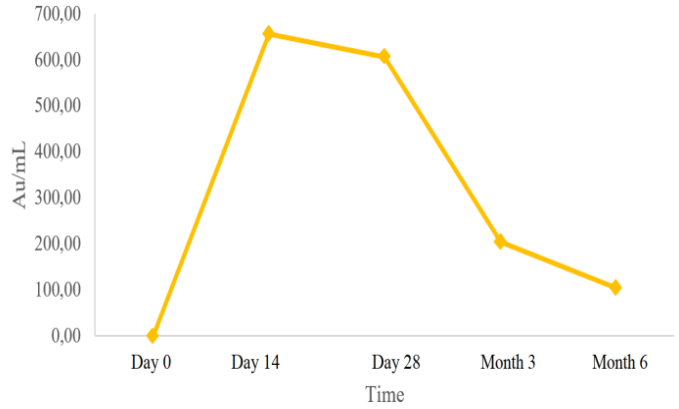

Figure 1. The fluctuation of S-RBD IgG median in the group without a history of COVID-19 infection

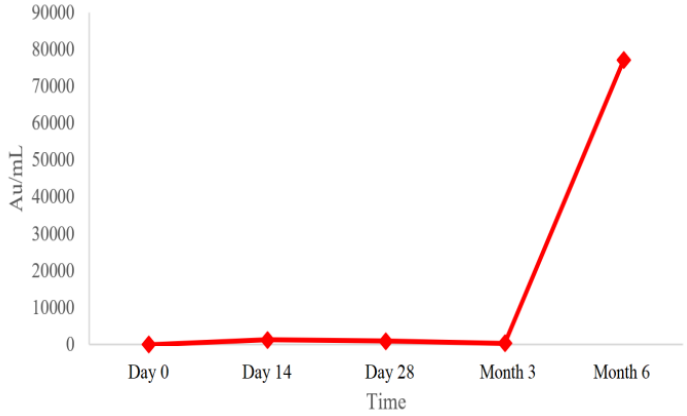

Figure 2. The fluctuation of IgG S-RBD median in a group with a history of COVID-19 infection after month 3 of the study

Table 3. Differences in pre- and post-vaccination S-RBD IgG antibody levels in subjects without a history of COVID-19 infection

Time	Participants (n)	Median	Friedman test χ^2 (p-value)	Wilcoxon test Z (p-value)				
				D 0	D 14	D 28	M 3	M 6
D 0	40	0.20	142.34 (< 0.001)	-	-5.51 (<0.001)	-5.51 (<0.001)	-5.51 (<0.001)	-5.50 (<0.001)
D 14	40	655.35		-	-	-3.79 (<0.001)	-5.01 (<0.001)	-5.24 (<0.001)
D 28	40	606.15		-	-	-	-5.00 (<0.001)	-5.09 (<0.001)
M 3	40	203.95		-	-	-	-	-4.48 (<0.001)
M 6	40	104.45		-	-	-	-	-

Notes: D: Day
M: Month

The purpose of this study was to see if there were any variations in S-RBD IgG levels in SARS-CoV-2 vaccine recipients from pre-vaccination (day 0) to month 6 in each group. Friedman's non-parametric statistical test was used to compare S-RBD IgG levels, followed by Wilcoxon Sign Rank Test if the Friedman test revealed a significant difference. The results of comparative test results on S-RBD IgG levels in SARS-CoV-2 vaccine (Sinovac) recipients in a group without a history of COVID-19 infection are shown in Table 3.

Table 4. Differences in pre- and post-vaccination S-RBD IgG antibody levels in group with a history of COVID-19 infection

Time	Participants (n)	Median	Friedman test χ^2 (p-value)	Wilcoxon test Z (p-value)				
				D 0	D 14	D 28	M 3	M 6
D 0	10	0.65	39.280 (< 0.001)	-	-2.80 (0.005)	-2.80 (0.005)	-2.80 (0.005)	-2.80 (0.005)
D 14	10	1237.80		-	-	-1.89 (0.059)	-2.80 (0.005)	-2.80 (0.005)
D 28	10	895.25		-	-	-	-2.80 (0.005)	-2.80 (0.005)
M 3	10	257.60		-	-	-	-	-2.80 (0.005)
M 6		77027.75		-	-	-	-	-

Notes: D: Day
M: Month

Table 5. Comparison of pre- and post-vaccination S-RBD IgG antibody levels between groups without and with a history of COVID-19 infection

S-RBD IgG (AU/mL)	Mean ± SD Median (min-max)		p
	Not infected with COVID-19 (n = 40)	Infected with COVID-19* (n = 10)	
Pre-vaccination (D 0)	0.2 (0.0 – 38.4)	0.7 (0.0 - 43.1)	0.834[b]
Post-vaccination			
Day-14	1194.4 ± 1269.3	1401.8 ± 768.3	0.607[a]
Day-28	888.7 ± 795.0	1085.6 ± 656.1	0.337[a]
Month-3	315.5 ± 453.1	286.7 ± 185.7	0.701[a]
Month-6	104.5 (0.0–1607.5)	77027.8 (1868.7 – 80000.0)	< 0.001[b]

Notes: *Subjects were infected with COVID-19 during the study (after month 3 and before month 6 of sampling). A two independent samples T-test; Mann-Whitney test.

The findings of Friedman and Wilcoxon tests on pre- and post-vaccination S-RBD IgG levels in patients not infected with COVID-19 revealed significant differences. S-RBD IgG levels were observed to have increased between pre- and post-vaccination and then decreased as post-vaccination time progressed.

Table 4 shows the findings of a comparative test on S-RBD IgG levels in recipients of the SARS-CoV-2 vaccine (Sinovac) in a group with a history of COVID-19 infection.

Friedman's comparative tests showed a p-value of 0.001 in S-RBD IgG levels in patients receiving the SARS-CoV-2 vaccine with a history of COVID-19 infection, indicating a significant difference in S-RBD IgG levels in those patients. The Wilcoxon test revealed that the majority of the patients had a p-value of less than 0.05, except for the S-RBD IgG level test on days 14 and 28, which had a p-value of 0.059. The Wilcoxon test revealed differences in S-RBD IgG in patients receiving the SARS-CoV-2 vaccine with a history of COVID-19 infection on days 0 to 6, while a non-significant difference was only found on observation day 14 and day 28.

Differences in pre-vaccination and post-vaccination SARS-CoV-2 IgG S-RBD antibody levels between subjects without and with a history of COVID-19 infection during the study period are shown in Table 5. S-RBD IgG antibody levels differed significantly in 6 months post-vaccination between the uninfected group and the group with COVID-19 infection history ($p < 0.001$).

DISCUSSION

This study aimed to examine the kinetics pattern of S-RBD IgG antibodies against the administration of the SARS-CoV-2 (Sinovac) vaccine up to 6 months post-vaccination. Vaccination can stimulate the production of various antibodies. The antibody formed against RBD is considered to be the most relevant one to assess the effectiveness of a vaccine concerning its neutralizing effect (Azkur et al. 2020, Liu et al. 2020).

This study on the kinetics of S-RBD IgG levels obtained a median pre-vaccination antibody level of 0.2 (0.0 –38.4), which means that it was non-reactive or did not have antibodies. This value indicates that all subjects had never been infected with COVID-19 before receiving the vaccination.

During this study, after sampling in month 3 and before sampling in month 6, 10 subjects developed COVID-19 infection. The infection of several of these subjects coincided with the presence of the second wave of the cases in Indonesia. The COVID-19 infection in these subjects caused an increase in the average level of IgG S-RBD in month 6 as many as 32 times. Therefore, this study made different observations between the group that was not infected with COVID-19 and the group with a history of COVID-19 infection. In month 6, there were differences in kinetic patterns between the group not infected with COVID-19 and the group with a history of COVID-19 infection. In the uninfected group, antibody levels tended to decrease, while in the group with a history of infection, the antibody levels increased very drastically.

The antibody kinetics described in this study were following the response to antibody formation in patients with COVID-19. Three seroconversion patterns in SARS-CoV-2 have been observed in previous studies. IgM, IgG, and NAb peak 2–3 weeks post-symptom onset and decline to undetectable levels within 6 weeks for IgM, whereas IgG and NAb titers pass through a plateau before falling within 2–3 weeks (Hamady et al. 2022).

Antibodies are formed from exposure of the immune system to vaccine antigens which stimulates the formation of memory B cells, which then differentiate into antibody-secreting cells. These antibody-secreting cells produce IgG molecules that are responsible for vaccine-induced immunity. The results of this study were consistent with several other studies which also found that immediately after vaccination, antibody titers tended to increase significantly until day 36 or the first-month post-vaccination (Terpos et al. 2021). A similar study assessing antibody response kinetics after vaccine administration has also been carried out on BNT162b2 mRNA vaccination, which found a sharp increase in S-RBD anti-IgG levels in vaccinated recipients after day 22 and remained high on day 50 (Trougakos et al. 2021).

A significant decrease in S-RBD IgG levels in this study was obtained from day 28 to month 3 post-vaccination ($p < 0.05$), and then decreased slowly until month 6 post-vaccination. The decrease in antibody levels that occurred in month 3 still showed levels above the threshold of positivity, which indicated that the immune response against SARS-CoV-2 was still active until month 6. These results were in agreement with a study which found that more than 90% of individuals infected with SARS-CoV-2 developed antibodies within one week of symptom onset and the antibody titers tended to persist for at least three months post-infection (Hall et al. 2021).

This study found a significant difference in S-RBD IgG antibody levels at month 6 between the group without a history of COVID-19 infection and the group with a history of COVID-19 infection, which was not followed by a significant difference in antibody levels at 3 months after the booster. In the two groups, the mean levels resulted in 3 months after booster (315.5 ± 453.1 vs. 286.7 ± 185.7; p=0.701). This finding showed that although antibody levels persisted in month 3, these levels did not reach the optimal value that was considered to have a neutralizing effect.

The increase in S-RBD IgG levels began on day 14 after the second dose of Sinovac vaccination. The highest increase was seen in the mean antibody levels on day 14 post-vaccination with two doses of Sinovac, which were 1194.4 ± 1269.3 Au/mL (169.6 ± 184.07 BAU/mL) in a group without a history of COVID-19 and 1401.8±768.3 Au/mL (199.05 ±109.09 BAU/mL) in a group with a history of COVID-19 infection. In the internal research by Abbott ARCHITECT 2021 and as listed on the SARS-CoV-2 IgG II Quant reagent kit, the equivalence of the PRNT50 titer (1:80) to the IgG S-RBD result was 1050 AU/mL (149.1 BAU/mL) (based on Abbott ARCHITECT 2020 and Abbott ARCHITECT 2021). The highest increase on day 14 was considered to have an optimal neutralizing effect against the SARS-COV-2 virus because the increase was more than 1050 AU/mL (149.1 BAU/mL). In 2021 the FDA has also published a test table of several reagents and tools that are acceptable for use in the manufacture of COVID-19 convalescent plasma, one of which is for Abbott SARS-CoV-2 IgG II Quant with qualifying results $\geq$ 840 AU/mL ($\geq$ 119.28 BAU/mL) (Bratcher-Bowman 2021).

Sinovac is effective in generating a faster and higher humoral immune system in the next Covid infection. This shows that memory cells in the immune system, either obtained from vaccination or previously infected, still survive for 10 months and will cause faster and higher antibody formation when the body is invaded by the same antigen (Ontañón et al. 2021).

Similar results were obtained by the study of Ontañón et al. (2021) on vaccinated health workers. The study revealed that antibody titers at two months post-vaccination were higher in a group with a previous history of SARS-CoV-2 infection than in a group that had never been infected. The study found that within 7 days after the first dose of vaccination, the group with a

history of SARS-CoV-2 infection experienced a 126-fold increase in antibody levels ($p < 0.001$). In the group without a history of infection, only 5 subjects showed positive antibody levels. Observations two months later found that antibody levels were still higher in the group with a history of previous infection.

Goel et al. (2021) examined the response of B and T lymphocytes in individuals receiving the SARS-CoV-2 mRNA vaccine by conducting a 6-month longitudinal study. Vaccination had been shown to produce spike-specific memory CD4 and CD8 T cells. Although antibodies often correlate with the effectiveness of vaccines, memory B cells and memory T cells are important components of the resistance response to viral antigens and have protective mechanisms in individuals who have acquired pre-existing immunity. When the same antigen enters the body, memory T cells proliferate very rapidly and provide a stronger immune response. These antibodies are useful for the control of early viral replication and limiting the spread of the virus in the host. Cellular immunity has the role of reducing or even preventing disease symptoms (that is, preventing hospitalization and death) and reducing the ability to spread the virus to others.

It can therefore be assumed that the underlying reason for the increase in S-RBD IgG antibody levels at 6 months post-vaccination between the uninfected group and the group with a history of COVID-19 infection in this study might be due to high viral load and the role of B and T memory cells from previous vaccination.

Strength and limitation

As the pandemic is still ongoing, this research serves to shed light on how the COVID-19 vaccine works. This study can demonstrate that two doses of Sinovac vaccine are effective in boosting S-RBD IgG antibody levels, even though other factors may reduce the efficacy. A limitation of this study was that it only evaluated the humoral immune response and did not evaluate the cellular immune response. Previous studies have proven a correlation between humoral and cellular immunity after vaccination (Lozano-Ojalvo et al. 2021). Other limitations of this study were that it was only conducted in a single-center, the small sample size, and the narrow age range of the subjects which might have limited the generalizability of the results.

CONCLUSION

Two doses of the Sinovac vaccine did produce antibodies, although the obtained humoral immunity tended to decrease in 3 months post-vaccination in healthy individuals. There was a significant difference in the mean S-RBD IgG antibody levels at 6 months post-vaccination between the group without a history of COVID-19 infection and the group with a history of COVID-19 infection. Further studies are recommended by conducting further observations on antibody kinetics after the 3rd booster vaccination and by conducting further multicenter studies using a larger sample size to obtain a better generalization of the results.

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Conflict of interest

None.

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Author contribution

JN, and CAP contributed to the conceptualization study design and methodology. CAP and MF were data collection, data analysis. MF were contributed to the final revise.

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Original Research Report

DISCOVERING PATTERNS OF CARDIOVASCULAR DISEASE AND DIABETES IN MYOCARDIAL INFARCTION PATIENTS USING ASSOCIATION RULE MINING

Anju Singh[1], Divakar Singh[2], Shikha Sharma[3], Kamal Upreti[4], Manish Maheshwari[5], Vimal Mehta[6], Jitender Sharma[7], Pratishtha Mehra[6], Pradeep Kumar Dabla[7]

[1]Sage University, Bhopal, India
[2]Barkatullah University Institute of Technology, Barkatullah University, Bhopal, India
[3]Department of Biochemistry, Chacha Nehru Bal Chikitsalaya, New Delhi, India
[4]Dr. Akhilesh Das Gupta Institute of Technology & Management, New Delhi, India
[5]Makhanlal Chaturvedi National University of Journalism and Communication, Bhopal, India
[6]Department of Cardiology, Govind Ballabh Pant Institute of Postgraduate Medical Education & Research/ Associated Maulana Azad Medical College, New Delhi, India
[7]Department of Biochemistry, Govind Ballabh Pant Institute of Postgraduate Medical Education & Research/ Associated Maulana Azad Medical College, New Delhi, India

ABSTRACT

Cardiovascular diseases (CVDs) are a major cause of mortality in diabetic patients. Hypertensive patients are more likely to develop diabetes and hypertension contributes to the high prevalence of CVDs, in addition to dyslipidemia and smoking. This study was to find the different patterns and overall rules among CVD patients, including rules broken down by age, sex, cholesterol and triglyceride levels, smoking habits, myocardial infarction (MI) type on ECG, diabetes, and hypertension. The cross-sectional study was performed on 240 subjects (135 patients of ST-elevation MI below 45 years and 105 age-matched controls). Association rule mining was used to detect new patterns for early-onset myocardial infarction. A hotspot algorithm was used to extract frequent patterns and various promising rules within real medical data. The experiment was carried out using "Weka", a tool for extracting rules to find out the association between different stored real parameters. In this study, we found out various rules of hypertension like "Rule 6" says that if levels of BP Systolic > 131 mmHg, LpA2 > 43.2 ng/ml, hsCRP > 3.71 mg/L, initial creatinine > 0.5 mg/dl, and initial Hb ≤15 g/dl (antecedent), then the patient will have 88% chance of developing hypertension (consequent). Similarly for diabetes mellitus with finding their lift and confidence for different support like "Rule 6", if MI type on ECG = 'Inferior Wall MI' with STATIN=No, and levels of Triglycerides ≤325 (antecedent), then the patient had a 67% chance of developing diabetes mellitus. We concluded that early-onset myocardial infarction is significantly associated with hypertension and diabetes mellitus. Using association rule mining, we can predict the development of hypertension and diabetes mellitus in MI patients.

Keywords: *Cardiovascular diseases; diabetes; hypertension; association rule mining; hotspot; myocardial infarction*

Correspondence: Pradeep Kumar Dabla, Department of Biochemistry, Govin Ballabh Pant Institute of Postgraduate Medical Education & Research/ Associated Maulana Azad Medical College, New Delhi, India. Email: pradeep_dabla@yahoo.com

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Highlights:

1. Association Rule Mining tools predict the association of early-onset Myocardial Infarction with Hypertension and Diabetes Mellitus.
2. Association Rule Mining tools using clinical and biochemical attributes can predict the development of Hypertension and Diabetes Mellitus in Myocardial Infarction patients.

INTRODUCTION

Cardiovascular diseases (CVDs) have become the leading cause of mortality globally since the turn of the century (Srinath et al. 2005). CVD occurred a decade earlier in the Indian population as compared to the European population, wherein CVD caused approximately 23% mortality in the elderly (<70 years of age). The fatality estimate in India is estimated to be double in comparison with the same age group (Joshi et al. 2007). The various factors responsible for the higher rate of CVD in the Indian population are hypertension, diabetes, metabolic syndrome, smoking, physical inactivity, unhealthy diet, and other environmental events which lead to the formation of the atheromatous plaque. Acute myocardial infarction (MI) is one type of CVD that alone is responsible for the nearly 1.5 million MI incidents yearly where nearly 33% of them lead to death (McNamara et al. 2019, Virani et al. 2021).

CVD is on the rise in practically all age groups presently, but numerous studies have recently revealed an increase in instances in the young population (less than 40 years of age) and increased mortality with acute coronary syndrome (Mohan 2005). The National Inpatient Sample data revealed that young MI patients had a higher predominance of risk factors, ischemic stroke, and a higher rate of hospital admission (George et al. 2011, Gupta et al. 2014). There is a scarcity of information about juvenile MI patients. Young MI patients are characterized as those who are under 45 years of age, according to the Framingham Heart Study (Doughty et al. 2002).

Traditionally, physicians diagnose CVDs based on their knowledge from their previous experience with patients with similar clinical presentations. However, healthcare workers and hospitals generate a huge amount of data that are difficult to be analyzed by the traditional approach. Association rule mining supports physicians in attaining more accurate diagnosis and early treatment to reduce mortality in CVD patients.

Among the various methods available in data mining, association rule mining extracts useful associations or causal relationships between sets of patterns present in the databases (Han et al. 2011, Hastie et al. 2009). The rules show the dependency of one item on another item and map it to discover the interesting relations between variables in the database. Exploratory data analysis in the medical domain is an emerging field and association rules mining plays a key role in finding the causes and solutions to various diseases. With the rapid growth of medical data sets, there is a need to explore the hidden patterns in the clinical data extracted patterns provide vital knowledge to medical professionals for making appropriate strategies and enhancing the performance of patient management tasks.

To find out the infrequent (rare) items, we have chosen low support and high confidence thresholds. Support is an indication of how frequently the items appear in the data whereas confidence indicates the number of times the if-then statements are found true. In the domain of business, a small number of rules may or may not be beneficial for customer analytics. Although we agree that confining low support and strong confidence yields a small number of rules where clinicians may infer some interesting patterns where they can explain even lesser-known incidents from such a small number of rules (Szathmary et al. 2010). Most of the combination of the symptoms will only be seen in a few patient instances, which is typically true in medical diagnosis. As a result, a method for mining the related rules and patterns will enable a most concentrated symptom investigation. In another study, the role of the Atherogenic Index of Plasma (AIP) was in conjunction with lipid indices like Lipid Tetrad Index (LTI) and Lipid Pentad Index (LPI) in identifying people who were at a higher risk of premature CA (Dabla et al. 2021).

Patil et al. (2010) aimed to find meaningful facts from the medical database and produce logical and user-friendly descriptions of patterns. They presented a model for association rules over numerical data and used an equal width mining interval method to desensitize continuous-valued elements, using an appropriate algorithm for extracting the fields to know whether the patient is going to develop diabetes mellitus or not. In another study, survival association rule mining is proposed, which addresses the various shortcomings in extracting rules (Simon et al. 2013). In the study, real data sets were used to extract the association rule. In another paper, association rule algorithm is applied to analyze the risk for diabetic patients. This study was performed to extract search relationships in the real data set (Soni et al. 2016). Shehabi and Baba (2021) suggested a new method, called MARC, to extract the more important association rules of two important levels: Type I and Type II. The approach relies on a multi-topographic unsupervised neural network model as well as clustering quality measures that evaluate the success of a given numerical classification model to behave as a natural symbolic model. Another software tool was devised for extracting frequent patterns and association rules from invoices provided by healthcare centers to improvise the quality of a large number of medical e-invoices reducing the irrelevant data (Agapito et al. 2019). Earlier mining rules were used to establish an association between collections of items in enormous databases (Vasoya & Koli 2016). Association rule mining was used recently to discover symptom patterns in COVID-19 patients rule mining (Tandan et al. 2021). As a result, in this paper, we focused on simple pattern mining techniques known as ARM (Association Rule Mining) to give a descriptive strategy for symptom rule extraction. We intended to uncover hidden correlations between symptom patterns in diabetic and hypertensive patients, which could help clinical decision-making for patient treatment.

A hotspot algorithm was applied to find patterns or associations between different attributes such as a complete set of biochemical evaluation testing along with detailed patient history including physical examination and electrocardiogram (ECG). Biochemical markers measured were lipid profile including total cholesterol, triglyceride, LDL-C, HDL-C, Apo A1, Apo B, and Lp(a) levels.

MATERIALS AND METHODS

This cross-sectional study was performed on the clinical data of cardiovascular disease patients presented at G.B. Pant Institute of Postgraduate Medical Education and Research in New Delhi, India. This research had been approved by the ethics

committee of the institute and written approved consent was obtained from participants. A total of 240 subjects were included in the study with proper informed consent. Out of the total, 135 patients were of ST-elevation MI who were below 45 years of age whereas age-matched controls enrolled were 105 in number. A complete set of biochemical evaluations was conducted along with detailed patient history, physical examination, and electrocardiogram (ECG). Biochemical markers measured were lipid profile including total cholesterol, triglyceride, LDL-C, HDL-C, Apo A1, Apo B, and Lp(a) levels.

The Acute MI (AMI) diagnosis was based on the established criteria as:1). Ischemic chest pain lasting 20 min or more, 2) ECG evidence of myocardial injury: (a) ≥0.1 mv ST elevation in two contiguous leads other than V2–V3 where the cut-off point of ≥0.2 mv in men ≥40 years, ≥0.25 mv in men <40 years, or ≥0.15 mv in women. (b) New horizontal or down sloping ST depression ≥0.05 mv in two contiguous leads and/or T-wave inversion ≥0.1 mv in two contiguous leads with prominent R-wave or R/S ratio >1, 3). Positive biomarkers were creatine kinase-MB fraction and cardiac troponins. Then, further analysis was performed on clinical data obtained to detect common patterns in the rules discovered utilizing association rule mining.

The algorithm of the proposed framework works in four major steps as given below, having three stages including pre-processing of the dataset to make a compatible dataset for the algorithm, frequent pattern generation by Hotspot algorithm, and generation of rules. Hotspot learns a bunch of rules (showed in a tree-like design) that augment/limit an objective variable/ worth of interest. With an ostensible objective, one should search for sections of the information where there is a high likelihood of minority esteem occurring (given the imperative of a base help)**.**

To mine association rules, the first step is to create a dataset compatible with the Hotspot algorithm. Initially, data are stored in a Microsoft Excel sheet, we had to change it into comma-separated values and then convert it into ARFF (attribute relation file format). In the pre-processing of mine association rules, we discarded a few irrelevant attributes from the dataset. We had applied the prepossessing technique to make data suitable for the hotspot algorithm. After the pre-processing, data were found to be compatible with the hotspot algorithm. The first step was pre-processing of the medical dataset. The step was the removal of irrelevant attributes continued with the removal of records with missing class values. The second step was applying Hotspot algorithms for targeted class values. The third step was to scan and find the support value for each item, then the removal of infrequent items based on support values. The last step was the generation of rules.

Association rule helps to find a meaningful pattern that can be obtained in those states when R occurs, S occurs with certain possibilities. Literature for Rules Measures had been taken from various available relevant research papers on this subject (An et al. 2005, Chen & Chen 2008, Lau et al. 2006, Ordonez 2006).

For finding out interesting rules, we can apply various measures to set constraints on extracted rules. The minimum constraints are support and confidence.

Support: It denotes the % of the rule within transactions containing R ∪ S.

Support (R≥S) = P (R ∪ S).

Confidences: for the rule hold of form R≥S, confidence score lies between 0 to 1.

Confidence (R≥ S) = P(S | R)

= Support (R ∪ S) / Support (R)

= P (R and S) / P (R)

Lift: for the rule of form R≥S, if the lift score is 1 then the antecedent R and Consequent S are independent. If a score of lift is greater than 1 means that R and S are positively correlated. If a score is less than 1 means R and S are negatively correlated.

Lift (R≥S) = Support (R ∪ S) / Support (R) x Support (S)

= P (R and S) / P (R) P (S)

We discovered many rules that apply to the data set with nominal and real values, which only included clinically attributed data and omitted irrelevant factors. The correlation between R and S is determined by the lift value; independent (=1), positively related (>1), and negative related (1). The "Confidence" measures have the disadvantage of possibly misrepresenting the importance of an association.

In an association of R & S, for example, the Confidence score only considers the importance of item R, but not S. If S is also required, then there is a greater chance that a pattern having R will also have S, increasing the confidence measure. By measuring the strength of the relationship between R and S, the metric lift overcomes this difficulty. The data in transaction format, as well as how ARM computed and built these measures and criteria, are depicted in Figure 2.

RESULTS

The clinic-epidemiological profile of the study population is presented in Table 1

Table 1. Demographic variable of the cases under study

Variable		N (%)
Total No. of cases		135
Sex	Male	126
	Female	09
Age (Years), Mean ± SD		36.0 ± 4.5
Number of participants (15-30 Years)		21 (15.6%)
Number of participants (31-45 Years)		114 (84.4%)
BMI (kg/m^2)		25.7 ± 4.31
BMI >30 (kg/m^2)		21 (15.5%)
Systolic blood pressure (mmHg)		118.4 ± 15.5
Diastolic blood pressure (mmHg)		75.6 ± 9.61
Heart rate (beats/min)		88.2 ± 11.3
Sedentary lifestyle		126 (93.3%)
History of drug intake of statin		18 (13.3%)
Diabetes mellitus		12 (8.89%)
Hypertension		17 (12.6%)
Dyslipidemia		12 (8.89%)
Personal history	Addiction (Smoking cigarettes and beedi)	95 (70.4%)
	Tobacco consumption	90 (66.7%)
	Alcoholic consumption	41 (30.4%)
Frequency of chest pain		130 (96.2%)
Sweating		110 (81.4%)
Breathlessness		85 (62.3%)
Syncope		14 (10.4%)
ECG Changes	Anterior wall MI	82 (60.7%)
	Inferior wall MI	48 (35.5%)
	Lateral wall MI	5 (3.7%)

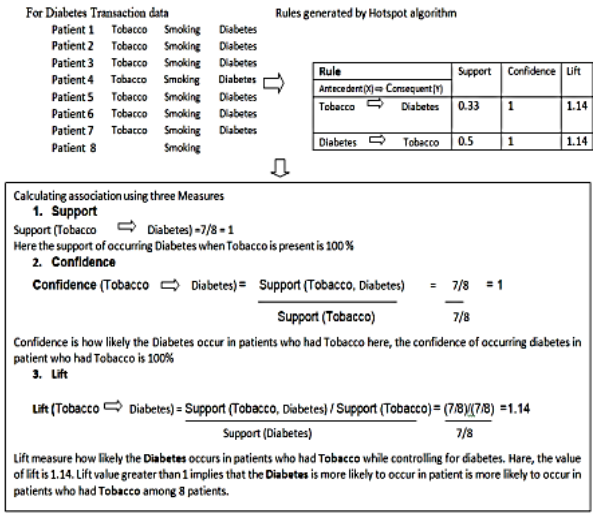

Figure 1. Example to show how ARM computed for diabetes transactional data

In Figure 1, data from eight patients were taken, and the rule mining method yielded two rules, with a support score of 0.33, confidence of 1, and lift of 1.14 for the antecedent (R) Tobacco and consequent (S) Diabetes in rule 1. According to Support 0.5, four out of eight patient data consist of the common attribute "Tobacco and Diabetes". With a confidence level of 0.80, 80 percent of Tobacco patients had Diabetes.

Similarly, lift 1.14 indicates that "Tobacco" and "Diabetes" are positively correlated. In Table 2 and Figure 2, significant rules for {Diabetes Mellitus = No} (N = 135 with 34 attributes in each) are given. Rule 2 says that if value of initial Hb = 7.2, Triglycerides >87, BP Diastolic ≤95} (antecedent), then the patient had a 100 % chance of {Diabetes Mellitus=No} (consequent). In Rule 3, if value of initial HbA1c ≤7.2, Hypertension = No and Heart Rate >70 (antecedent), then the patient had a 100% chance of "Diabetes Mellitus = No" (consequent).

Frequent Pattern for support value was 0.2 to 0.8 (min 20% to 80% of Diabetes Mellitus = No) and confidence (Chance of occurrence of both Antecedents and Consequents) for value was 0.96 to 1' with following attributes and their combinations: initial Hb value >13.7, Heart Rate >70, Triglycerides >87, BP Diastolic ≤95, Hypertension=No, Triglycerides ≤239, initial HbA1c ≤8.6, Heart Rate >70. {Diabetes Mellitus= Yes}.

Rule 6 says that if MI type on ECG='Inferior Wall MI', with STATIN=No, and value of Triglycerides ≤325 (antecedent), then the patient had a 67% chance of {Diabetes Mellitus}. Frequent Pattern For support value 0.3 to 0.6 (min 30-60% of Diabetes Mellitus) and confidence (Chance of occurrence of both Antecedents and Consequents) for valve 0.6 to 1 (60% to 100%) following and their combinations: initial Hb >4.6 to ≤13.7, Alcohol = Never, ApoB >0.61 to ≤0.84, Total cholesterol >114 to ≤192, BP Diastolic >62 to ≤142, ApoA1 >0.73 to ≤1.23, BMI >26.44 to ≤27.8159, LDL >47, Heart Rate >93 to ≤109, HDL >22.7 to ≤42.2, hsCRP >5.95 to ≤105, Age >18, STATIN=No, MI type on ECG=Inferior Wall MI.

In Table 3 and Figure 3, significant rules for {Hypertension = No} (N = 135 with 34 attributes in each) are given. Rule 1 says that if the value of MI type on ECG = " Inferior Wall MI" and value of BP Systolic ≤118 (antecedent), then the patient had a 100 % chance of {Hypertension = No} (consequent). In the next Rule 4, if value of initial Hb value > 11.5, and value initial HbA1c ≤12.3,Diabetes Mellitus = No,BMI ≤32.8125, hsCRP ≤182.01 (antecedent), then the patient had a 100% chance of "Hypertension = No" (consequent). Frequent patterns for support value 0.2 to 0.9 (min 20% to 90% of Hypertension) and confidence (Chance of occurrence of both Antecedents and Consequents) for valve 0.93 to 1 were observed.

Table 2. Significant rules for diabetes mellitus in 135 patients with 34 clinical attributes

Rules	Antecedents (R)	Consequents (S) {diabetes mellitus}	Support	Confidence	Lift
R1	{initial_Hb_ value > 13.7, Heart_Rate >70}	{No}	0.2	1	1.16
R2	{initial_HbA1c ≤7.2, Triglycerides >87, BP_Diastolic ≤95}	{No}	0.6	1	1.16
R3	{initial_HbA1c ≤7.2, Hypertension=No, Heart_Rate >70}	{No}	0.7	1	1.16
R4	{Triglycerides ≤239, Heart_Rate >70, initial_HbA1c ≤8.6}	{No}	0.80	0.98	1.13
R5	{initial_HbA1c ≤8.6, Heart_Rate >70}	{No}	0.80	0.96	1.12
DM=Yes⇓ R6	{Triglycerides >239, MI type_on_ECG=Inferior Wall MI, STATIN=No, Triglycerides ≤325}	{Yes}	0.3	0.67	7.83
R7	{Heart_Rate >96, HDL ≤37.4, initial_Hb_value ≤13.7, Age >32, BMI ≤27.6398}	{Yes}	0.5	1	11.75
R8	{initial_Hb_value ≤12.9, Alcohol=Never, ApoB ≤0.84, Total_cholesterol >114, BP_Systolic >107}	{Yes}	0.6	0.78	9.14
R9	{Heart_Rate >93, HDL ≤37.4, ApoA1 ≤1.23, BMI ≤27.8159, initial_Hb_value ≤13.7}	{Yes}	0.6	0.7	8.22
R10	{Alcohol=Never, LDL >49, hsCRP ≤105, initial_Hb_value ≤15.2, ApoA1 >0.73}	{Yes}	0.9	0.23	2.69

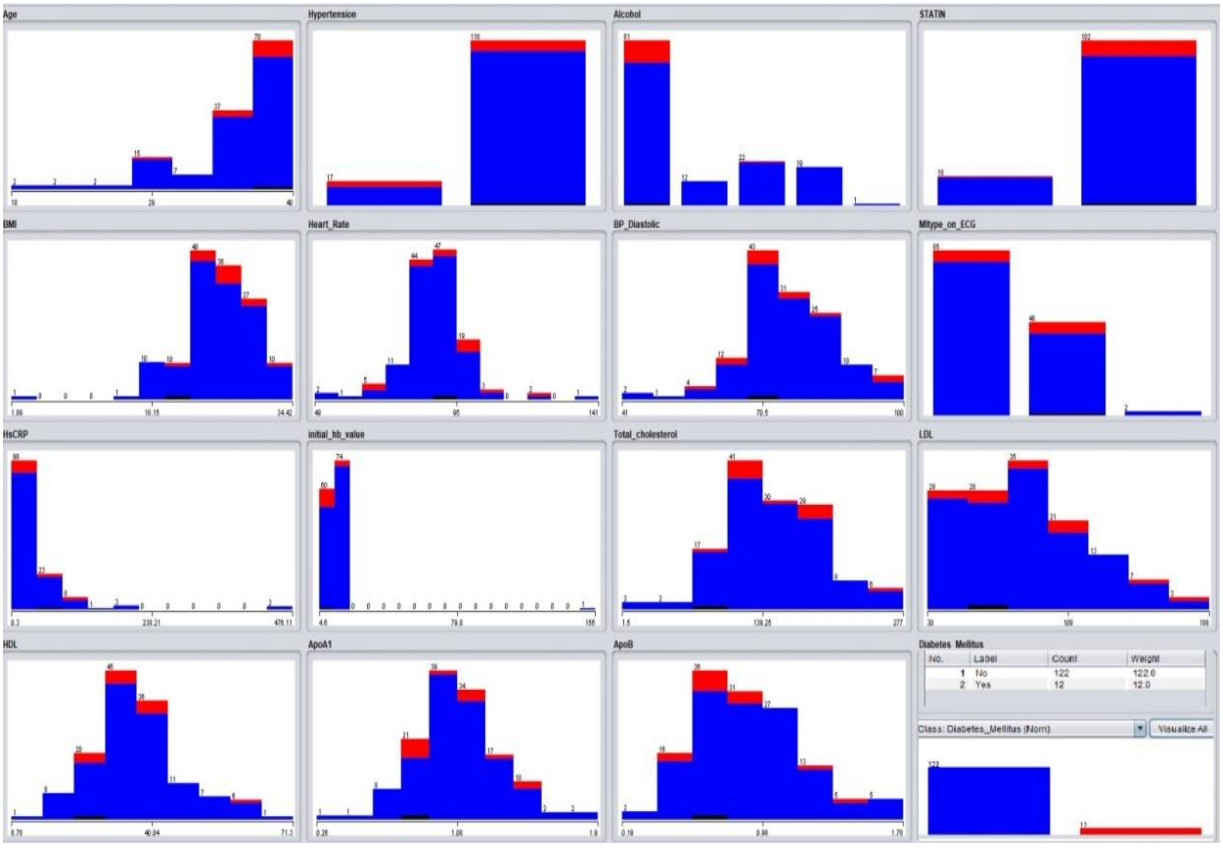

Figure 2. Association of different clinical parameters with diabetes mellitus

In Table 3 and Figure 3, significant rules for {Hypertension=Yes} Rule 6 says that if value of BP Systolic > 131, value of LpA2 >43.2, value of hsCRP >3.71, value of initial creatinine >0.5, and value of initial Hb ≤15 (antecedent), then the patient had an 88% chance of Hypertension (consequent). Frequent Pattern for support value 0.4 to 0.99 (min 40 % to 99% of Hypertension) and confidence (Chance of

occurrence of both Antecedents and Consequents) for valve 0.19 to 0.88 following attributes and their combinations: BP Systolic >102, LpA2 >15.7, hsCRP >1.79, initial creatinine > 0.5, initial Hb ≤15.7, ApoB ≤1.25, ApoA1 ≤1.33, HDL >8.78, LDL ≤115 Total cholesterol >1.5 to ≤229, Physical Activity=No, Heart Rate >77 to ≤103.

Table 3. Significant rules for Hypertension in 135 patients with 34 clinical attributes

Rules	Antecedents (R)	Consequents (S) {hypertension}	Support	Confidence	Lift
R1	{MItype_on_ECG=Inferior Wall MI, BP_Systolic ≤118}	{No}	0.2	1	1.19
R2	{LpA2 ≤39.9, HDL >19.1, Triglycerides >52}	{No}	0.4	1	1.19
R3	{initial_Hb_value >12.6, ApoA1 ≤1.42, initial_creatinine_val ≤1.6, BP_Diastolic ≤92}	{No}	0.6	0.96	1.15
R4	{initial_Hb_value > 11.5, initial_HbA1c ≤12.3, Diabetes_Mellitus=No, BMI ≤32.8125, HsCRP ≤182.01}	{No}	0.8	0.96	1.15
R5	{BP_Systolic ≤144, Followup_status=Alive, LDL ≤148}	{No}	0.9	0.93	1.11
Hypertension = Yes ⇓ R6	{BP_Systolic >131, LpA2 >43.2, hsCRP > 3.71, initial_creatinine_val >0.5, initial_Hb_value ≤15}	{Yes}	0.4	0.88	7.26
R7	{BP_Systolic >122, LpA2 >39.9, hsCRP >2.78, Physical_Activity=No, Total_cholesterol ≤229}	{Yes}	0.6	0.71	5.92
R8	{LpA2 >39.9, BP_Systolic >115, Physical_Activity=No, Total_cholesterol >84, Heart_Rate >77}	{Yes}	0.8	0.4	3.32
R9	{hsCRP >1.79, BP_Systolic >102, LpA2 >15.7, Physical_Activity=No, initial_Hb_value ≤15.7}	{Yes}	0.99	0.2	1.64
R10	{LpA2 >15.7, BP_Systolic >102, Physical_Activity=No, initial_Hb_value ≤15.7, Heart_Rate ≤103}	[Yes}	0.99	0.19	1.57

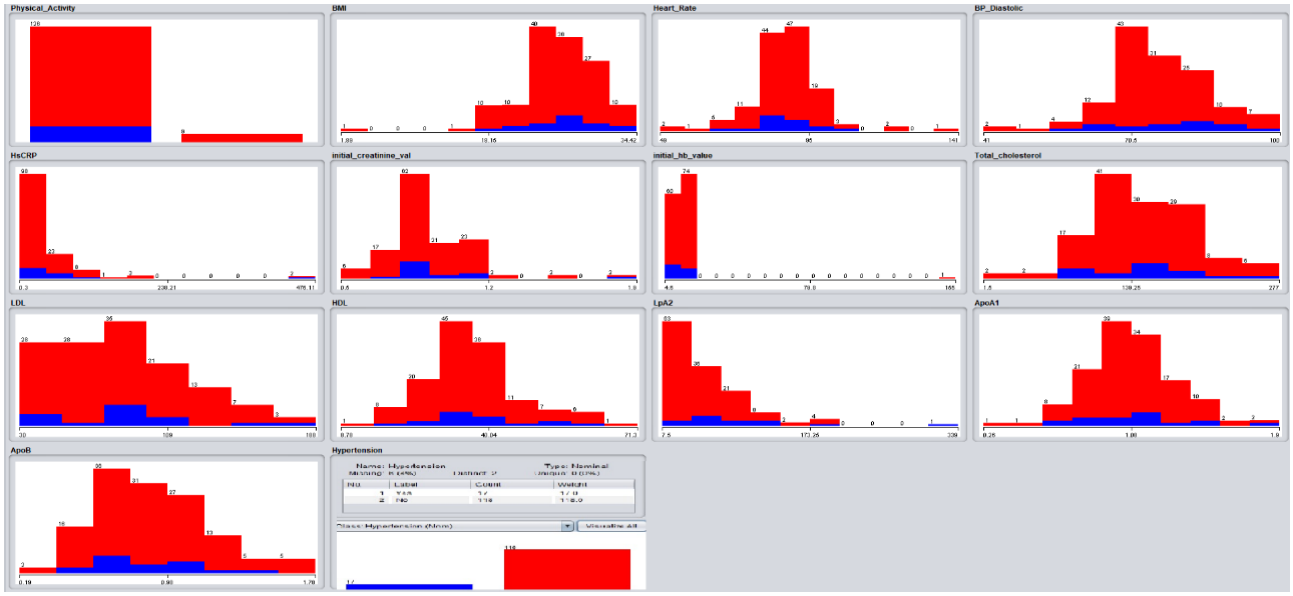

Figure 3 Association of different clinical parameters with hypertension

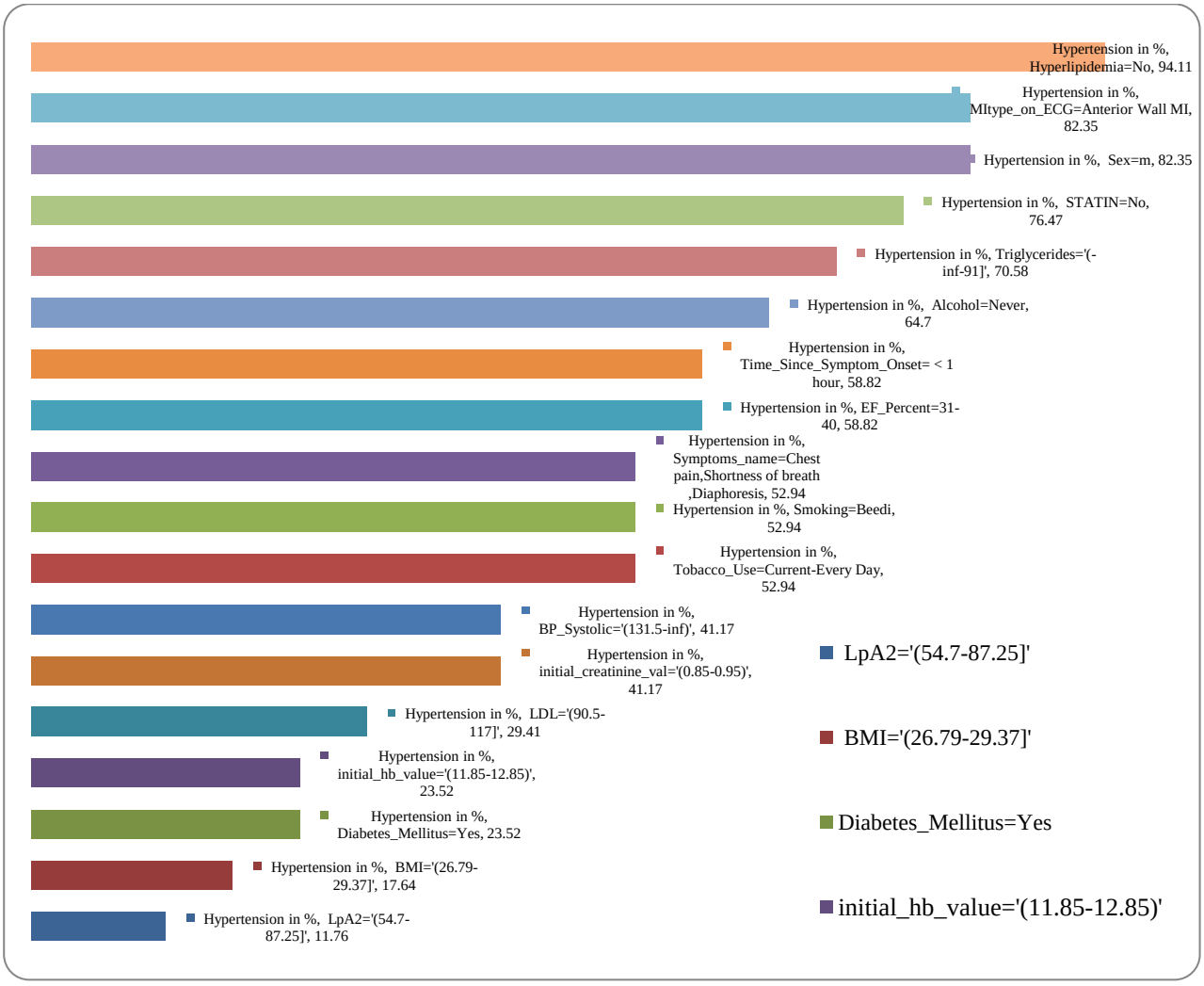

Figure 4. Relative frequency of different parameters for hypertension (N = 135)

DISCUSSION

In this study, 8.9% of the patients were diabetic, 12.6% were hypertensive, and 8.9% had a history of dyslipidemia, which was slightly low in comparison to previous studies where diabetes and hypertension were seen in 14.7 % and 38.1 % of young MI patients, respectively (Chan et al. 2012, McManus et al. 2011). Hypertension is under-diagnosed in young individuals, and if left untreated for a lengthy period, it might lead to a higher risk of MI in this age group (Chan et al. 2006). Although diabetes is less common in young people, it is still a hazard factor for MI in this age group. The adjusted OR of MI among 45-year-old men with diabetes was found to be 8.34% (95 percent CI, 1.67–41.6) as compared to non-diabetic young people (Oliveira et al. 2009). When plasma Lp(a) levels rise, in the absence of other risk factors, the risk of coronary artery disease increases with a high TC/HDL ratio (Dai et al. 2018). In the current study, the average BMI was found to be 25.7±4.31 kg/m^2, with 15.5% of the patients having a BMI of more than 30 kg/m^2. Available data supported our finding that young MI patients had a higher BMI than older MI patients (Hipp et al. 2000).

In our study, we found out various rules of cardiovascular diseases and classified them by finding their lift and confidence. In this paper, Hotspot was used to extract frequent patterns and various promising rules within real medical data. Thirty-four attributes of 135 individual patients were considered for the experiment. The experiment was carried out using the "Weka" tool. Weka is one of the tools used for extracting rules to find out the association between different stored real parameters.

Table 2 lists the ten significant rules for diabetic patients in order of highest support scores. There was a 100 percent certainty that a patient had an HDL value was 28.25 to 33.65 if he or she had a value of “BP Systolic” was 106.5 to 113.5 and Age was more than 39.5. As a result, the patients died. ARM came up with 127 regulations for men and no rules for women. Between the sexes, there was a variance in symptom rules. Figure 2 shows the relative frequency of different parameters for diabetic patients. We can see in the figure that if BMI is ranging between 26.79 to 29.37, then the chances of Diabetes is 33 percent. The association rule in Table 2 and Figure 2 clearly shows that the combination and values of these attributes were responsible for diabetes. This work will be beneficial for understanding patterns of different medical parameters for diabetic patients.

We can see rules in Table 3 and Figure 3 that different medical parameters were responsible for hypertension. For Hypertensive patients, 17% had a BMI value which was greater than 26.7. Similarly, 94% have had Hyperlipidemia, 82% sex was male, 82% had MI type on ECG was Anterior Wall MI, 70% had Triglycerides value below 91, 64% were not consuming alcohol, and 59% had ejection fraction (EF) percent between 31-40. The association rule in Table 3 and Figure 3 shows that the combination of these attributes was responsible for hypertension. Figure 4 shows the Relative Frequency of different parameters in Hypertensive patients. We can see in the Figure that if BMI is ranging between 26.79 to 29.37 then the chance of hypertension is 17.64%.

Strength and limitation

This work contributes to existing studies by further prove the validity of association rule mining in predicting the development of hypertension and diabetes mellitus, especially among myocardial infarction patients. However, as this was a single-center study, the study population might not be diverse and therefore resulted in a lack of universal findings.

CONCLUSION

We conclude that the Hotspot algorithm handles data with real value and generates rules that hold the highest confidence value, lift (>1) assists us in the advanced detection of hypertension and diabetes. In the present study, Diabetes Mellitus has been directly related to the levels of initial hemoglobin, alcohol, ApoB, ApoA1, total cholesterol, BMI, LDL, HDL, hsCRP, heart rate, diastolic blood pressure, age, statin use, and MI type on ECG. ARM techniques identify different patterns and rules to predict the development of diabetes mellitus in myocardial infarction patients. Also, our study finds patterns for hypertension and overall rules among patients, utilizing rules combination of clinical parameters like systolic blood pressure, heart rate, physical inactivity, and serum levels of LpA2, hsCRP, creatinine, hemoglobin, ApoB, ApoA1, HDL, LDL, and total cholesterol in myocardial infarction patients.

Thus, the association rule mining technique could be used to identify patterns utilizing clinical attributes and biochemical laboratory tests to predict the development of hypertension and diabetes mellitus in early-onset myocardial infarction patients.

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Conflict of interest

None.

Funding disclosure

None.

Author contribution

AS, DS, KU,VM, and JS contributed to the conceptualization study, design and methodology. SS,MM and PM were data collection, data analysis. PKD were contributed to the final check the manuscript and grammar.

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Original Research Report

UROGENITAL FISTULA PATIENTS PROFILE AT A TERTIARY HOSPITAL IN SURABAYA, INDONESIA FROM 2015 - 2021

Muhammad Arif Hakim Jamhari[1], Mohammad Ayodhia Soebadi[2], Johan Renaldo[1]

[1]Department of Urology, Faculty of Medicine, Universitas Airlangga/Dr. Soetomo General Academic Hospital, Surabaya, Indonesia
[2]Department of Urology, Faculty of Medicine, Universitas Airlangga/Universitas Airlangga Teaching Hospital, Surabaya, Indonesia

ABSTRACT

A fistula is an extra-anatomical channel between two or more hollow organs, or between an organ and the body surface. WHO estimated there were two million patients with untreated urogenital fistula, with 130,000 new cases every year. The ideal approach for urogenital fistula depends on surgeon preference and individual clinical characteristics. Accordingly, we aimed to determine the profile of patients with a urogenital fistula at a tertiary hospital of Dr. Soetomo General Academic Hospital in Surabaya, Indonesia, from 2015 to 2021. A retrospective study with a descriptive design was carried out by medical records data retrieval of patients with urogenital fistula. It included age, etiology, anatomical location, surgical management, and recurrence rate. The study population consisted of 55 patients. The majority of the patients were among the 41-50 y.o. age groups (41.17%), while the least were in the <20 years group (1.96%). History of obstructed labor was the most common etiology (70.59%). Fistulas in the study population were also associated with a history of trauma (15.68%) and malignancy (11.76%). The vesicovaginal fistula was the most common type of fistula (88.23%). Other types found include urethrovaginal, ureterovaginal, rectovesical, rectovaginal, and vesicocolon fistulas. The transvaginal approach was preferred in almost all study populations. A total of two cases of vesicovaginal fistula recurred (3.39%). In general, patients with urogenital fistula are prevalent in the 4th decade age group, with the most common etiology being a history of obstructed labor. Transvaginal surgery is the treatment of choice with good results and low recurrence rates.

Keywords: *Urogenital fistula; vesicovaginal fistula; transvaginal repair; illness*

Correspondence: Johan Renaldo, Department of Urology, Faculty of Medicine, Universitas Airlangga/ Dr. Soetomo General Academic Hospital, Surabaya, Indonesia. E-mail: joeurologi@gmail.com

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Highlights:

1. Vesicovaginal fistula is the most common urogenital fistula.
2. The transvaginal approach is preferred in treating urogenital fistula.

INTRODUCTION

A fistula is an extra-anatomical channel between two or more hollow organs, or between an organ and the body surface. It estimated to account for l–4% all urogenital fistulas cases (Alamoudi et al. 2017, Harzif et al. 2021). The classification of fistulas is generally based on the origin of an involved organ or anatomical location and the point of termination, where the abnormal channel could develop in several adjacent structures. As such, urogenital fistula in women is defined as an abnormal channel that forms between the urinary tract (urethra, bladder, ureter) and gynecological organ (vagina, uterus) (Abrams et al. 2012).

Bodner-Adler et al. (2017) reported a success rate equal to 93.8% in a systematic review and meta-analysis of the management of vesicovaginal fistulas in women following benign gynecological surgery. Clinical manifestations among patients vary based on the urinary tract involved. Fistula can greatly affect the patient's quality of life, in terms of functional and psychological well-being (Hilton 2016).

The global prevalence of urogenital fistulas is unknown, but the World Health Organization (WHO) estimates that there are two million women with untreated urogenital fistulas, with 130,000 new cases each year (Abrams et al. 2012). In developing countries, fistula is a consequence of poor perinatal care and is directly related to one of the major risks of mortality in pregnant women, specifically prolonged or obstructed labor. Urogenital fistula is also considered a difficult complication of urological and obstetric-gynecological procedures, especially in countries with inadequate standards of antenatal and obstetric care (Mocumbi et al. 2017). However, obstructed labor is still regarded as the main factor which contributes to the development of urogenital fistula, besides medical intervention or iatrogenic causes (Tasnim et al. 2020).

The ideal surgical repair approach for urogenital fistula depends on surgeon preference and individual clinical

characteristics. Several factors can affect the success of fistula repair. Accordingly, we aimed to determine the profile of patients with a urogenital fistula at a tertiary hospital of Dr. Soetomo General Academic Hospital in Surabaya, Indonesia from 2015 to 2021.

MATERIALS AND METHODS

Our study was a descriptive study with a retrospective design. It was conducted by collecting the data, so that several outcomes can be compared simultaneously. Usually, a retrospective study uses existing data that have been recorded for reasons other than research (Hess 2004). The data were collected from the medical records of urogenital fistula patients treated in the urology ward of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia from January 2015 to December 2021. The data collected were grouped according to age, location, etiology, and management. All the grouping results are displayed descriptively in the form of tables and narratives. The research data obtained are displayed descriptively in diagrams and narration. The inclusion criteria of this study were patients with a diagnosis of urogenital fistula who were treated and received therapy in the urology ward of Dr. Soetomo General Academic Hospital, Surabaya. Meanwhile, the exclusion criteria were patients with a urogenital fistula diagnosis not treated in the Urology ward of Dr. Soetomo General Academic Hospital Surabaya.

RESULTS

There were 51 patients with urogenital fistula treated in the Urology ward of Dr. Soetomo Hospital in the period between January 2015 to December 2021. The youngest patient was 17 years old, while the oldest patient was 85 years old. Table 1 shows that the age group with the highest number of cases was 41 to 50 years (41.17%), while the lowest number of cases was found in patients aged less than 20 years (1.96%).

The etiology of most urogenital fistulas is due to prolonged labor (70.59%), followed by trauma (15.68%) and malignancy (11.76%), as shown in Table 2. Table 3 shows vesicovaginal as the most common anatomic location as the site of pathology (88.23%). Ureterovaginal and ureterouterine fistulas were the rarest types, with only 1 patient in each group. All fistula-type fistulas reported were treated using a transvaginal approach. The fistula recurrence was found in only 2 vesicovaginal cases (3.39%) as shown in Table 4.

Table 1. Age distribution of urogenital fistula patients

Age	Urogenital fistula (n = 51)
<20 years old	1
20-30 years old	8
31-40 years old	10
41-50 years old	21
51-60 years old	9
>60 years old	2

Table 2. Etiology of urogenital fistula cases in research subjects

Etiology	Urogenital fistula (n = 51)
Obstructed labor	36
Trauma	8
Malignancy	6

Table 3. Types of urogenital fistula based on anatomical location

Type of urogenital fistulas	Number of cases (n = 51)	Surgical approach
Vesicovaginal	45	Transvaginal
Urethrovaginal	4	Transvaginal
Ureterovaginal	1	Transvaginal
Ureterouterine	1	Transvaginal

Table 4. Urogenital fistula recurrence rate

Type of urogenital fistulas	Recurrence rate
Vesicovaginal	2
Urethrovaginal	0
Ureterovaginal	0
Ureterouterine	0

DISCUSSION

Urogenital fistula is relatively uncommon in well-resourced countries. Successful repair remains a challenge for specialists (Wall 2006). Moreover, in many so-called low-resource countries, obstetric fistulas are still very common (Danso et al. 1996). This is due to differences in access to obstetric care, as surgical etiology is more common in well-resourced countries. The majority of surgical fistulas are associated with gynecological procedures, especially with hysterectomy (Harkki-Siren et al. 1998). However, there have not been many studies that have focused on urogenital fistulas in general, especially in Indonesia. In 2016, there was a similar study conducted at Cipto Mangunkusumo Hospital, Jakarta, which reported urogenital cases that occurred during 2011-2016, with previous study also documented cases from 1998-2008 (Djusad et al. 2016, Taher et al. 2013). Dr. Soetomo General Academic Hospital, Surabaya, is the largest general hospital in East Java, and the top

referral hospital for the eastern part of Indonesia (Widarta et al. 2015).

In our study, the total number of urogenital fistula patients from January 2015 to December 2021 was 51. The patients in this study were women with an age range of 17-85 years, with the age group with the most frequent cases of urogenital fistula being 41 to 50 years (41.17%). This finding was in contrast to the research conducted by Saeed et al. (2016) where most patients with urogenital fistulas were in the group with an age range of 20 to 30 years (Saeed et al. 2016), while in our study, urogenital fistula found in patients in this age range was only 15.68%.

The most common cause that we found in cases of urogenital fistula during the last 7 years was obstructed labor. This was in line with the studies that we found in developing countries, which stated that the most common causes of urogenital fistulas were uterine cases, such as obstructed labor (Pradhan et al. 2020, Saeed et al. 2016). Even in the research conducted by Mocumbi et al. (2017), it was also found that obstructed labor was the leading cause of urogenital fistulas (Mocumbi et al. 2017). Fistula cases in developing countries can be found in every 1000 deliveries, with a prevalence of about 0.1% to 0.5% per 1000 pregnancies. This number may not represent the true number of cases due to high undetected urogenital fistula cases (Hillary et al. 2016).

The proposed causes other than obstructed labor are related to pelvic surgery. However, trauma is also one of the reasons for the occurrence of urogenital fistulas in developed countries, such as iatrogenic trauma after a hysterectomy surgery, which is the most common cause of urogenital fistulas in the UK (Hilton 2016), and female genital mutilation, which was found to be a significant risk factor for the occurrence of urogenital fistulas obtained in a study in Turkey (Birge et al. 2016). Additionally, urological procedures for distal ureteral stones can also cause this condition (Lo et al. 2019).

The most common location for urogenital fistulas in our study was the vesicovaginal area. A vesicovaginal fistula is a distressing condition with abnormal communication between the vagina and bladder, leading to urinary incontinence, resulting in continuous urine leakage through the vagina (Malik et al. 2018, Medlen & Barbier 2022). Vesicovaginal fistula is rare in the developed world. It also remains one of the most significant global public health challenges. It has a much higher prevalence in the underdeveloped and developing parts of the world (Eilber et al. 2003). However, the prevalence and incidence in females worldwide are difficult to pronounce, given the significant stigmatization in many populations (Medlen & Barbier 2022).

It is estimated that there are 2-3 million women with untreated fistulas worldwide, and about 30,000-130,000 new cases occur annually, of which > 95% are in developing countries (Abrams et al. 2012). Surgical approaches that can be used to manage urogenital fistulas are divided into a transvaginal approach, transvesical approach, transabdominal approach, laparoscopic approach, and robotic-assisted repair (Ghoniem & Warda 2014, Milani et al. 2018, Purkait et al. 2017, Talla et al. 2017).

The most common method used to manage simple urogenital fistulas is the transvaginal approach. Although the fistula was located near the vaginal stump, it could be well elevated with a surgeon's finger in the rectum. Thus, the vaginal and rectal walls could be mobilized and separated adequately, and the fistula between these walls could be securely sutured without tension. In similar situations, transvaginal simple closure has a high probability of success.

The repair approach should be decided on a patient-by-patient basis. Consultation to gastrointestinal surgeons can be done if necessary (Matsuyama et al. 2022). Meanwhile, currently, the transvesical approach is rarely used, and the indication for a transabdominal approach is for complex fistulas, which require the interposition of a tissue flap between the bladder and vagina (Hadzi-Djokie et al. 2015, Stamatakos et al. 2014). Most surgical approaches performed at this center for urogenital fistulas are transvaginal approaches.

Complications of urogenital fistula include frequency disturbances, urgency, urgency incontinence, recurrence, stress urinary incontinence, ureteral obstruction, and bowel obstruction (Ghoniem & Warda 2014). In our study, we found 2 cases of recurrence (3.92%), which only occurred in the vesicovaginal urogenital fistula type. Recurrent fistulas may appear within 3 months of primary repair. The abdominal approach is usually preferred in patients with large fistulas (more than 3 cm), supraregional fistulas, fistulas near or involving the ureteral orifice, and recurrent fistulas after transvaginal repair.

Strength and limitation

Our study had many limitations, including the small number of urogenital fistulas recorded in the center. Therefore, further studies are needed to assess the overall profile and distribution of urogenital fistulas in Indonesia, and even in the world. It would be even better if a similar study could be conducted in major education centers in Indonesia to obtain accurate data on the prevalence and epidemiology of urogenital fistulas. Discussions related to risk factors or comorbidities would also be much better if included in future research.

CONCLUSION

Urogenital fistula cases in a female patient treated at Dr. Soetomo Hospital, a tertiary referral hospital, are mainly found in patients over 40 years, with the most common etiology related to obstetric causes or prolonged labor. Repair measures with a transvaginal approach can treat various types of urogenital fistulas, including vesicovaginal fistulas, urethrovaginal fistulas, ureterovaginal fistulas, and ureterouterine fistulas. The low recurrence rate indicates that the management of cases of urogenital fistula at this tertiary referral hospital brings satisfactory results.

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Conflict of interest

None.

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None.

Author contribution

MAHJ and MAS was contributed the study's design, data collection, and data analysis. JR made intellectual revisions to the study and gave the final approval for publication

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Original Research Report

SPIKE-RECEPTOR BINDING DOMAIN (SRBD) ANTIBODIES SECRETION IN COVID 19 SURVIVORS AND NON-SURVIVORS POST-PRE-ENDEMIC VACCINATION

Museyaroh, Evy Diah Woelansari, Dwi Krihariyani

Department of Medical Laboratory Technology, Health Polytechnic Ministry of Health Surabaya, Surabaya, Indonesia

ABSTRACT

The development of a vaccine for SARS-COV-2 began in mid-2020 with the aim of stimulating an individual's immune response against SARS-CoV-2 infection. The purpose of this study was to determine the levels of post-vaccine SRBD antibody secreted in COVID-19 survivors and non-survivors. Antibodies are considered to play a more important role in evaluating immunity because antibody tests may provide information about a person's immune status against SARS-CoV-2. The study was conducted at Husada Utama Hospital, Surabaya, Indonesia, in April – May 2021. The samples were taken prospectively with a total sample of 60 patients, consisting of 40 non-survivors and 20 survivors of COVID-19 who had received Sinovac vaccine doses 1 and 2. Examination of Sars-CoV-2 SRBD antibody was conducted by using CL series of Mindray device by means of CLIA method. The average level of antibody was assessed in each sample group and the results were subjected to the Mann Whitney test. The mean SRBD antibody level in female patients was 428.24 ± 271.25, while in male patients it was 310.40 ± 113.71 U/mL. The results of the Mann Whitney test revealed a P-Value of 0.09 > 0.05, indicating no difference in post-vaccine SRBD antibody levels between females and males, but there were differences in SRBD antibody levels in COVID-19 survivors and non-survivors with a P-Value of <, i.e. 0.00 < 0.05 There was no difference in post-vaccine SRBD antibody levels between females and males in COVID-19 survivors and non-survivors, but there were differences in post-vaccine antibody levels between COVID-19 survivors and non-survivors.

Keywords: *COVID-19; SRBD; virus; good health and well-being; vaccine*

Correspondence: Museyaroh Muza, Department of Medical Laboratory Technology, Health Polytechnic Ministry of Health, Surabaya, Indonesia. Email: museyaroh21@gmail.com

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Highlights:

1. The research this for determine the presence of immune response post-vaccine
2. The results of this study indicate that there are differences in immune responses, in survivors patients have higher SRBD antibody levels than non-survivors

INTRODUCTION

Globally, the COVID-19 pandemic is still ongoing, including in Indonesia. As of April 13, 2022, the number of confirmed cases of COVID-19 in Indonesia was 6,036,909 people with recovered cases of 5,814,688 people (96.3%) and a death rate of 155,746 people (2.6%) (World Health Organization 2022). Clinical manifestations of COVID-19 can develop into pneumonia, respiratory failure, and even death (Özdemir 2020). About 80% of the cases are classified as mild or moderate and 13.8% experience severe illness, and 6.1% of patients fall into a serious critical condition (Han & Yang 2020). Deterioration and death generally occur in older people with the congenital disease (50-75%) (Özdemir 2020).

The spread of SARS-CoV-2 from human to human became the main source of transmission so the spread became more aggressive (Susilo et al 2020). Transmission of SARS-CoV-2 from symptomatic patients occurs through droplets released from a person infected with the SARS-CoV-2 virus when coughing or sneezing (Ong et al. 2020). The SARS-CoV-2 virus can transmit viable aerosols (generated via a nebulizer) for at least 3 hours (van Doremalen et al. 2020). Lung epithelial cells are the main target of the SARS-CoV-2 virus, in some cases, it has been reported that SARS-CoV-2 transmission from human to human occurs through the binding of the Receptor Binding Domain (RBD) and cellular receptors belonging to the host cell, namely the Enzyme Modifier. Angiotensin 2 (ACE2) (Rothan & Byrareddy 2020).

The development of a vaccine for SARS_COV-2 began in mid-2020 with the aim of stimulating an individual's immune response to SARS-CoV-2 infection. In early 2021, the government began implementing a community vaccine program with the priority for the health workers. In this first stage, the vaccine used was an inactivated vaccine platform (Irsan et al. 2022). Viruses that infect the body will carry antigens that will be recognized by the body's immune system. Vaccines containing attenuated viruses or parts of viruses that are not pathogenic (antigens) can trigger an immune

response in the body that receives the vaccine 2 by the formation of antibodies (Rotty et al. 2022).

The antibody test for SARS-CoV-2 aims to detect the body's immune response to infection with the SARS-CoV-2 virus either naturally or due to vaccination (Röltgen & Boyd 2021). The antibodies that can be detected are antibodies to the spike protein (S) and the nucleocapsid protein (N) of the SARS-CoV-2 virus, while based on their effects, the antibodies are divided into two. The first one is the Neutralizing Antibody (NAb), which is an antibody that works by blocking the bond between the pathogen and the host cell, while the second one is the non-neutralizing antibody (non-NAb) is an antibody that acts by other mechanisms (opsonization, complement activation, antibody-dependent cellular cytotoxicity (ADCC). These non-NAbs include antibodies to proteins N (anti-N) and against S proteins other than RB. In SARS-CoV-2 infection, NAb primarily refers to antibodies to the Receptor Binding Domain (RBD) subunit of the Spike-Receptor Binding Domain (S-RBD). However, not all S-RBD antibodies have a neutralizing effect. Neutralizing SARSCoV-2 antibodies are found in the form of IgG, IgM, and IgA (Pang et al. 2021).

Monitoring antibody levels in post-vaccinated patients is very important to determine the effectiveness of the vaccine, especially for health workers at the frontline of the COVID-19 pandemic (Choi & Cheong 2021). However, the current protective resistance of existing vaccines is unknown and the nature of the antibody cycle decreases over time. Therefore, the purpose of this study was to determine the difference in the levels of post-vaccine Spike-Receptor Binding Domain (S-RBD) antibody in COVID-19 survivors and non-survivors because Spike-Receptor Binding Domain (S-RBD) antibody examination is considered to play a more important role for the purpose of evaluating immunity as this test is capable to provide information about a person's immune status against SARS-CoV-2 (Xu et al. 2020).

MATERIALS AND METHODS

This was a descriptive-analytic study using the cross-sectional method. This study was conducted at Husada Utama Hospital Surabaya, Indonesia, in May – June 2021. The samples were taken prospectively with a total sample of 60 samples consisting of 40 non-surviving and 20 surviving COVID-19 patients. Sixty patients had received Sinovac vaccine doses 1 and 2. The samples were taken ± 3 weeks after vaccine dose 2 and Sars-CoV-2 SRBD antibody examination using CL series of Mindray device with Chemiluminescent Immunoassay (CLIA) method. Assessment of the average level of antibody in each sample group was performed, and the results were subjected to Mann Whitney statistical test using IBM SPSS Statistics 26.

RESULTS

Of 60 COVID-19 patients involved as samples in this study, 40 were non-survivors, consisting of 31 females and 9 males, while 20 were survivors consisting of 16 females and 4 males (Figure 1).

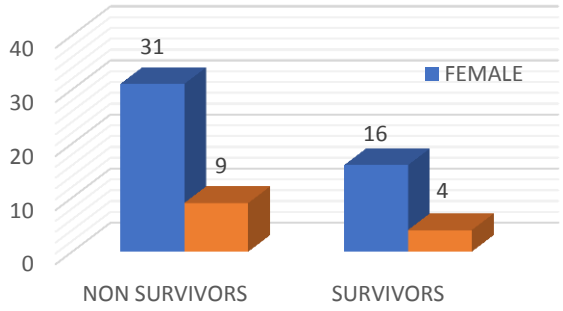

Figure 1. COVID-19 survivors and non-survivors' gender

Table 1 explains post-vaccine SRBD antibody levels for survivors of COVID-19. The average SRBD antibody level in females was 428.24 ± 271.25 U/mL with a maximum level of 1000.00 U/mL and a minimum level of 172.10 U/mL, while in males, the average SRBD antibody level was 310.40 ± 113.71 U/mL with the maximum level of 458.80 U/mL and the minimum level of 187.22 U/mL.

Table 1. Levels of post-vaccine SRBD antibodies among COVID-19 survivors based on gender

	Mean ± SD (U/mL)	Maximum (U/mL)	Minimum (U/mL)
Female	428.24 ± 271.25	1000.00	172.10
Male	310.40 ± 113.71	458.80	187.22

Post-vaccine SRBD antibody levels in COVID-19 non-survivors showed that the average SRBD antibody levels in female patients were 60.06 ± 30.94 U/mL with a maximum level of 117.99 U/mL and a minimum level of 14.53 U/mL, while in males, the average level of SRBD antibody was 37.38 ± 17.82 U/mL with the maximum level of 72.81 U/mL and the minimum level of 7.30 U/mL (Table 2)

Table 2. Levels of post-vaccine SRBD antibody among COVID-19 non-survivors by gender

	Mean ± SD (U/mL)	Maximum (U/mL)	Minimum (U/mL)
Female	60.06 ± 30.94	117.99	14.53
Male	37.38 ± 17.82	72.81	7.30

Mann Whitney test revealed the p-value of 0.09 > 0.05, indicating no difference in post-vaccine SRBD antibody levels in female and male COVID-19 survivors, while for non-COVID-19 survivors the P-value was 0.75 > 0.05, indicating no difference in post-vaccine SRBD antibody levels between female and male patients.

Table 3. Levels of post-vaccine SRBD antibody in doses 1 and 2

	Mean ± SD (U/mL)	Maximum (U/mL)	Minimum (U/mL)
COVID-19 survivals	404.67 ± 55.88	1000	172
COVID-19 non-Survivals	54.96 ± 4.72	117.99	7.30

The average post-vaccine SRBD antibody level in COVID-19 survivors was 404.67 ± 55.88 U/mL with a maximum value of 1000 U/mL and a minimum value of 172 U/mL while the post-vaccine SRBD antibody level in non-COVID-19 survivors was 54.96 ± 4.72 U/mL with a maximum value of 117.99 U/mL and a minimum value of 7.30 U/mL. Kolmogorov-Smirnov normality test revealed a p-value of 0.03 < 0.05, indicating that the data were not normally distributed so it was followed with the Mann Whitney test and the results of the p-value were 0.00 < 0.05, indicating differences in the levels of post-vaccine SRBD antibody between COVID-19 survivors and non-survivors. COVID-19 survivors had higher SRBD antibody levels than non-COVID-19 survivors.

DISCUSSION

In this study, among COVID-19 survivors and non-survivors who had received Sinovac 1 and 2 vaccines, there were more female than male patients. This could be because there were more female than male populations who had received the vaccines. In contrast, Hidayati (2020) found that in Indonesia male-dominant population confirmed positive COVID-19. They made up more than half of the total patients confirmed with COVID-19. Clinical manifestations in male patients were much worse than in female patients. The percentage of male patients who died was much higher than of female patients. This may be related to cigarette smoking habit, which was more often in males than in females, resulting in worse respiratory tract disease among male patients (Rothe et al. 2020). Mann Whitney statistical test showed no differences in post-vaccine SRBD antibody levels between females and males, but there were differences in post-vaccine SRBD antibody levels in COVID-19 survivors and non-survivors. The Average post-vaccine SRBD antibody levels were higher in COVID-19 survivors.

SARS-COV-2 has 4 structural proteins Spike (S), Membrane (M), Envelope (E), and Nucleocapsid (N) proteins. S protein role in receptor binding and fusion. This protein is encoded by the S gene and is functionally divided into 2 subunits, namely S1 role in binding to ACE2 receptors while S2 role in fusion. N protein has an important role in viral pathogenesis, replication, and RNA packaging. Antibodies to N protein are frequently detected in COVID-19 patients (Tang et al. 2020, Chen et al. 2021).

Antibodies to the SARS-CoV-2 virus are acquired either naturally by SARS-CoV-2 virus infection or due to vaccination. The difference in antibody levels between COVID-19 survivors and non-survivors is related to the immune response to COVID-19 when the virus enters the host (Takita et al. 2022). Spike protein portion of the virus binds to the ACE2 receptor after replicating in the viral host cell and then detaches itself and is phagocytosed by Antigen Presenting Cells (APCs), such as macrophages or dendritic cells, then antigens from SARS-CoV-2 are presented to helper T cells which then will activate B cells. The activated B cells will proliferate and differentiate into plasma B cells and memory B cells. The plasma B cells then release specific receptors in the form of antibodies, the IgM, IgG, or IgA. SARS-CoV-2 (Lee et al. 2010). The significant increase in SRBD antibodies in COVID-19 survivors could be due to memory B cells having recognized antigens from SARS-CoV-2 vision so that when a similar antigen enters the body, the body's immune response will quickly release antibodies. Examination of SRBD antibody levels after vaccination can be one way of monitoring antibody responses in individuals, especially in someone who has a high risk of being exposed (Deshpande et al. 2021).

The S (spike) and RBD (receptor binding domain) proteins in SARS-CoV-2 are the main targets for vaccine manufacture, because the specific antibodies formed against these proteins can prevent the virus from binding to the Angiotensin-Converting Enzyme 2 (ACE2) receptor as a port of entry into the immune system in the host cell. This has resulted in the development of various antibody titer tests using protein S and RBD targets. In Indonesia, in the early stages of the government's public vaccination program, vaccines with an inactivated vaccine platform were

used. This vaccine is known to exhibit good immunogenicity by inducing neutralizing antibodies against SARS-CoV-2, and this vaccine has been effectively preventing COVID-19 and death caused by SARS-CoV-2 infection. B and plasma cells are some important keys in the immune system against SARS-CoV-2 infection (Jin et al. 2020). According to several studies, there are differences in the speed of antibody formation in each individual. According to Barbosa et al. (2020), the rate of increase in SARS-CoV-2 antibodies is different for each individual. In patients with mild clinical symptoms, specific antibodies appear earlier, usually on day 7 when IgM is lower and IgG continues to increase. In patients with severe clinical symptoms of SARS-CoV-2, antibody seroconversion appears longer usually on day 12 and IgM continued to increase. Meanwhile, in COVID-19 patients, it occurs between 7-12 days after the onset of symptoms, generally IgM is produced first and IgG is produced later. The presence of IgG lasts a long time in the body (Hoffman et al. 2020). Hsueh et al. (2004) emphasized that the increase in IgG occurred on average 10 days after the onset of clinical symptoms in COVID-19 patients and the peak of this antibody seroconversion was in 15 days. According to Dohla et al. (2020), seroconversion occurs sequentially for IgM and then IgG with a median time of 11 and 14 days, respectively, so if the sample is taken less than that time, it is likely that antibodies have not been formed and the test results will be false negative. IgM can be detected in the blood of a person infected with the SARS-CoV2 virus for 3-6 days after the onset of clinical symptoms and IgG can be detected 8-13 days after infection with the SARS-CoV-2 virus (Long et al. 2020). Therefore, it is important to monitor the antibody levels of post-vaccinated patients to determine the effectiveness of the vaccine, especially for health workers who are at the forefront of handling COVID-19 and as an evaluation of whether an individual should be re-vaccinated or not (Li et al. 2020).

Stregth and limitation

This study stimulates an individual's immune response against the virus. The methods used to examine the SRBD antibody levels add to the scientific rigor of the study. The study was conducted at a single hospital in Indonesia, which may limit the generalizability of the findings to other populations.

CONCLUSION

There are no differences in post-vaccination Spike-Receptor Binding Domain (SRBD) antibody levels between females and males. There were differences in SRBD antibody levels in post-vaccination between survivors and non-survivors. COVID-19, COVID-19 survivors have higher SRBD antibody levels than non-COVID-19 survivors.

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Conflict of interest

None.

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Author contribution

M: conceptualization, methodology, investigation, writing-reviewing editing, software, data curation, and writing-editing, methodology, EDW: Validation and Editing–reviewing, DK: validation.

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Case Report

UNUSUAL CHOANAL ATRESIA IN CHILDREN

Yunis Sucipta Ibnu, Irwan Kristyono
Department of Otorhinolaryngology-Head and Neck Surgery, Faculty of Medicine, Universitas Airlangga/ Dr. Soetomo General Academic Hospital, Surabaya, Indonesia

ABSTRACT

Choanal atresia is a developmental failure of the nasal cavity to connect with the nasopharynx. The cause is either unilateral or bilateral nasal obstruction. Bilateral choanal atresia is a very rare condition and diagnosed soon after birth because neonates are obligate nasal breathers. Delayed diagnosis can cause death due to respiratory distress. The objective of this study was to report bilateral choanal atresia in 5-year-old boy who survived by breathing through his mouth using a simple tool made by his parent. It was a very rare condition because the posterior nasal cavity was covered by medial wall malformations of both maxillary sinuses which fused with the posterior nasal septum. The surgery method for this patient was posterior septectomy with transnasal endoscopic to create a neochoanae. The post-operative patient could breathe normally through his nose. Six weeks later, the nasal endoscopic evaluation indicated the patient's patent neochoana.

Keywords: *Bilateral choanal atresia; children; posterior septectomy; human and health*

Correspondence: Yunis Sucipta Ibnu, Department of Otorhinolaryngology Head and Neck Surgery, Faculty of Medicine, Universitas Airlangga/ Dr. Soetomo General Academic Hospital, Surabaya, Indonesia. Email: yunis.dr@gmail.com

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Highlights:

1. Unusual CA in a 5-year-old boy with paranasal sinuses malformation in the ORL-HNS.
2. Transnasal endoscopy posterior septectomy was successfully done.

INTRODUCTION

Choanal atresia (CA) is a rare case, with only 10 cases reported in literatures (Anajar et al. 2007; Verma et al. 2016; Kars et al. 2020; Tatar et al.2012). Choanal atresia is a failure in connecting the nasal cavity to the nasopharynx. It occurs in 1:8000 of live births, more prevalent in women than men, 2:1 respectively (Sutikno & Thaufiqurrakhman 2021).

Choanal atresia is a relatively uncommon but well-recognized condition characterized by the anatomical closure of the posterior choanae in the nasal cavity. The posterior choanae anatomic boundaries include the undersurface of the body of the sphenoid bones superiorly, the medial pterygoid lamina laterally, the vomer medially, and the horizontal portion of the palatal bone inferiorly. The actual narrowing could be caused by one of the abovementioned bony components. Correctly identifying and addressing the point of obstruction is the key to surgical success.

teristics of CA follow a "2–1" rule, namely the ratio of unilateral to bilateral CA, female to male, and the right-sided to left-sided CA (Hengerer et al. 2008). It is a very rare condition that causes a blocked nose, due to the failure of posterior choanal formation. Roederer first described the discovery of this disease in 1755 (Flake & Ferguson 1964). Emmert et al. were the first to demonstrate the use of curved trochar in transnasal repair of bilateral CA in a 7-year-old boy (Kwong 2015). This malformation occurs in 1 out of 5,000-7,000 births with a female and male ratio of 2:1. Neonates are obligate nose breathers so bilateral CA results in fetal severe respiratory distress (Leung et al. 2014).

The diagnosis is confirmed by nasal endoscopy and CT scan. This malformation requires immediate treatment. Repair of CA can be done with transnasal puncture technique, transpalatal, or transnasal endoscopy (Kwong 2015).

This was a case report of a male neonate with CA that survived his 5 years of life and underwent repair with posterior septectomy technique using a transnasal endoscopy approach. Surgery for CA is performed under general anesthesia. A self-retaining nasal speculum is used to expose the nasal cavity and the atretic plate (Balasubramanian 2015). The case in this study was very interesting because of the unusual anatomical malformations of the patient's nasal cavity.

CASE REPORT

A 5-year-old boy came to the outpatient ORL-HNS Department of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, on Ma 3, 2017, with nasal obstruction since birth, came out with clear and dilute liquid from both nostrils, distorted odor, and widening nose (Figure 1).

Figure 1. Clinical appearance of the patient.

From history-taking, there was no problem during pregnancy and delivery. The patient was born at a primary medical service in Maluku and got helped by a midwife. After the birth, the patient was not crying and had cyanosis with no spontaneous breath from the nose. The patient's father put his finger within the baby's mouth to support breathing. To replace his father's fingers, he made rolled gauzes (Figure 2). Then the patient was consulted to higher medical service and obtained oxygen support. When he was 3 months old, a pediatrician tried to insert a nasogastric tube but failed. The pediatrician suggested performing another diagnostic at a higher medical service in Java. In the ORL-HNS Department of Dr. Soetomo General Academic Hospital, the patient was diagnosed with CA and Congenital Talipes Equinovarus (CTEV). The previous doctor decided to correct CTEV first and then the choanal atresia when the patient was older.

Figure 2. McGovern nipple was made personally by the patient's parents.

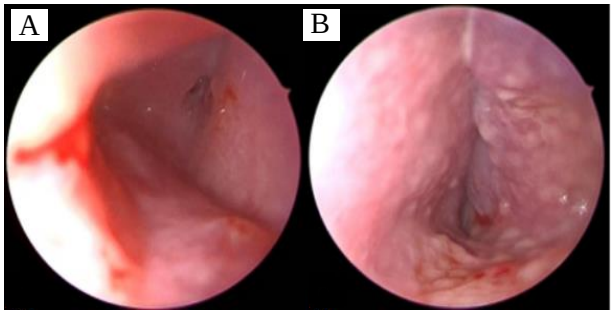

Figure 3. Pre-operative nasoendoscopy of right (A) and left (B) nasal cavity.

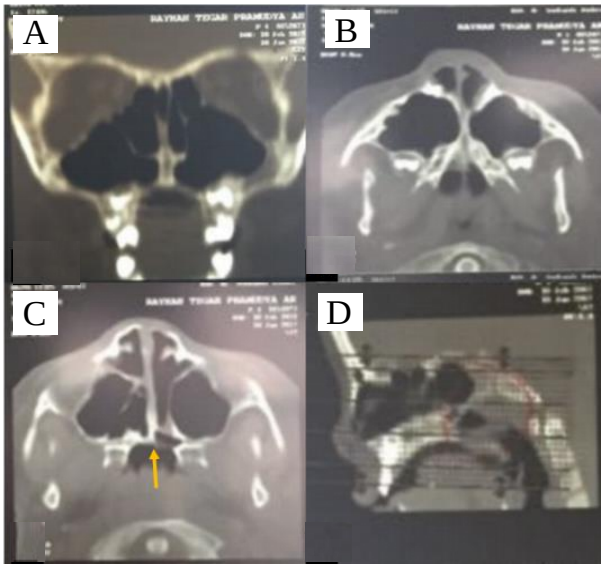

Figure 4. Paranasal sinuses CT scan. Coronal (A), axial (B, C), and sagittal views show bone-type choanal atresia with true choanal behind the malformation paranasal sinuses (yellow arrow).

From the physical examination, anterior rhinoscopy of the nasal cavity appeared narrow. Right, left middle, and inferior turbinates were not found. Medial walls malformation of both maxillary sinuses that merge with a posterior nasal septum in medial line indicated no defect of the palate. Pre-operative nasoendoscopic exploration confirmed the anterior rhinoscopy findings (Figure 3).

The CT scan result on January 10, 2017 from Soebandi Hospital when the patient was 5 years old showed that both maxillary antrum medial walls merged to nasal septum with the entire sinus walls intact. The structure covered the true choana on the posterior aspect. This finding supported the claim of bony type bilateral CA with paranasal sinuses malformation (Figure 4).

The surgery was done in two steps. First, surgery was performed on July 28, 2017 to break down both left and right medial wall maxillary sinuses. We made a wider passage by drilling the thick nasal floor and reducing the

malformed mucosa on both nasal cavities in the next surgery (Figure 5).

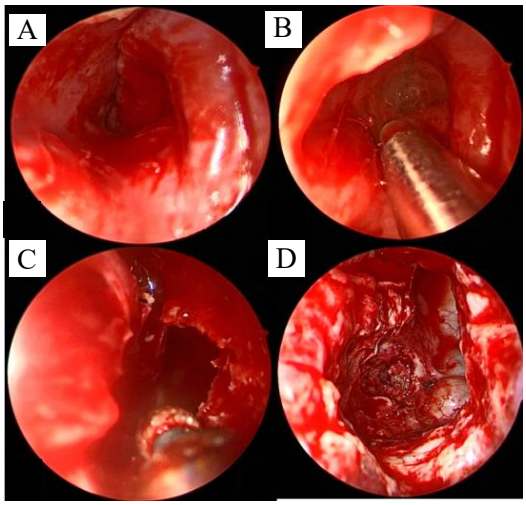

Figure 5. First surgery for malformed nasal floor(A). In the next step, we made a wider passage by drilling malformed nasal floor (B) and breaking down both maxillary sinuses (C). The nasal cavity (D) became wider.

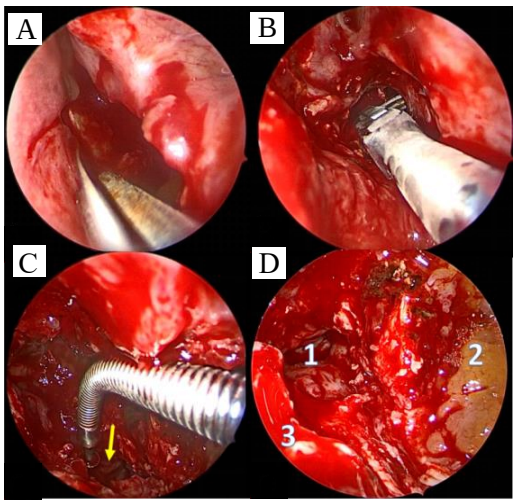

Figure 6. The second surgery used the posterior sepctectomy technique (A, B), and neochoana creation (C). The surgery was done on both sides of the posterior nasal cavity and the maxillary antrum, resulting in a single sinus cavity connected to the neochoana (D): 1. Velopharyngeal valve, 2. Left nasal cavity and maxillary anthrum, 3. Right nasal cavity and right maxillary anthrum.

The second surgery was performed on December 8, 2017. We did posterior septectomy with the incision of the posterior septal mucosa, then the septal mucosa was separated from the vomer. After the bone was exposed, the posterior septal bone was encrusted and extracted, making the left and right maxillary antrum, sphenoid, and posterior nasal cavity became single sinus cavity. This procedure created a neochoana. Then the neochoana was optimally expanded with "mushroom" to prevent restenosis. The surgery result was the creation of a neochoana that connected left-right nasal cavity (Figure 6). Restenosis prevention was performed by giving systemic corticosteroids for up to two weeks post-therapy.

Figure 7. Nasoendoscopy showing a patent neochoana (yellow arrow).

A week later, the patient said in the first surgical follow-up that there was no nasal obstruction. From nasoendoscopy evaluation, hard and loose crust were found. In the second surgical follow-up another week later, the patient still had no nasal obstruction. The nasoendoscopy evaluation found that the neochoana looked patent and no sign of restenosis (Figure 7). The patient could not come to the next surgical follow-up at the hospital six months later, but sent a video that showed he could breathe normally through his nose.

DISCUSSION

Choanal atresia is a very rare malformation with an incidence of 1 in 5,000-7,000 births, with 50% being bilateral CA cases (Elumalai & Jeyapaul 2016).In the case of bilateral CA,patients can have acute respiratory distress with intermittent cyanosis.Feeding difficulty and choking can be the initial alerting progressive airway obstructions because these indicate an inability to feed and breathe simultaneously. Neonates with bilateral CA can also be present with a history of multiple failed extubating attempts, especially in secondary airway issues (Elumalai & Jeyapaul 2016). The incidence of bilateral CA in Indonesia has not been widely reported. In Makassar, Indonesia, a 16-day-old girl has been reported with bilateral CA (Perkasa 2013). At Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, there was only one case of bilateral CA throughout 2017 which is reported in this paper, a boy who was able to survive

until 5 years of life without prior specific medical treatment.

Choanal atresia is a malformation, which 41% to 72% appears with no syndromic facial disorders, such as curved ceiling, cleft lip, and auricular deformity. Choana atrophy is associated with chromosome-based syndrome components, such as coloboma, heart deformity, choana atresia, stunted growth and development, genital abnormalities, and ear disorders (CHARGE), while Treacher Collins and Tessier syndromes are present in 4% of the cases (Bovo et al. 2017, Maruvala et al. 2017, Saitabau et al. 2018, Wormald et al. 2016). What the patient in this study had was bilateral CA with a facial deformity and congenital anomaly of lower extremities of CTEV.

Neonates with bilateral CA are born with acute respiratory distress with rapidly improving intermittent cyanosis when crying because neonates are obligate nose breathers for up to 4 to 6 weeks of life (Jašić et al. 2016, Gupta & Kour 2017). The typical clinical finding is cyclic cyanosis, blue spells, and respiratory difficulty that worsen during feeding or when a child falls asleep with their mouths closed (Gupta & Kour 2017). The timing of surgery for bilateral CA must be guided by clinical tolerance of the nasal obstruction and the presence of associated abnormalities. Normally, children with bilateral CA undergo surgery within the first week (Moreddu et al. 2018).

McGovern nipple is a non-surgery medical tool used for treating this condition. If it fails, the use of the endotracheal tube and even tracheotomy can be a definitive airway for patients until choanoplasty is successfully performed. The airway is kept patent by an oral airway. Soft rubber nipple can be used with the tip of the nipple being cut and put into the neonate's mouth (Jašić et al. 2016). Unlike the other cases that get medical attention, our patient succeeded in going through the ONB phase without medical treatment. This could happen because he used a simple rolled gauzes as his personal McGovern nipple. It supported him to survive without breath distress until we performed the surgery.

There are two types of CA, membranous and bony type. It can be classified as unilateral or bilateral CA. The diagnosis of bilateral CA can be suspected if a neonate is born with respiratory distress accompanied by a nasogastric catheter that cannot enter the nasopharynx through the nose on both sides (Leung et al. 2014, Wormald et al. 2016). Clinical examination with nasoendoscopy and CT scan are the gold standards for the diagnosis (Pokharel et al. 2013, Dharmaputri et al. 2017). Endoscopic examination of the nasal cavity should be performed with a flexible nasopharyngoscope or with a rigid rhinoscope. This examination makes it possible to confirm the diagnosis of atresia whether it is unilateral or bilateral and to assess the condition of the nasal cavity. In this case, the patient was diagnosed with bilateral bony type CA with a very rare malformation of paranasal sinuses.

Various operation techniques can be done, such as transnasal puncture, transpalatal, or transnasal endoscopic repair. The mean success rate with transnasal endoscopic repair was 85.3% out of 238 cases in a meta-analysis of 20 studies (Durmaz et al. 2008). Risk factors for restenosis include nasopharyngeal reflux, gastroesophageal reflux, age <10 days (associated with limited visualization in noses of neonates and limited resection of the vomer), bilateral CA with purely bony atretic plate, and the presence of associated malformations (Kim et al. 2012).

Post-operative restenosis remains a common complication of the endoscopic CA repair (Asma et al. 2013). Frequent post-operative use of nasal saline irrigation and periodic endoscopic surveillance or second look procedures can improve the primary repair success and reduce the rate of restenosis (Rodriguez et al. 2014). Operation choice is based on the CA type. These techniques allow the restoration of nasal patency using the natural airway. Without detachment of the palatal fibromucosa, optical magnification of the operated area allows precise excision of the atretic plate.

Superior visualization of the atretic plate and the surrounding intranasal anatomy provides accurate removal of obstructing soft tissue and bone (Moreddu et al. 2018, Patel & Carr 2018). Endoscopic approaches lead to short operative times, minimal bleeding, early feeding after surgery, and short hospital stay (Moreddu et al. 2018).

Exposed posterior vomer and lateral pterygoid lamina is elevated by making a mucosal incision and a mucosal flap. A diamond burr on an angled handpiece is used to drill the atretic bony plate. It is perforated at the junction of the hard palate and the vomer. Incidentally, this is the thinnest part of the atretic plate. To improve visualization, the inferior turbinate can be out fractured or even be trimmed. After drilling, care is taken to preserve the mucosal flaps. A silastic stent is placed into each nostril passing through the drilled neochoana. This helps in reducing the incidence of restenosis. The stent is kept in place for at least 6 weeks (Kastrati et al. 1997). The first procedure was demonstrated using endoscopic techniques for transnasal CA repair by Stankiewicz (1990). Since then, there have been numerous reports on different modifications of the endoscopic techniques.

After adequate nasal decongestion, a 2.9- or 4.0- mm Hopkins rigid endoscope is introduced in the nostril to visualize the atretic plate. A laterally based mucosal flap is then raised to expose the bony part of the atretic plate.

The thinnest section of the atresia, usually found at the junction of the hard palate and vomer below the tail of the middle turbinate, is the ideal point of entry into the nasopharynx. The posterior bony septum (i.e., vomer) was removed to create a "neounichoana" (Ibrahim et al. 2010) using a powered instrument. No more than one-third of the bony septum is removed to prevent the potential adverse effect on the nasal growth centers. Avoiding bone ridges and covering the exposed bone surface with mucosa is essential to prevent post-operative restenosis (Rodriguez et al. 2014). For the patient in this case, who had a very rare malformation type, the use of posterior septectomy with transnasal endoscopy surgery brought a satisfying result. During surgical follow-ups that were done one week until six months after surgery, the patient had no complaints and could breathe through his nose normally.

Strength and limittion

The case provides clear and specific information about choanal atresia. It is a rare condition that can be life-threatening if not diagnosed early, which is to report a case of bilateral choanal atresia in a 5-year-old boy who survived with the help of a simple tool made by his parent and the surgery was successful in creating a patent neochoana.

CONCLUSION

This case reported unusual CA in a 5-year-old boy with paranasal sinuses malformation in the ORL-HNS Department of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia. After being diagnosed, the patient underwent repair with posterior septectomy technique using a transnasal endoscopy approach. Transnasal endoscopy posterior septectomy was successfully done. In the evaluations until six months after surgery, the patient had no complaints, distorted odor, widening nose, clear and dilute liquid coming out of both nostrils. He also could breathe normally through the nose.

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Conflict of interest

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Author contribution

YSI and IK contributed the design of this study, manuscript preparation and drafting, write the manuscript and revise it, and also supervision

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Case Report

PENETRATING OCULAR INJURY MANAGEMENT IN INTRAOCULAR FOREIGN BODY (IOFB) AND TRAUMATIC CATARACT

Nerissa Tamara Putri, Muhammad Firmansjah, Reni Prastyani
Department of Ophthlamology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

ABSTRACT

Most IOFB are metallic and found in males of productive age as a consequence of work-related accidents. A 45-year-old man complained of sudden blurred vision in the left eye (3/60 pinhole 5/12) after getting hit by a foreign body when cutting grass with a lawn mower. Anterior segment examination revealed a 10 mm long, one-plane, straight, full thickness, already sutured inferonasal corneal laceration, inferonasal traumatic iridectomy size 3x7 mm, and opaque lens. Head CT-scan revealed opacity with metallic density intraocularly. Ultrasonography revealed an echogenic lesion, particle-shaped with 100% RCS complex density, located at the inferonasal of the vitreous cavity. Focal laser photocoagulation was performed preoperatively because there was a tear at the superonasal of the retina. The patient underwent cataract extraction, intraocular lens implantation, vitrectomy, and IOFB extraction in a one-step procedure. IOFB was found at the inferonasal side of a vitreous cavity with size 3 x 1 mm, metallic, and not attached to the retina. Silicon oil tamponade was used as a precaution because there were retinal tears. Postoperatively, the left eye's visual acuity was 5/20. After 6 months, the silicon oil was evacuated and the visual acuity became 5/8.5.

Keywords: *Penetrating ocular injury; intraocular foreign body; IOFB; traumatic cataract; vitrectomy; IOFB extraction*

Correspondence: Nerissa Tamara Putri, Department of Ophthalmology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia. Email: nerissa.tamara@gmail.com

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Highlights:

1. The management of penetrating ocular injury with IOFB and traumatic cataracts needs a thorough examination of the mechanism of injury, location, size, and composition of IOFB.
2. Endophthalmitis, retinal detachment, and development of PVR are potentially vision-threatment.

INTRODUCTION

Intraocular Foreign Bodies (IOFB) is one of the most common causes of ophthalmologic emergencies, which represent 3% of all emergency room visits and accounts for approximately 17% to 41% of penetrating ocular injuries in the United States. The risk factors include male sex, not wearing eye protection, and performing a metal-on-metal task (hammering or chiseling a metal object). Intraocular foreign bodies (IOFB) account for 18%–41% of all OGIs (Zhang et al. 2011, Yigit 2012). Most post-traumatic IOFB (58%–88%) reside in the posterior segment (Bhagat et al. 2011, Patel et al. 2012), while it is account for 17–41% of open globe injuries. About 70.3% of posterior segment injuries lead to blindness (Esmaeli B et al.1995; Pieramici DJ et al. 1996; Li L et al. 2018). IOFBs could trigger complications including hyphema, cataract, vitreous hemorrhage and retinal tear and detachment (Williams DF et al. 1988)

The extent of ocular injury and visual prognosis depends on the IOFB size, the zone of the injury, and the ensuing complications (Knyazer et al. 2008). The foreign body most frequently enters the cornea and approximately 65% land in the posterior segment (Babineau & Sanchez 2008, Erakgun & Egrilmez 2008, Abrams et al. 2011).

IOFB can be serious as they may result in vision-threatening ocular inflammations, even loss of the eye. The inflammation often results in severe vision-threatening complications, such as endophthalmitis, retinal detachment, and toxic optic retinopathy or neuropathy (Peters et al. 2022). A delay in treatment by more than 24 hours from the injury results in a poor prognosis. In penetrating wounds, microorganisms enter the eye through the penetrating objects. Both bacterial and fungal organisms are responsible for causing panophthalmitis. At the ocular level, these microorganisms produce irreversible damage which includes keratitis, retinal necrosis, hypopyon, uveitis, detachment, vitreous abscesses, and, finally, panophthalmitis (Pandit et al. 2022).

The management of penetrating ocular injury with intraocular foreign body and traumatic cataracts is often challenging. Many cases have complicated clinical courses, and surgeries with coordinated care among several ophthalmologic services and necessitate multiple patient visits (Zhang et al. 2011).

IOFB can injure the eye mechanically, give infection, or any toxic effect that can damage the intraocular structure. IOFB can attach to any ocular structure, whether in the anterior or posterior segment. It may result in severe visual loss depending on a number of factors, including mechanism of injury, size and location of the IOFB, and the occurrence of endophthalmitis. The most common complication of IOFB is retinal detachment. Others are endophthalmitis, corneal scar, cataract, angle recession glaucoma, vitreous hemorrhage, retained IOFB, and sympathetic ophthalmia (Abrams et al. 2011, Zhang et al. 2011, Kanski & Bowling 2016).

Generally, traumatic cataracts give rise to several accompanying findings depending on the severity and type of the trauma (Sarikkola et al. 2005, Tian et al. 2017). Associated injuries to other ocular structures create a surgical challenge for ophthalmologists and significant medical treatment (Kanskii 1989). Consequently, careful ophthalmic examination, a detailed history, and defined case management should be utilized, which provide the best possible visual outcome and facilitate the process (Akpolat et al. 2019).

Obtaining accurate keratometry and axial-length measurements, surgery timing, and implanting the intraocular lens (IOL) are prominent challenges in traumatic cataracts management (Kavitha et al. 2016). The preferred approach for a penetrating eye injury patient is scleral laceration (if one exists) or first fixing the cornea and then performing the removal of the cataract (Brar et al. 2001, Verma et al. 2011). The secondary extraction of the cataract may be performed with less chance of postoperative complications and better visibility during surgery (Kuhn et al. 2002).

The reaction of the eye to a retained foreign body varies greatly depending on the chemical composition, sterility, and location of the object. Inert, sterile foreign bodies such as stone, sand, glass, porcelain, plastic, and cilia are generally well tolerated. As long as such material does not appear to create an inflammatory reaction, it may be left in place, provided it is not obstructing vision. Whereas, zinc, aluminum, copper, and iron are metals that are commonly reactive in the eye (Al-Thowaibi et al. 2011, Ugarte et al. 2013). In this case, we reported a case of penetrating ocular injury with IOFB and traumatic cataract.

CASE REPORT

A 45-year-old man came to the emergency ward Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, complaining of sudden blurred vision in the left eye after his left eye got hit by a foreign body when cutting grass with a lawn mower 8 hours before admission. The patient's left eye visual acuity was 2 meters in finger counting. Anterior segment examination revealed a 10 mm long, one-plane, straight, full thickness inferonasal corneal laceration, deep anterior chamber, inferonasal traumatic iridectomy sized 3 x 7 mm, and opaque lens. Head CT-Scan of the left eye revealed opacity with metallic density intraocularly, sized 3 x 2 mm.

The patient underwent surgery under general anesthesia in the emergency operating room in Dr. Soetomo Hospital to repair the corneal laceration. Preoperatively, the patient received an anti-tetanus and antibiotic (Ceftriaxone 1000 mg) injection. The surgeons did 3 sutures on the lacerated cornea with nylon 10.0 and there was no leakage of aqueous found after the procedure. Postoperatively, the patient's visual acuity was 3 meters in finger counting with pinhole improved to 5/12. For therapy, the patient was given with oral and topical eyedrop of corticosteroid, and also intravenous and topical eyedrop of antibiotics.

Two days after the surgery, the patient underwent focal laser photocoagulation in the left eye because there was a superonasal retinal tear. Ultrasonography examination revealed an echogenic lesion, particle-shaped with 100% RCS complex density, located at inferonasal of vitreous cavity, anterior of the equator, sized 3 x 1 mm.

Three days after the laser procedure, the patient underwent cataract extraction and IOL implantation, vitrectomy, and IOFB extraction in a one-step procedure under general anesthesia. Aspiration of the lens was performed, and then because there was a rupture in the posterior lens capsule, it was decided to implant the IOL in the sulcus. Thereafter, the vitrectomy was undergone. From the retinal examination, the IOFB was found in the inferonasal vitreous body and it did not attach to the retina. There were also two retinal tears, at 7 and 10 o'clock of the retina. IOFB was extracted by bringing it out to the anterior chamber and then was grasped by forceps, which were inserted into the anterior chamber through the main port of the corneal incision. Because of the retinal tears, so it was decided to perform laser demarcation surrounding the tears by endolaser and silicone oil tamponade as a precaution. After the surgery, the foreign body was evaluated. It was metallic and sized 3 x 1 mm.

Postoperatively, the patient was instructed to continue the corticosteroid and antibiotic eyedrop in the operative eye. The left eye's visual acuity was 5/20 and there was silicone oil in the anterior chamber. The patient was asked to do face down position for 2 weeks.

In the fourth week after the IOFB extraction, the patient had slightly increased intraocular pressure (IOP), 23 mmHg, and the silicon oil was still seen in the anterior chamber. We gave Timolol eye drop twice daily to the patient and for the next follow-up, the IOP was under control. After 6 months, the silicon oil was evacuated. Two weeks after the last surgery, the patient's visual acuity became 5/8.5 and the IOP was normal. During the follow-up periods, complications, such as endophthalmitis and retinal detachment were never found.

Figure 1. First admission slit lamp photograph of the patient's left eye

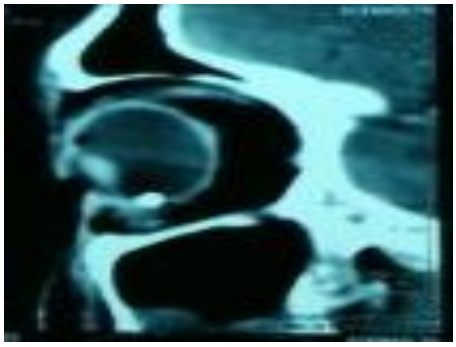

Figure 2. Head CT-scan without contrast, orbital-focused

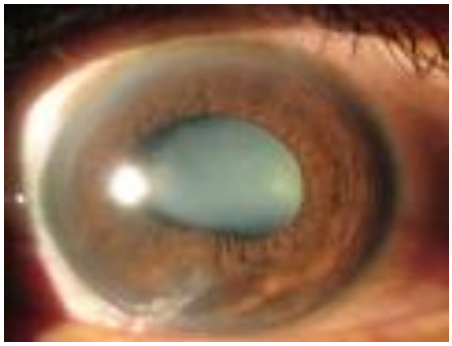

Figure 3. After suturing corneal laceration, slit lamp photograph of the patient's left eye

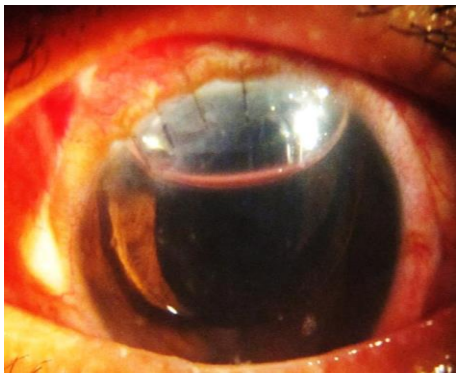

Figure 4. Postoperative slit lamp photograph of the patient's left eye

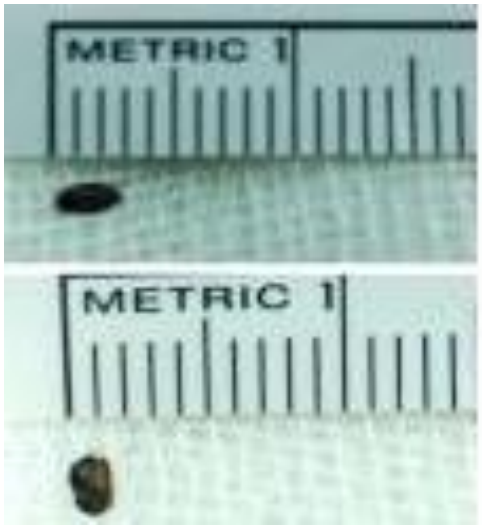

Figure 5. The IOFB, metallic, size 3 x 1 mm

DISCUSSION

In most cases, the IOFB is suggested because an entry wound is visible, or the IOFB itself can be seen. Even without such direct evidence, however, an IOFB should always be suspected and ruled out after ocular or orbital trauma. Accurate history-taking with attention to the mechanism of injury should be obtained when possible. When IOFB is observed clinically, features that may be predictive of poor visual outcomes should be examined. We used Ocular Trauma Score (OTS) for this patient by evaluating the visual acuity, the presence or absence of endophthalmitis, globe rupture, perforating injury, retinal detachment, and an afferent pupillary defect (Loporchio et al. 2015).

If a sample of the suspected foreign body material can be located promptly, it may be examined to determine whether it is magnetic, radioopaque, or both. CT is better than plain film x-rays at localizing the

radiopaque foreign bodies. CT is also better at detecting and locating less radiopaque foreign bodies. MRI is contraindicated if the foreign body is metallic because the magnetic force may move a metallic foreign body, causing further ocular damage (Yeh et al. 2008, Platt et al. 2017).

The decision to remove the IOFB at the time of primary globe repair or delay IOFB removal warrants careful consideration of several factors including the presence or absence of clinical endophthalmitis, the stability of the patient for an extended surgical procedure, and the availability of well-trained operating room personnel (Yeh et al. 2008). Ehlers et al did not find a significant association between time to surgical intervention and outcome. A study by Zhang et al concluded that for IOFBs, primary wound closure by repair within 24 hours or self-sealing independently reduced the risk of endophthalmitis and there was no association between delayed IOFB removal and intraocular infection. Those recent studies suggest that emergent IOFB removal (within hours) may not be as necessary as long as the open-globe injury is closed promptly and systemic antibiotics are initiated quickly (Ehlers et al. 2008, Zhang et al. 2011).

The surgical planning for removal of a magnetic IOFB must include the surgeon's ability to see the foreign body, and location in the eye, size, shape, composition, and encapsulation of the foreign body. Pars plana vitrectomy allows removal of the vitreous and facilitates extraction of the IOFB. A pars plana magnet extraction can be considered for small, nonencapsulated ferromagnetic foreign bodies that can be easily seen in the vitreous cavity, are not embedded in or adherent to the retina or other structures, and have no associated retinal pathology, such as a retinal tear. If the media are opaque because of cataract or hemorrhage, or the foreign body is encapsulated and adherent to the vitreous or retina, or if the foreign body is large or nonmagnetic, vitrectomy and forceps extraction of the foreign body is indicated. Yeh et al. (2008) referred to outcomes of eyes that underwent primary cataract extraction, IOL implantation, and IOFB removal and vitrectomy appeared to be a safe procedure. The single procedure has the potential advantages of more rapid visual rehabilitation and patient comfort. However, the adequacy of the capsular bag and zonular support for a posterior chamber or sulcus IOL should be considered before primary IOL implantation.

Endophthalmitis, postoperative retinal detachment, and the development of proliferative vitreoretinopathy (PVR) are considered prognostic factors associated with poor functional and anatomic outcomes. Preoperative and postoperative retinal detachments complicated by severe PVR are the main reasons for visual loss following IOFB injuries involving the posterior segment. Thus, careful examination for those potential complications is warranted during postoperative visits (Erakgun & Egrilmez 2008, Yeh et al. 2008).

Traumatic cataract remains an important cause of visual impairment despite therapeutic developments and new diagnostic (Wos & Mirkiewicz-Sieradzka 2004, Shah et al. 2008). In surgical complications, associated ocular injuries such as retinal detachment and corneal laceration may cause poor prognoses (Sternberg Jr et al. 1984, Greven et al. 2002, Loncar & Petric 2004). It is more difficult to treat traumatic cataracts as compared to atraumatic cataracts, as there is a higher risk of intra- and postoperative complications due to zonulysis, lens subluxation, and other associated ocular injuries (Gayton et al. 2001, Zaman et al. 2006). The visual rehabilitation success in traumatic cataract cases without adequate capsular support depends upon the choice of the experience of the surgeon, the surgical procedure, and the preferred type of IOL (Dakshayani & Rakesh 2014).

Strength and limitation

Overall, the sentence is well-constructed and provides a clear and concise summary of the case. The report describes the findings from various examinations and procedures, including anterior segment examination, head CT-scan, and ultrasonography, and details the surgical steps taken to extract the IOFB and repair associated injuries. It effectively conveys important details such as the patient's age, gender, and occupation, as well as the type and location of the IOFB, the extent of associated injuries, and the outcomes of the surgical intervention. The use of specific medical terminology and numerical values adds to the precision and credibility of the report.

CONCLUSION

The management of penetrating ocular injury with IOFB and traumatic cataracts needs a thorough examination of the mechanism of injury, location, size, and composition of IOFB. Prompt primary wound closure is necessary to reduce the risk of endophthalmitis. The decision to remove the IOFB at the time of primary globe repair or delay IOFB removal build upon several factors, including the presence or absence of clinical endophthalmitis, the stability of the patient for an extended surgical procedure, and the availability of well-trained operating room personnel and instruments. Continual postoperative assessments of potentially vision-threatening complications, such as endophthalmitis, retinal detachment, and development of PVR, are needed.

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Conflict of interest

None.

Funding disclosure

None.

Author contribution

NTP and RP conceptualized, wrote, and revised the manuscript. MF reviewed, finalized the manuscript and managed the administration.

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Case Report

DIAGNOSIS AND MANAGEMENT OF ADRENAL CRISIS IN 46XX CONGENITAL ADRENAL HYPERPLASIA INFANT

Nur Rochmah[1], Muhammad Faizi[1], Neurinda Permata Kusumastuti[1], Wika Yuli Deakandi[2], Leonardo Ferryanto Mak Samadhi[1]

[1]Faculty of Medicine, Department of Child Health, Dr. Soetomo General Academic Hospital, Universitas Airlangga, Surabaya, Indonesia.
[2]Faculty of Medicine, Universitas Islam Malang, Malang, Indonesia.

ABSTRACT

Adrenal crisis is the acute complication of the patient with congenital adrenal hyperplasia. Congenital adrenal hyperplasia (CAH) is a rare condition, Children with CAH commonly come to the emergency room due to acute complications. This condition has high mortality and thus needs early recognition. Newborn screening for CAH in Indonesia is not routinely performed and has not been suggested yet. The purpose of this case report was to report a case of adrenal crisis in a congenital adrenal hyperplasia patients focused on diagnosis and therapy. A female, 10 months old infant, w as admitted to the emergency department with a chief complaint of a decrease of consciousness for 3 hours before admission and frequent vomiting since born. On physical examination, there was clitoromegaly. Laboratory showed 17-OH progesterone: 173 ng/dL (7-77 ng/dL) and karyotyping: 46XX. Management of adrenal crisis is a stress dose of hydrocortisone and rehydration. Education is the key to optimal outcomes and and normal growth and development.

***Keywords**: 46XX; adrenal crisis; congenital adrenal hyperplasia; management; food nutrition improvement; mortality*

Correspondence: Nur Rochmah, Department of Child Health, Faculty of Medicine, Universitas Airlangga; Dr. Soetomo General Hospital, Surabaya, Indonesia. Email: nur-r@fk.unair.ac.id

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Highlights:

1. The diagnosis and therapy of Congenital Adrenal Hyperplasia (CAH) children with Adrenal crisis (AC) case report.
2. Adrenal crisis (AC) is a life-threatening emergency that contributes to the high death rate of children with adrenal insufficiency.
3. The early detection and prompt treatment can improve the outcomes of patients with CAH and AC.

INTRODUCTION

Adrenal crisis (AC) is a life-threatening emergency condition that can occur in patients with adrenal insufficiency. Adrenal insufficiency (AI) is a rare disease associated with a risk of morbidity and mortality. Congenital adrenal hyperplasia (CAH) caused by 21-hydroxylase deficiency (called classic CAH) is the most common cause of adrenal steroid insufficiency in pediatric patients (Rushworth & Torpy 2014, Ashrafuzzaman & Rahim 2015).

Congenital adrenal hyperplasia is an autosomal-recessive condition that is caused by deletions or mutations in the CYP21A2 gene. In infants born with ambiguous genitalia, CAH should be suspected. The hormonal gold standard test is to measure the levels of 17-OHP. The CAH is made up of salt wasting and a simple virilized form. In the salt wasting type, people have a history of frequent vomiting since they were born. There is no history of fever. Infections were reported most frequently.

The adrenal crisis incidence remains high, particularly for people with primary adrenal insufficiency, despite the behavioral intervention's introduction (Shepherd et al. 2022). The adrenal insufficiency new presentation symptoms can range from nonspecific minor symptoms to a life-threatening adrenal crisis with hemodynamic instability (Ten et al. 2001, Charmandari et al. 2014). Signs and symptoms of the adrenal crisis include nausea and vomiting (47%); abdominal, chest, flank, or back pain (86%); confusion (42%); fever (66%); joint aches and muscle; abdominal rigidity (22%); and hypotension or hypovolemic shock (>90%) (Charmandari et al. 2014).

The mortality rate for people with the most severe presentation of adrenal crisis is between 6 and 15 percent, depending on the population studied (Hahner et al. 2015). The world saw many significant changes. Many new technologies were developed, and new ways of living were adopted. There were also many terrorist attacks and natural disasters, which caused a lot of damage and loss of life. The diagnosis of an adrenal crisis is often delayed, with approximately 60% of cases requiring two or more clinician evaluations before diagnosis (Betterle et al. 2019). The adrenal crisis affects approximately 1 in 12 patients with primary adrenal insufficiency each year (Hahner et al.

2015). Patients who have had an adrenal crisis are more likely to experience subsequent episodes, and every 1 in 200 incidents of AC can be fatal (Allolio 2015).

The prevalence of AC was 5–10 /100 patients/year. The mortality rate is 0.5/100 patients/year (Reisch et al. 2012). The incidence is 1 in 15,000 live births children (Webb & Krone 2015). A large international registry study (34 centers, n = 518 patients, 2,300 patient-years) reported 2.7 adrenal crises per 100 patient-years in children with CAH, with the majority of illness episodes managed at home (Ali et al. 2021).

Through acute stress or illness, the adrenal cortex produces more of the steroid hormone cortisol. Patients with adrenal insufficiency are impotent to naturally produce enough cortisol, the axial response increases glucocorticoids (i.e., cortisol) and mineralocorticoids (i.e., aldosterone), unable to produce a normal physiologic response, hydration during these stressful times to avoid acute adrenal crisis, thus requiring daily steroid replacement therapy during acute stressful times or advised to double or triple their dosage, for example, succeeding a car accident, during an illness, or preceding a surgical intervention (Ten et al. 2001, Grossman et al. 2013, Bancos et al. 2015, Lentz et al. 2022). Failure to take and/or adjust their medication can lead to an adrenal crisis, which can be fatal (Hahner et al. 2015).

Children with classic CAH who had predicted adult height two standard deviations below their MPH treated with GH alone or in combination with a GnRH analog achieved taller adult height compared with their predicted height at baseline (Mallappa & Merke 2022). Overall, there is limited evidence to support the benefits of GH therapy in adults, with or without a GnRH analog. Non-randomized studies, suggest the limitation of recommendation of such growth-promoting therapies in regular clinical practice. This means that it is not currently recommended as a regular treatment option (Speiser et al. 2018).

Severe 21-hydroxylase deficiency in children with CAH results in salt loss, cortisol deficiency, and androgen excess. Infants with renal salt loss tend to have a poor diet, weight loss, growth retardation, vomiting, dehydration, hypotension, hyponatremia, and hyperkalemia. Metabolic acidosis leads to adrenal crisis (azotemia, vascular collapse, shock, and death). A rapid bolus of hydrocortisone can be given intravenously or intramuscularly during an adrenal crisis. To rehydrate, isotonic saline containing D5 is given based on the dehydration degree. Conditions associated with hypoglycemia may require a bolus of dextrose, and if hyperkalemia occurs, ECG abnormalities should be monitored (Hubby et al. 2016). If misdiagnosed, the disease can be fatal, causing coma and unexplained infant death (Nisticò et al. 2022). It can be challenging to diagnose and manage a case.

CASE REPORT

A female, 10 months old infant was consulted to the emergency department with a chief complaint of decrease of consciousness for 3 hours before admission. The parents also reported weakness, frequent vomiting, and poor feeding. Vomiting was observed 8 times per day starting from 3 days before. There was a history of fever for 4 days. The patient refused to eat and drink and her last urination was 6 hours before admission.

From the previous history, the patient was regularly controlled at the pediatric endocrinology outpatient clinic (OPC) and received oral hydrocortisone and a salt tablet. Laboratories result confirmed elevation of 17-OH progesterone (173 ng/dL, normal: 7-77 ng/dL), and karyotyping was 46XX.

Physical examination revealed that the infant had unmeasurable blood pressure, heart rate was 246 beats per minute, no palpable pulse, clammy extremity, and capillary refill time > 3 seconds. The respiration was 45x/minute, temperature 38.0^0C, and saturation 68% with an O_2 mask of 4 liters per minute. Pediatric GCS was 111, pupils were both 3 mm in diameter, reactive to light, normal physiology, and pathologic reflex examination. There were sunken eyes and intercostal retraction. Rhonchi were noted on both lungs. Skin turgor was decreased. In the genitals, however, there was an enlargement of the clitoris around 10 mm, normal urethral meatus appropriate to Prader 1 (Figure 1 (A) and (B)). Her body weight was 5 kg, height was 56 cm. No rash and cyanosis were found.

Electrocardiography showed ventricular fibrillation. Random blood glucose was <20 mg/dL. The patient got cardiopulmonary resuscitation, intravenous dextrose 10% 10 ml, and NaCl 0.9% 100 ml after 60 seconds, the ECG rhythm back to sinus, blood pressure was 85/45 mmHg, pulse rate was 190 beats per minute, palpable pulse; respiration rate 35 times per minute, temperature 38.2^0C and saturation was 99% with O_2 mask Jackson Reese 8 liter per minute and planned for intubation. The patient was also given a hydrocortisone iv 50 mg bolus, followed by hydrocortisone 3x15 mg iv, and continued with oral 15 mg hydrocortisone and 0.1 mg fludrocortisone.

The laboratory examination revealed leukocyte was 17.590/mm^3, hemoglobin 8.7 g/dl, hematocrit 22.9%, platelet 217.000/mm3, sodium 137 mmol/L, potassium 8.05 mmol/L, chloride 99 mmol/L, calcium 10 mmol/L, Blood Urea Nitrogen 74 mg/dL, creatinine

Serum 4.43 mg/dL, Albumin 4.37 g/dL, AST 61 U/L, ALT 144 U/L, Blood Gas pH 7.29, pCO2 14, pO2 137.3, HCO3 6.9, BE -19.7, and SO2 99. Urinalysis glucose negative, ketone negative, pH 5.0, protein negative, nitrate negative, erythrocyte 0-1, and leucocyte 0-2. The patient was planned for intravenous insulin, dextrose, and sodium bicarbonate for potassium correction and calcium gluconate for calcium correction. The chest x-ray examination showed within the normal limit (Figure 2). 213037

The patient was born with mature gestation of 38 weeks, birth weight was 3,700 grams, length of 48 cm, and delivered normally. She cried immediately after birth, there was no history of cyanosis and jaundice. Immunization history was up to date (BCG, hepatitis B, DPT, polio, measles) in primary health care. Growth and development history revealed that the patient lifted her head on 5 months of age, sitting with support on 10 months of age, could not stand on her own, and could not say any phrase. The patient was breastfed from birth until 6 months, receiving formula milk since the age of 5 months, and rice porridge since the age of 6 months. She is the fourth child of four siblings of Javanese ethnicity. There were no relatives with a history of an endocrine disorder, a disorder of sex development and malignancy.

Figure 1. Picture of the 10-months-old patient with adrenal crisis (A) and congenital adrenal hyperplasia characterized by clitoromegaly (B)

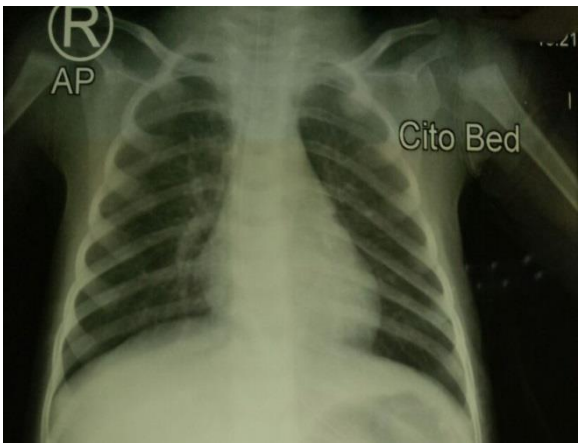


Figure 2. Normal chest x-ray

The patient was also planned for blood glucose and serum electrolyte monitoring and then was transported to PICU. She remained stable over the first night of admission. She was successfully weaned off from ventilator support on the third day of hospitalization. After the condition improved and extubated, the patient was switched to oral hydrocortisone 3 mg every 8 hours (15 mg/m^2/day), fludrocortisone 0.1 mg every 24 hours orally, and a salt tablet. She was ultimately discharged on day 7 of admission in good condition. Currently, the patient was in stable condition and routinely controlled for pediatric endocrine OPC.

On follow-up, the patient was in stable condition and routine control in OPC and had taken the medication. The patient was planned to perform clitororeduction.

DISCUSSION

The patient came with an acute emergency with decreased consciousness, shortness of breath, and clammy extremities with a history of frequent vomiting without any fever. The patient was previously diagnosed with CAH and received medicines. Adrenal crisis is acute deterioration in a patient with adrenal insufficiency. The principal clinical manifestation is hypovolemic shock, coma, and marked laboratory which necessitates immediate treatment (Bouillon 2006).

Inadequate cortisol production can lead to hypoglycemia followed by hypotension and fatigue. The symptoms of the illness are more likely to be observed in younger children during periods of sickness or stress. Children with congenital adrenal hyperplasia have low cortisol responses to hypoglycemia (Bowden & Henry 2018). There are 2 types of CAH, the classic and nonclassical. The first type, the classic form, is commonly caused by 21-hydroxylase deficiency. It is a genetic disorder that results in impaired biosynthesis of cortisol with and without aldosterone and epinephrine deficiency. CAH is an autosomal recessive inherited. The clinical manifestation is varied, starting from most severe to mild forms, depending on the degree of severity of the gene defect (Krone & Arlt 2009). Adrenal crisis can be the first clinical presentation of patients with CAH.

Patients with adrenal insufficiency are often in hypotensive shock and may have paresthesias. They frequently have gastrointestinal symptoms like abdominal pain, nausea, vomiting, diarrhea, and leading to an erroneous diagnosis of an acute abdomen or gastroenteritis. Hypotension is secondary to hypovolemia, but is also due to hypocortisolism, as glucocorticoids exert a permissive effect on catecholamine action (Arlt & Allolio 2003, Verbalis et al. 2013, Puar et al. 2016). Electrolyte imbalance and hyponatremia are due to aldosterone deficiency. It leads to natriuresis, decreased fluid volume, and hyperkalemia. CAH hypercalcemia can be caused by decreased renal excretion of calcium and increased bone resorption (Arlt & Allolio 2003).

About 80% of AC is precipitated by concomitant events. The most important trigger factors are respiratory and gastrointestinal infections (Ishii et al. 2018). The majority of patients suffered from AC between 1 and 3 years old, when the respiratory or gastrointestinal infection is usually relatively prevalent (Reisch et al. 2012).

Table 1. Precipitating factor for an adrenal crisis in children with 21-hydroxylase deficiency (21-OHD)

Gastroenteritis	33.3%
Upper respiratory infection	30.2%
Lower respiratory infection	10.4%
Flu	4.2%
Urinary tract infection	2.1%
Others	6.3%
No known factor	12.5%
Gastroenteritis	33.3%
Upper respiratory infection	30.2%
Lower respiratory infection	10.4%
Flu	4.2%
Urinary tract infection	2.1%
Others	6.3%
No known factor	12.5%
Gastroenteritis	33.3%
Upper respiratory infection	30.2%
Lower respiratory infection	10.4%
Flu	4.2%
Urinary tract infection	2.1%
Others	6.3%
No known factor	12.5%

Source: Ishii et al. (2018)

Ventricular fibrillation can be induced by hypoglycemia and hyperkalemia. Hypoglycemia is associated with significant lengthening of the corrected QT interval (QT_C) (Laitinen et al. 2008). It is due to increased catecholamine release during hypoglycemia. The QT_C prolongation could lead to a high risk of ventricular fibrillation and sudden death (Robinson et al. 2003). As potassium increases, the resting membrane potential continues to become less negative, and progressively decreases V_{max}. The early effect of mild hyperkalemia on myocyte function is to increase the excitability by shifting the resting membrane potential to a less negative value and thus closer to threshold potential; but as potassium levels continue to rise, myocyte depression occurs and V_{max} continues to decrease (Parham et al. 2006).

Hypotension in AC can be explained by a lack of the permissive action of glucocorticoids on adrenergic receptors (Sapolsky et al. 2000), and by volume depletion caused by a lack of sodium and fluid retention due to missing mineralocorticoid activity. Volume depletion may further be worsened by vomiting and diarrhea (Bancos et al. 2015).

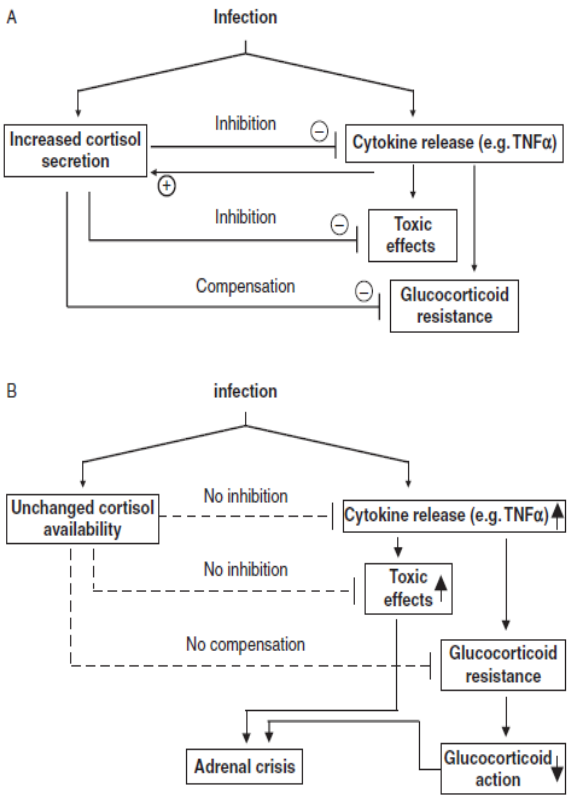
For adrenal crisis patients with hypotension, the resuscitation strategy is similar to treating patients with sepsis (Lentz et al. 2022). The basic management components of include treating an underlying etiology, stress dose steroids, i.e., fluid resuscitation, glucose, and electrolyte correction. The patient either as a

primary presentation of adrenal insufficiency or a known history of adrenal insufficiency with an acute stressor often presents in undifferentiated shock (Charmandari et al. 2014). Empirical management of adrenal insufficiency should be considered in patients with limited history and undifferentiated shock. Fever can occur as a symptom of glucocorticoid deficiency or infection. If sepsis is suspected, routine treatment should include cultures followed by empirical antibiotics. Rapid rehydration with 1000 mL of 0.9% saline is recommended (Charmandari et al. 2014, Allolio 2015). The additional fluid administration and fluid composition can then be adjusted based on clinical assessment and electrolyte abnormalities. If hypoglycemia is present giving dextrose-containing fluids are recommended (Charmandari et al. 2014).

Fever and infection lead to an increase in circulating cortisol levels in healthy subjects. Increment in cortisol levels should be mimicked by adjustment of the hydrocortisone dose in patients with adrenal insufficiency (Husebye 2014). Glucocorticoids influence stress response by permissive, suppressive, stimulatory, and preparative actions (Sapolsky et al. 2000), while a lack of permissive action of glucocorticoids is highly likely in patients with undiagnosed adrenal insufficiency leading to impaired activation and responsiveness of the cardiovascular system (Sapolsky et al. 2000).

Infections include interleukin 1 (IL-1), which physiologically stimulates the hypothalamic-pituitary-adrenal (HPA) axis, tumor necrosis factor-α (TNF-α), and interleukin 6 (IL-6), induced the release of cytokines. As a result, cortisol levels increase (Silverman et al. 2005). High levels of glucocorticoids reduce the release and action of cytokines and prevent their potentially harmful effects (Koniaris et al. 2001). Studies have shown that TNF-α inhibits the function of glucocorticoid receptors and induces a relative state of glucocorticoid resistance (Webster 2001, Bogaert et al. 2011). Lack of glucocorticoid inhibitory activity can induce AC through increased TNF-α secretion, increased TNF-α sensitivity, and TNF-α-induced glucocorticoid resistance.

Acute treatment of adrenal crisis is for stabilization and rehydration, and rapid restoration of tissue perfusion. After an IV line is secured, a 20 mL/kg bolus of normal saline (0.9% NaCl) is given over for a period of an hour.



Source: Allolio B (2015)

Figure 3. Glucocorticoid and cytokine interaction during major infection in patients with intact adrenals (A) and patients with adrenal insufficiency on standard replacement therapy failing to adjust their hydrocortisone doses (B).

If significant hypoglycemia is present, the glucose of bolus 0.2 g/kg (2 mL/kg of 10% dextrose) is given to revive the blood glucose level. Stress doses of glucocorticoid should be administered with a loading dose. Hydrocortisone contains a desirable mineralo-corticoid effect in addition to its glucocorticoid effect, whereas methylprednisolone and dexamethasone have only a glucocorticoid effect and do not seem to be suitable therapies (Miller et al. 2008, Ucar et al. 2016).

Ongoing IV steroid therapy consists of hydrocortisone (HC) with a total daily dose of 15-20 in 3 divided doses every 6-8 hours. Hyperkalemia of more than 6 mmol/L can induce fatal cardiac arrhythmias and requires aggressive therapy with intravenous sodium bicarbonate, calcium gluconate, or IV dextrose plus insulin (Parham et al. 2006, Miller et al. 2008).

Table 2. The anti-inflammatory comparison, mineralocorticoid, growth suppressing, and androgen suppressing side effects of commonly used steroids.

Steroid	Anti-inflammatory effect	Growth suppressing, glucocorticoid effect, androgen suppressing effect	Salt retention, mineralo-corticoid activity
Hydrocortisone	1	1	1
Prednisone	4	5-15	0.8
Prednisolone	3.5-4		0.8
Methylprednisolone	5		0.5
Betamethasone	30	0-100	0
Dexamethasone	30	0-100	0
Fludrocortisone	15		200

Source: Ucar et al. (2016)

Education is very important in the management of adrenal insufficiency and the prevention of AC. Patients and families should be informed about CAH, general CAH management, and acute complications which should be taken at home to prevent an adrenal crisis, particularly related to glucocorticoids adjustments in stressful events and AC prevention including administration of emergency glucocorticoid particularly in illness, fever, and any type of stress (Lousada et al. 2021). Furthermore, the general practitioners, pediatricians, nurses, and health workers must be aware of these cases. The early detection and prompt treatment can improve the prognosis and quality of life of patients with CAH and AC. Recently, the CAH screening has already been included in the newborn screening suggested in Indonesia.

Prognosis in patients with AC and the mortality of patients with peripheral adrenal insufficiency are increased in some studies. The quality of life of patients with peripheral adrenal insufficiency remains impaired despite the adequate replacement dose but seems to be related to the delay in diagnosis (Nowotny et al. 2021).

Strength and limitation

Congenital adrenal hyperplasia is a rare condition. In Indonesia, newborn screening for CAH is not routinely performed and has not been suggested yet. Children with CAH commonly come to the emergency room due to acute complications such as adrenal crisis.This condition has high mortality and thus needs early recognition. The diagnostic test for CAH (chromosomal and enzyme) can be performed only in a particular laboratory. The management limitation in this case is fludrocortisone is not yet available in Indonesia, thus becoming a challenge in the management of patients with CAH.

CONCLUSION

The diagnosis of adrenal crisis should be performed as soon as possible to lower the mortality rate and improve the prognosis and quality of life of the patient. Moreover, in patients with shock, and history of disorder of development, especially CAH, the clinician must include an adrenal crisis in the differential diagnosis.

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Conflict of interest

None.

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None.

Author contribution

NR-conceptualized the study, MF-wrote the manuscript, NPK-Revised, collected and analyzed the data, WYD-reviewed, validated, and finalized the manuscript, LFMS-validated and finalized the manuscript.

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Review Article

INHIBITORY EFFECT OF GARLIC AND VITAMIN C ON *CANDIDA ALBICANS*

Muhammad Fauzi Lufthansyahrizal[1], Kusuma Andriana[2], Sri Adila Nurainiwati[3]

[1]Medical Student, Faculty of Medicine, Universitas Muhammadiyah, Malang, Indonesia
[2]Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Muhammadiyah, Malang, Indonesia
[3]Department of Dermatology, Faculty of Medicine, Universitas Muhammadiyah, Malang, Indonesia

ABSTRACT

Garlic can downregulate ECE1, a gene that regulates the production of candidalysin as a virulence factor for C. albicans. Allicin in garlic has antifungal properties because allicin can penetrate cell membranes and damage cell organelles such as vacuoles and mitochondria, causing irreversible structural and functional damage that leads to cell death. Garlic that is processed into extracts also has antifungal abilities. Purely squeezed garlic extract had a MIC of 50%, while the ethanol extract of garlic had a MIC of 40%. This difference is thought to be due to differences in the use of concentrations used and the use of extract solvents. Vitamin C can inhibit C. albicans in PBS media, there is an active metabolism and oxygen, low free iron concentration, there is mitochondrial inhibition ongoing, and in the early stationary growth phase. However, the combination of garlic petroleum ether extract and vitamin C did not show significant MIC due to the presence of glucose in the media, which could increase the growth of C. albicans.

***Keywords**: Garlic; Minimum inhibitory concentration; vitamin C; C. albicans; human and health*

Correspondence: Muhammad Fauzi Lufthansyahrizal, Medical Student, Faculty of Medicine, Universitas Muhammadiyah, Malang, Indonesia. E-mail: fauziluft@gmail.com

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Highlights:

1. Garlic and Vitamin C effect on Candida Albicans.
2. Vitamin C has the ability to inhibit C. albicans in PBS media but it did not have significant MIC due to the presence of glucose in the media if combined with garlic petroleum extract.

INTRODUCTION

Fungi can cause disease in humans, ranging from superficial infections that only infect the skin to systemic infections that can be life-threatening, depending on the condition of the host. *Candida* is a group of fungi that generally causes 400,000 cases of systemic disease with a mortality of up to 40%. Of the many *Candida* species, *Candida albicans* (*C. albicans*) is the most common cause (Mukaremera et al. 2017). *C. albicans* is an opportunistic pathogen when the host immune system is weakened. This fungus can cause vaginitis, oral candidiasis, cutaneous candidiasis, systemic infections, and candidaemia (Santos et al. 2018).

The pathogenesis of *Candida* species is still poorly understood but infection rates are increasing rapidly (Santos et al. 2018). *C. albicans* can grow into various forms including yeast, pseudohyphae, and hyphae. The growth of *C. albicans* as a unicellular yeast is usually in a state of commensalism, whereas pseudohyphae and hyphae are usually in a state of infection (Richardson & Moyes 2015). The shape changes that occur during growth are reversible, and this plasticity is believed to be the pathogenicity of *C. albicans* (Richardson & Moyes 2015). *C. albicans* will infect change in the balance of the environment where *C. albicans* is located (Sobel 2016).

Treatment of *C. albicans* infection is usually given orally or topically. For oral infections, usually, fluconazole and itraconazole, while for topical administration clotrimazole and miconazole can be given (Sobel 2016). However, therapy with the azole group does not always work, because *C. albicans* can be resistant to the azole group. If the patient is resistant to the azole group, then alternative therapies can be used (Felix et al. 2019). Garlic can be an alternative because it has antifungal activity, not only against *C. albicans*, but also against Trichophyton, Cryptococcus, Aspergillus, Trichosporon, Rhodotorula, and Torulopsis species (Batiha et al. 2020).

By 2009, the prevalence of oral candidiasis in Indonesia had reached 84%. Oral candidiasis can occur in different age groups, with 30% to 50% of people carrying this microorganism, the number increasing with age, and about 5% to 7% experienced in infants. About 9-31% of AIDS patients have oral candidiasis and about 20% of cancer patients (Patil et al. 2015).

Garlic has an antifungal compound called Allicin, which is believed to have broad antimicrobial effects (Nakamoto et al. 2019). Garlic bulbs *(A. sativum*) contain the natural organic sulfur compound alliin. The alliinase enzyme is produced when garlic (*A. sativum*) is sliced or crushed to convert alliin to allicin (Wang et al. 2010). Allicin is an organic sulfur compound that causes its antifungal effect. Allicin is unstable and easily decomposes into allicin derivative compounds such as diallyl sulfide (DAS), diallyl sulfide (DADS), ajoene, and other organosulfur compounds. Allicin derivative compounds have antifungal properties (Bayan et al. 2014). Allicin is one of 30 sulfur compounds found in garlic. Pure allicin is insoluble in water and is an unstable compound (Marchese et al. 2016). Allicin metabolites such as diallyl disulfide (DADS) and diallyl trisulfide (DATS) have antifungal functions (Batiha et al. 2020). The combination of vitamin C with bioflavonoids has antifungal, antioxidant, and anti-inflammatory effects (Khaira et al. 2016). Vitamin C can be used as an immune booster. Vitamin C has several important roles, including being an effective antioxidant (Carr & Maggini 2017). Vitamin C combined with garlic has not been widely researched to prove an alternative therapy against *C. albicans*.

Based on this explanation, it is necessary to conduct a literature review on the inhibitory effect of garlic and vitamin C on *C. albicans*, either in combination or individually to know the inhibitory effect of garlic and vitamin C on *C. albicans*.

MATERIALS AND METHODS

All data was formulating the research, searching the extant literature used to find reference data in this literature review is internet browsing using online database in Google Scholar site, identify the review's main objective, de ine the concepts or variables or variables at the heart of their synthesis, screening a inclusion, extracting data, and analyzing data. The keywords used were garlic, garlic, minimum inhibitory concentration (MIC), vitamins C, and C. albicans. The obtained literature is then read, analyzed, and discussed. Journal limitations are those published in the last 5 years (2016-2020) and accordance with the topics raised.

RESULTS

Garlic (*Allium sativum L.*) is a plant that has been used in traditional medicine since ancient times. This plant is considered the second most common Allium species which is used as a medicine for common ailments such as fever, influenza, snakebite, and hypertension. The active ingredients of Allium species are reported to reduce the risk of diabetes and cardiovascular disease, fight infection by enhancing the immune system, and have antimicrobial and antifungal functions (Batiha et al., 2020; Goncharov et al., 2016; Marchese et al., 2016). Infections were reported most frequently.

Garlic in general has a broad spectrum of targets including antibacterial, antiviral, antifungal, and antiprotozoal. Garlic which is processed into extract has antifungal activity against *C. albicans* (Agustantina & Soekartono 2021). Garlic extract exhibits a broad fungicidal spectrum covering diverse species, such as *Candida*, *Trichopython*, *Cryptococcus*, *Aspergillus*, etc. The solvents reported having antifungal activity are aqueous, ethanol, methanol, and petroleum ether. Garlic extract acts on cell walls and causes irreversible structural damage, leading to loss of structural integrity and proliferative ability. These changes cause damage to organelles and nucleus leading to cell death. Moreover, allicin and garlic oil penetrate cell membranes, and cell organelles such as mitochondria cause organelle damage and cell death (Batiha et al. 2020).

The fungicidal action of garlic is thought to be mediated by inhibition of lipid, nucleic acid, and protein synthesis or by inhibiting the formation of *C. albicans* hyphae (Felix et al. 2019). The active ingredient responsible for being a fungicidal agent in garlic is allicin. In this regard, allicin plays a central role in the biological activity of garlic. Allicin is considered a potent compound that has a significant antifungal function which has been confirmed through in vitro assays with pure allicin, whereas so far it is in vivo activity has not been confirmed through preclinical and clinical trials (Petropoulos et al. 2018).

The garlic ethanol extract was tested by the Kirby-Bauer method with concentrations of 100%, 80%, 60%, and 40% to inhibit the growth of fungi with a diameter of 21.4 mm of the inhibition zone; 18.6 mm; 14.8 mm and 11.6 mm respectively, while the 20% concentration could not inhibit growth (Andayani & Kurniawan 2013). Garlic petroleum ether extract was inhibited at a concentration of 500 l. 750 l and 1000 l with a zone of inhibition diameter of 19.46 mm, respectively; 27.46 mm and 31.11 mm (Khaira et al. 2016). The minimal inhibition level (MIC) of the concentration of pure garlic juice that has been diluted in stages (serial dilution) is 25% by the dilution method. Meanwhile, with the UV-Vis spectrophotometric measurement method, MIC was at a concentration of 50% because at a concentration of 25% the absorbance still increased (Rambet et al. 2017). Li et al. (2016) conducted a study on the antifungal activity of garlic oil against *C. albicans*, and the results showed antifungal activity at a minimum concentration of 0.35 g/mL. In patients who received garlic therapy and were responsive, it was found that the expression of candidalysin (ECE1) was down-regulated. Meanwhile, in unresponsive patients, ECE1 showed an increase (Said et al. 2020).

Research conducted by Avci et al. (2016) yielded several findings. First, vitamin C can kill *C. albicans* in

phosphate-buffered saline (PBS) media, a medium commonly used in studies using photodynamic therapy (PDT), but there is no evidence that vitamin C kills *C. albicans* in other growth media or PBS. containing glucose. Second, vitamin C requires active metabolism and oxygen to kill *C. albicans* in PBS media. Third, the killing effect of vitamin C is increased at low free iron concentrations and in the inhibitory state of mitochondria. Fourth, the killing effect of vitamin C depends on the growth phase of *C. albicans*, the early stationary phase of *C. albicans* is sensitive to vitamin C. Garlic petroleum ether extract combined with vitamin C did not show significant MIC, only 15.4 mm (Khaira et al. 2016).

Garlic that has been processed into extract has antifungal activity against *C. albicans* (Agustantina & Soekartono 2021). The ability of garlic (A. sativum) to inhibit fungi is believed to be due to its antifungal compounds. The compound that acts as an antifungal agent is allicin. Allicin inhibits protein and nucleic acid synthesis, but lipid synthesis is completely inhibited, and inhibition of lipid synthesis may be the main reason for the antifungal activity of garlic (A. sativum) (Masoudi & Rahimi 2017). Lipids are one of the components of the Candida cell wall and are mainly in the form of phospholipids and sterols. Inhibition of lipid synthesis increases the permeability of fungal cell membranes, causing fungal cytoplasmic leakage and causing fungal cytolysis (Nurhasanah et al. 2017). The fungicidal action of garlic is thought to be mediated by inhibition of lipid, nucleic acid, and protein synthesis or by inhibiting the formation of *C. albicans* hyphae (Felix et al. 2019). Garlic oil against *C. albicans* has antifungal activity. This is indicated by the results of the study in the form of antifungal activity at a minimum concentration of 0.35 g/mL (Li et al. 2016).

The study by Said et al. (2020) showed that patients who received garlic therapy and were responsive to therapy found that ECE1 expression showed down-regulation. Whereas in unresponsive patients, ECE1 shows up-regulation activity. With the dilution method, pure garlic juice at concentrations of 100%, 50%, and 25% showed the results in the form of a clear test tube, which means the growth of *C. albicans* was inhibited. Meanwhile, by measuring the UV-Vis spectrophotometer, only the concentration of 100% and 50% decreased in absorbance, while the concentration of 25% increased, so the MIC is at a concentration of 50% (Rambet et al. 2017). Andayani & Kurniawan (2013) examined the ethanolic extract of garlic with the results of concentrations that could inhibit the growth of *C. albicans* were 100%, 80%, 60%, and 40% with an inhibitory diameter of 21.4 mm; 18.6 mm; 14.8 mm and 11.6 mm respectively. The concentration of 20% did not produce inhibition diameter. So that the MIC is at a concentration of 40%.

Vitamin C has many activities that can boost immunity. Vitamin C increases the proliferation of T and B lymphocytes. In addition, ascorbic acid is a very effective antioxidant because of its ability to donate electrons, thereby protecting important biomolecules that the body needs (proteins, carbohydrates, nucleic acids, and fats) from damage caused by oxidants (Carr & Maggini 2017). Research conducted by Avci et al. (2016) yielded several findings. First, vitamin C can kill *C. albicans* in PBS media, a medium commonly used in studies using PDT, but there is no evidence that vitamin C kills *C. albicans* in other growth media or PBS. containing glucose. Second, vitamin C requires active metabolism and oxygen to kill *C. albicans* in PBS media. Third, the killing effect of vitamin C is increased at low free iron concentrations and in the inhibitory state of mitochondria. Fourth, the killing effect of vitamin C depends on the growth phase of *C. albicans*, the initial stationary phase of *C. albicans* is sensitive to vitamin C. Another study conducted by Khaira et al. (2016) used garlic petroleum ether extract with a concentration of 1000 l, and extract of 750 l. + DMSO 250 l, extract 500 l + DMSO 500 had an inhibition zone of 31.11 mm; 27.46 mm; 19.46 mm respectively. Meanwhile, when combined with vitamin C, only extract concentration of 500 l + vitamin C 500 l had an inhibition zone diameter of 15.4 mm.

DISCUSSION

Garlic oil can penetrate the plasma membrane because it has lipophilic characteristics. Several organelles such as mitochondria and vacuoles were damaged in *C. albicans* cells and caused allicin-induced cell death. Garlic oil therapy also downregulated several proteins and genes, causing impaired cellular metabolism of *C. albicans*. This also agrees with the results of other studies which state that garlic therapy lowers ECE1 regulation. ECE1 is a gene that functions to produce a cytotoxin called candidalysin. Garlic extract using ethanol and petroleum ether as solvents showed activity to inhibit the growth of *C. albicans*. The difference in the results of the dilution and diffusion methods is thought to be because the dilution method is pure juice, while the diffusion method uses ethanol as a solvent.

Another cause could be the difference in the percentage concentration of each method. In the dilution method, from a concentration of 100% then 50% it drops to 25%, and so on. While the diffusion method, the concentration is 100%, 80%, 60%, 40% and 20%. Garlic (A. sativum) has greater inhibitory power. This could be because allicin derivatives, namely diallyl disulfide (DADS), diallyl sulfide (DAS), and ajoene

have antibacterial activity but are not as strong as allicin (Upadhyay 2016). Another study found that DADS compounds did not show good antifungal activity unless used at very high doses (Borlingus et al. 2014).

Vitamin C studied with *C. albicans* in PBS media using the PDT method showed activity to inhibit the growth of *C. albicans*. The antifungal activity was increased in PBS media, active metabolism and the presence of oxygen to kill *C. albicans* in PBS media, low free iron concentration, and inhibition of mitochondria and the early stationary growth phase. Meanwhile, the combination of garlic petroleum ether extract and vitamin C did not show significant results. This is due to research with a combination of garlic petroleum ether extract and vitamin C using sabouraud dextrose agar media which contains glucose. The presence of glucose can increase the growth of *C. Albicans*, while PBS media, it does not have glucose.

Strength and limitation

The strength of this study is that it presents a clear and concise overview of the antifungal properties of garlic and its extracts. The study provides specific information about the mechanisms by which garlic can inhibit the growth of C. albicans, including its ability to downregulate ECE1 and damage cell organelles. Additionally, the study provides quantitative data on the MIC of different garlic extracts, which adds credibility to the argument.

CONCLUSION

Garlic oil has antifungal activity. Garlic also downregulated ECE1 which is a virulence factor. The ethanol extract of garlic has a MIC at a concentration of 40%, while the pure pressed garlic has a MIC of 50%. The antifungal activity of vitamin C was increased in PBS media, active metabolism and the presence of oxygen, low free iron concentration, mitochondrial inhibition, and in the early stationary growth phase. The combination of garlic petroleum ether extract and vitamin C in SDA media did not show significant results because of the presence of glucose which increased the growth of *C. albicans*.

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Conflict of interest

None.

Funding disclosure

None.

Author contribution

MFL conceptualized and supervised the study, validated, reviewed, and finalized the manuscript. KA managed the administration, collected and analyzed the data, and wrote the manuscript. SAN validated, reviewed, and finalized the manuscript.

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Review Article

HOOKWORM IN STRAY CATS (*Felis silvestris catus*) AS CUTANEOUS LARVA MIGRANT AGENT (CLM) IN HUMANS

Fadhil Ihsan Mahendra[1], Soebaktiningsih[2], Risma Karlina Prabawati[3]
[1]Medical Program, Faculty of Medicine, Universitas Muhammadiyah, Malang, Indonesia
[2]Department of Parasitology, Faculty of Medicine, Universitas Muhammadiyah, Malang, Indonesia
[3]Department of Neurology, Faculty of Medicine, Universitas Muhammadiyah, Malang, Indonesia

ABSTRACT

Cats are the host of a wide variety of microorganisms including ectoparasites and endoparasites.One of the endoparasites that infect cats is hookworm. The hookworms consists of two groups, the animal hookworms, and the human hookworms. The manifestation that can be caused by animal hookworms to humans is Cutaneous Larva Migrant (CLM). This study aimed to discover whether hookworm in stray cats (Felis silvestris catus) can cause CLM in humans. We performed a systematic search in Pubmed/Medline and Cochrane published between 2016 and 2021 with no restrictions by language, research country, or type of research design . The results of the analysis showed that the high level of hookworms infection in stray cats could increase the risk of CLM in humans. Based on the study, we could conclude that the high prevalence of hookworm infection in cats plays an important role in the increased risk of zoonoses in humans which in turn could also increase the prevalence of CLM in humans.

Keywords: *Hookworm; stray cat; cutaneous larva migrant; infectious disease*

Correspondence: Soebaktiningsih, Department of Parasitology, Faculty of Medicine, Universitas Muhammadiyah, Malang, Indonesia. Email: wrdsbt9@gmail.com

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Highlights:

1. Risk factors that can increase the incidence of CLM in humans include male sex, children aged <15 years, low-income people, and daily behaviour of walking outdoors without using footwear, especially on the sand.
2. Risk factors that play the most role in increasing the incidence of CLM in humans are walking outdoors without using footwear, especially on the sand.

INTRODUCTION

Cutaneous Larva Migrant (CLM) is a skin disease caused by filariform larvae of animal hookworms (Baple & Clayton 2015). The prevalence of CLM is very high, especially in developing countries with tropical-subtropical climates (Reichert et al. 2016). The incidence rate of CLM can increase up to fifteen times higher in the rainy season (Leung et al. 2017). The prevalence of hookworm infection in Thailand varies from 0.6% to 13.4%, while in Indonesia, it is 2.4%, 0.6%, 5.1%, 1.6%, and 1.0% from 2002 to 2006 with one of its manifestations is CLM (Kladkempetch et al. 2020).

Stray cats that live freely around human habitations often roaming around dirty places, making them a habitat for various kinds of parasites, one of which is animal hookworm (Taetzsch et al. 2018, Wang et al. 2019). The population of stray cats is also very large and continues to increase. Based on the World Society for the Protection of Animals (WSPA) in 2008, there were 15 million cats in Indonesia, the third-largest in the world (Farantika & Susanti 2019). The large population and the habitats of stray cats close to humans increase the risk of spreading parasites from cats to humans and causing zoonotic diseases (Jia-Chi et al. 2016). Research conducted by da Silva et al. (2020), that there was a relationship between the presence of animal hookworm eggs in stray cat feces and 59 cases of CLM in humans in Votuporanga, Sao Paulo, Brazil. Besides, the high prevalence of hookworm infection in cats affects the incidence of zoonotic diseases in humans (Pumidonming et al. 2017).

This study aimed to determine whether there is a relationship between the increase in the stray cats population and the physical environment that can support the growth of animal hookworm to the increase in the prevalence of CLM in humans. CLM is a disease that can be diagnosed based on clinical findings. This disease can cause discomfort to patients such as itching and triggering them to tend to scratch. The habit of scratching can lead to secondary skin infections such as cellulitis. In addition, in rare cases, CLM can cause Loeffler syndrome. Therefore, the incidence of CLM can be understood, therapy can be given effectively, and zoonotic infections can be controlled in the future.

MATERIALS AND METHODS

We studied this hypothesis by performing a systematic search of two comprehensive online databases (Pubmed/Medline and Cochrane) using the following keywords: <cutaneous larva migrans> or <creeping eruption> or <CLM> or <HrCLM> AND <stray cat> AND <hookworm>. The diagnosis of CLM was always clinical. Patients were included without considering gender or age. Only literature published between 2016 and 2021 was included to ensure relevance with regard to the current epidemiologic situation. No restrictions by language, research country, or type of research design were applied. Both full-text papers and abstracts were included, as well as case reports and case series were considered. References from selected literature were evaluated, while experts in the field were consulted as additional search sources.

Primary outcomes were prevalence and risk factors for cutaneous larva migrants in humans. Secondary outcomes were prevalence and risk factors of hookworm infection in stray cats that could increase the incidence of CLM in humans. Due to the nature of the data, no meta-analysis or summary measures were calculated.

RESULTS

Several studies show the prevalence rate of stray cats infected by hookworm. The results of a study conducted by Szwabe and Blaszkowska (2017) using the sedimentation technique on a total of 68 fecal samples from stray cats in Poland showed that only 3% of the stool samples studied were positive for hookworm. Another study was conducted by Korkmaz et al. (2016) on 100 fecal samples from stray cats in Kirikkale, Turkey using the flotation technique. The study found that parasites were found in 47% of the total samples, while only 2 samples were positive for hookworm (4.2%). Another study using the flotation technique was also conducted by Fu et al. (2019). In this study, 308 stray cat feces samples were collected from 8 cities in Guangdong Province, China. The results obtained were as many as 47 positive stool samples containing hookworm (15.26%) (Table 1).

The next research discussed the risk factors that affected hookworm infection in cats. The results of research conducted by Wahyudi et al. (2017) using direct smear, sedimentation, flotation, and McMaster techniques on 180 samples of stray cat feces in Surabaya showed that worm eggs were positively found in 68 samples (37.8%), while hookworm eggs were found in 42 samples (23.3%). Research using a similar technique was conducted by Rabbani et al. (2020) on 120 samples of stray cats and domestic cat feces in Lumajang, East Java, Indonesia. The results of the study showed that 68.33% of cat feces samples contained gastrointestinal parasites, including 18.33% hookworms. A total of 7/60 samples of domestic cat feces and 15/60 samples of stray cat feces contained hookworm. Besides, it was found that 2 domestic cats of <1 year old and 5 domestic cats of >1 year old were infected by hookworm, while 4 stray cats of <1 year old and 11 cats of >1 year old were infected by hookworm.

Another study conducted by Oktaviana et al. (2014) used the flotation technique on 80 samples of a stray cat and domestic cat feces. The results obtained 19/40 samples of stray cat feces (47.5%) and 10/40 samples of domestic cat feces (25%) contained hookworm. Besides, 17/45 male cats (37.8%) and 12/35 female cats (34.3%) were infected by hookworm. The results of research conducted by Fu et al. (2019) showed that of the 47 stray cats, 8/47 aged <1 year (17.02%) and 7/47 >1 year (14.89%) were positively infected by hookworm, while 19.14% of male cats and 12.76% of female cats were positively infected by hookworm (Table 2).

Subsequent research also discussed the risk factors that most affected hookworm infection in cats. The results of research conducted by Rabbani et al. (2020) using a cross-sectional study method showed that the physical environment which includes soil texture, temperature, humidity, hygiene, and sanitation are risk factors that could affect the level of hookworm infection in cats. Based on the statistical analysis of the study, it obtained the following data, where sandy soil texture had an infection prevalence of 33.1% with a p-value of 0.764, wet soil had an infection prevalence of 47.7% with a p-value of 0.028, a temperature of more than 28.6-29.5C has an infection prevalence of 55.8% with a p-value=0.000, a humidity of 66% has an infection prevalence of 55.8% with a p-value=0.000, and poor water sanitation has an infection prevalence of 43.8% with p-value=0.000. A similar study was conducted by Fu et al. (2019) found that sandy soil texture has an infection prevalence of 47.2% with a p-value of 0.537, the temperature has an infection prevalence of 61.1% with a p-value of 0.000, and humidity has an infection prevalence of 61.1% with p-value=0.000 (Table 3).

Table 1. Prevalence of stray cats infected by hookworm

Lists of study	Method	Sample	Result
Szwabe and Blaszkowska (2017)	Sedimentation technique	68 fecal samples from stray cats in Poland	As many as 3% of the total samples were detected positive for hookworm
Korkmaz et al. (2016)	Flotation technique	100 fecal samples from stray cats in Kirikkale, Turkey	As many as 47% of all samples were found to be parasitic, only 2 samples were positive for hookworm (4.2%)
Yeqi Fu et al. (2019)	Flotation technique	308 stray cat feces samples from 8 cities in Guangdong, Province, China	A total of 47 stool samples were positive for hookworm (15.26%)

Table 2. Risk factors that affected hookworm infection in cats

Lists of study	Method	Sample	Result	
Wahyudi et al. (2017)	Direct smear, sedimentation, flotation, and McMaster	180 samples of stray cat feces in Surabaya	42 samples (23.3%) were positive for hookworm eggs	
Rabbani et al. (2020)	Direct smear, sedimentation, flotation, and McMaster	120 samples of a stray cat and domestic cat feces in Lumajang	Cat infected by hookworm	
			Domestic cat (n=60)	Stray cat (n=60)
			Number of cat • 7 (11.6%) Age (years old) • <1 y.o: 2 (28.57%) • >1 y.o: 5 (71.42%)	• 15 (25%) • <1 y.o: 4 (26.66%) • >1 y.o: 11 (73.33%)
Oktaviana et al. (2014)	Flotation	80 samples of a stray cat and domestic cat feces in Denpasar	Cat infected by hookworm	
			Domestic cat (n=40)	Stray cat (n=40)
			10 (25%)	19 (47.5%)
			Female (n=35)	Male (n=45)
			12 (34.3%)	17 (37.8%)
Yeqi Fu et al. (2019)	Flotation	47 stray cats	Cat infected by hookworm	
			Age • <1 year : 8 (17.02%) • >1 year : 7 (14.89%) Gender • Female: 12.76% • Male: 19.14%	

Table 3. Risk factors that most affected hookworm infection in cats

Lists of study	Variable	Prevalence of infection	p-value
Rabbani et al. (2020)	Sandy soil	33.1%	0.764
	Wet soil	47.7%	0.028
	Temperature >28.6-29.5C	55.8%	0.000
	Humidity 66%	55.8%	0.000
	Poor water sanitation	43.8%	0.000
Yeqi Fu et al. (2019)	Sandy clay loam	47.2%	0.537
	Temperature	61.1%	0.000
	Humidity	61.1%	0.000

Further studies discussed the prevalence of CLM in humans in several countries. The results of research by Sow et al. (2017) using a retrospective study method showed that the prevalence of CLM in France was 1-3% found in people who recently returned from endemic countries. The case study conducted by Guidice et al. (2019) found that there were 5 cases of autochthonous CLM (patients with no history of travel to tropical countries or CLM that occurred in the local area) in France in the last 25 years. Another study conducted by Reichert et al. in 2016, that the prevalence of CLM in Brazil was around 0.2% to 4.4-14.9% of the total general population, in the dry season and rainy season, respectively.

Subsequent studies discussed the risk factors that increased the incidence of CLM in humans, including gender, age, economic conditions, daily behavior, and environmental conditions. The research results of Reichert et al. (2016) in Manaus, Brazil showed that the number of CLM infections found in humans was caused by several factors, such as gender, including 44 males (13.4%) and 22 females (4.6%) cases. Based on age groups, it consisted of <4 years, 5-9 years, 10-14 years, 15-19 years, and >20 years with 15 (8.6%), 23 (14.4%), 16 (18.2%), 1 (2.2%), and 11 (3.3%) cases respectively. The economic conditions of the subject included poor, intermediate, and rich with 37 (11.5%), 21 (8%), and 8 (4%) cases respectively.

Other factors such as daily behavior (i.e., walking on the groundbarefoot, wearing footwear, walking on the sandy ground with no footwear, frequently wearing footwear, and always wearing footwear with 14/58 (24.1%), 52/731 (7.1%), 29/111 (26.1%), 33/420 (7.9%), and 4/269 (1.5%), respectively. In the case of environmental conditions which included whether or not the soil was contaminated with cat feces, found that as many as 17/103 cases (16.5%) were in an environment, where cat feces were present and 49/702 cases (7%) were found in an environment with no cat feces.

The results of another study conducted by Reichert et al. (2016) show data on the incidence of CLM per year on several factors such as gender, including male (0.86) and female (0.25); regarding the economic conditions of the people, including poor (0.68), intermediate (0.47), and rich (0.31); regarding daily behavior such as walking on the ground barefoot (0.78) and wearing footwear (0.48), walking on the sandy ground by never wearing footwear (0.90), often wearing footwear (0.49), and always wearing footwear (0.29). Another study conducted by Sow et al. (2017) obtained data on the number of CLM infections in humans toward several factors such as gender, including 22 cases (51.2%) in males and 21 cases (48.8%) in females; based on age, namely aged <25 years, 25-50 years old, and >50 years old with 9 (20.9%), 29 (67.5%), and 5 (11.6%) cases respectively. Similar research was also conducted by Heryantoro (2011) in Kulon Progo, Indonesia, that obtained data on the number of CLM infections in humans toward several factors such as gender, there are 54 cases (67.5%) in male and 26 cases (32.5%) in female; based on age, namely aged <15 and >15 years old with 46 (57.5%), and 34 (42.5%) cases, respectively (See Table 4).

Another research discussed the risk factors that most affected increasing the incidence of CLM in humans which included gender, age, economic conditions, daily behavior, and environmental conditions. The results of statistical analysis from the research of Reichert et al. (2016) were as follows: gender included male (OR = 3.21) and female (OR = 1); age <4 years (OR = 2.80), 5-9 years old (OR = 4.99), 10-14 years old (OR = 6.61), 15-19 years old (OR = 0.66), and >20 years old (OR = 1); the economic condition of the people which includes poor (OR = 3.16), intermediate (OR = 2.10), and rich (OR = 1); daily behavior such as walking on the ground barefoot (OR = 4.16), wearing footwear (OR = 1), walking on the sand with never wearing footwear (OR = 23.43), often wearing footwear (OR = 5.65), and always wearing footwear (OR = 1); the environmental condition which includes whether or not the soil was contaminated with cat feces, the environment that did contained cat feces (OR = 2.63), and the environment that did not contain cat feces (OR = 1). A similar study was conducted by Reichert et al. (2016) where the data obtained from statistical analysis based on the percentage of CLM incidence of each individual per year are as follows, gender includes male (0.86) and female (0.25); age <4 years (0.38), 5-9 years (0.46), 10-14 years (0.93), and 15-18 years (0.26); The economic condition of the people which includes the poor (0.68), intermediate (0.47) and rich (0.31); daily behavior such as walking on the ground barefoot (0.78), with wearing footwear (0.48), walking on sand with never wearing footwear (0.90), often wearing footwear (0.49), and always wearing footwear (0.29) (Table 4).

Table 4. Risk factors that increased the incidence of CLM in humans

		Variable	CLM (%)	OR (CI 95%)		p-value
Reichert et al. (2016)	Gender	Male	44 (13.4)	3.21		<0.001
		Female	22 (4.6)	1		
	Age	≤ 4 years old	15 (8.6)	2.80		0.012
		5-9 years old	23 (14.4)	4.99		<0.001
		10-14 years old	16 (18.2)	6.61		<0.001
		15-19 years old	1 (2.2)	0.66		0.695
		≥ 20 years old	11 (3.3)	1		
	Economic condition	Poor	37 (11.5)	3.16		0.004
		Intermediate	21 (8.0)	2.10		0.081
		Rich	8 (4.0)	1		
	Daily behavior	Walking on the ground				
		Barefoot	14/58 (24.1)	4.16		<0.001
		With wearing footwear	52/731 (7.1)	1		
		Walking on the sandy ground				
		Never wearing footwear	29/111 (26.1)	23.43		<0.001
		Often wearing footwear	33/420 (7.9)	5.65		0.001
		Always wearing footwear	4/269 (1.5)	1		
	Environmental condition	Animal feces on compound	17/103 (16.5)	2.63		0.001
		No animal feces on compound	49/702 (7.0)	1		
Reichert et al. (2018)	Gender	Male	57	0.86	3.41	<0.001
		Female	21	0.25	1	
	Economic condition	Poor	41	0.68	2.15	0.024
		Intermediate	23	0.47	1.51	0.259
		Rich	11	0.31	1	
	Daily behavior	Walking on the ground				
		Barefoot	14	0.78	1.57	0.126
		With wearing footwear	64	0.48	1	
		Walking on the sandy ground				
		Never wearing footwear	25	0.90	3.24	0.002
		Often wearing footwear	44	0.49	1.66	0.168
		Always wearing footwear	9	0,29	1	
Sow et al. (2017)	Variable			CLM (%)		
	Gender	Male		22 cases (51.2)		
		Female		21 cases (48.8)		
	Age	<25 years old		9 (20.9)		
		25-50 years old		29 (67.5)		
		>50 years old		5 (11.6)		
Heryantoro et al. (2012)	Gender	Male		54 cases (67.5)		
		Female		26 cases (32.5)		
	Age	<15 years old		46 (57.5)		
		≥15 years old		34 (42.5)		

DISCUSSION

Prevalence of stray cats infected by hookworm

Regional conditions (climate, humidity, temperature and soil conditions) are important things that may affect prevalence rates. State that geographical factors of a region can affect prevalence rates, other factors including climate (Abu-Madi et al. 2008). The difference in the prevalence of hookworm infection in cats obtained from Poland (3%) (Szwabe & Blaszkowska 2017) and Turkey (4.2%) (Korkmaz et al. 2016) compared to China (15.26%) (Fu et al. 2019) was quite far (See Table 1). This is because Poland and Turkey are not tropical countries, while Guangdong Province, China, is an area with a tropical climate. Based on these three studies, the climatic conditions of an area affect the prevalence of hookworm infection in cats. The tropical climate has high humidity so that it is a fertile ground for the life of parasitic worms. Tropical climates have a higher prevalence of hookworm infection in cats than in non-tropical areas. This is because high humidity is an optimum condition for the development and dissemination of various species of

worm diseases and areas with tropical climates tend to have warm temperatures between 23-30°C, humidity levels of 80-100%, and the existence of a long rainy season that can maintain the scale of infection in endemic proportions, support larval growth, and help infective larvae to survive on the ground. In other conditions, lower temperatures making egg development takes longer or inhibits egg's hatch (Farantika, R et al. 2019; Sucitrayani et al., 2014)..

Risk factors that affected hookworm infection in cats

Another factor that made of the high prevalence of worm infections in stray cats is because most cats forage in trash cans. Stray cats live in moist and dirty areas where these envinronments are ideal conditions for the development of an infective form of worm larvae (Oktaviana et al., 2014). Based on the previous four studies (Table 2), it is known that stray cats are more at risk for hookworm infection than domestic cats, because stray cats live untreated, consume food that is not nutritious, and live in a dirty, humid, and poor sanitation environment that are ideal conditions for the development of infective larvae of hookworms. The prevalence of hookworm infection in cats aged <1 year and >1 year did not have a significant difference, as well as the prevalence of hookworm infection in male and female cats. We briefly reported that the most important factor influencing the level of hookworm infection in cats is the physical environmental conditions which include hygiene, temperature, humidity, and sanitation, with the risk factors that most affect the level of hookworm infection in cats (i.e., temperature and humidity with a p-value of 0.000) (Table 3).

Prevalence and risk factors of CLM in humans

The data on CLM prevalence in humans obtained from each region may vary because there are several factors that influence it, especially climate. The prevalence of CLM in humans in Brazil was higher than in France because Brazil is a country with a tropical climate, while France does not have a tropical climate. In tropical countries, the prevalence of CLM in animals and humans tends to be high. The high prevalence of hookworm infection in cats plays an important role in increasing the risk of zoonoses in humans which can increase the prevalence of CLM in humans (Pumidonming et al. 2017).

Based on the previous four studies, males were more at risk of developing CLM than females, because they were more likely to have contact with the ground than females. Research conducted by Reichert et al. (2016) stated that the age most at risk for CLM was children or individuals aged <15 years, because they tent to play outdoors without wearing footwear, resulting in direct contact between the skin and the ground or sand. Different statements were obtained from a study that the age most at risk for CLM is individuals aged 25-50 years (Sow et al. 2017). This difference can occur because the research was conducted in France, which was not a CLM endemic country, so the collected data comes from people who have traveled or have just returned from a CLM endemic country.

Another factor that can increase the risk of getting CLM is economic conditions. In this case, the poor tend to be at risk for CLM, because people with low economy usually live simple and are limited life. People with low economy tend to live in dirty and slum environments and consume less nutritious food, so they are vulnerable to getting CLM. Another influential factor in increasing the risk of developing CLM is walking outdoors (i.e., on the sandy ground) with no shoes. Sandy soil is one of the physical environmental factors that support the development of hookworm larvae. Walking outside barefoot will increase direct contact between sand or soil with the skin, which then allows infective larvae to penetrate directly into the skin, causing the CLM. It can be concluded that the most influential risk factor in increasing the incidence of CLM in humans is daily behavior, such as walking on the sand barefoot.

Our study can answer the question of why developing countries with tropical climates have a higher prevalence of CLM than non-tropical countries. Based on the results of the study, we can determine the risk factors that play the most role in causing hookworm infection in stray cats, zoonotic infections, and the incidence of CLM in humans. Tropical countries have a higher prevalence of hookworm infection in cats and humans than non-tropical countries; physical environmental conditions that include hygiene, temperature, humidity, and sanitation affect the rate of hookworm infection in cats and humans; the high prevalence of hookworm infection in cats plays an important role in increasing zoonotic infections in humans which then can increase the prevalence of CLM in humans. Developing countries with tropical to subtropical climates have a physical environment (temperature and humidity) that supports the growth of animal hookworm larvae. In addition, the management and control of the stray cat population are also not good. Environmental hygiene and water sanitation in some places in developing countries are also poor. That was the cause of the high prevalence of CLM in

developing countries, especially those with tropical-subtropical climates.

Strength and limitation

In this study, we found that there were not many studies that discussed hookworm and CLM. There were also little data on the prevalence of CLM, especially in Indonesia. Many researchers had discussed the number of hookworm eggs in cat or dog feces, but only a few had associated it with the prevalence of CLM. Therefore, the further research study is suggested to discuss the relationship between the animal hookworm eggs in stray cat feces and the incidence of CLM in an area.

CONCLUSION

Hookworm in stray cats (*Felis silvestris catus*) can cause CLM in humans. The high prevalence of hookworm infection in cats plays an important role in the increased risk of zoonoses in humans which in turn can increase the prevalence of CLM in humans. In addition, tropical climate, sandy soil, and physical environmental conditions including temperature, humidity, hygiene, and sanitation affect the level of hookworm infection in cats and humans.

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Conflict of interest

None.

Funding disclosure

None.

Author contribution

FIM, S, and RKP contributed in the conception of the study idea, data collection and analysis, revise the manuscript. S was final approval to be published and agreement to be accountable for all aspects.

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