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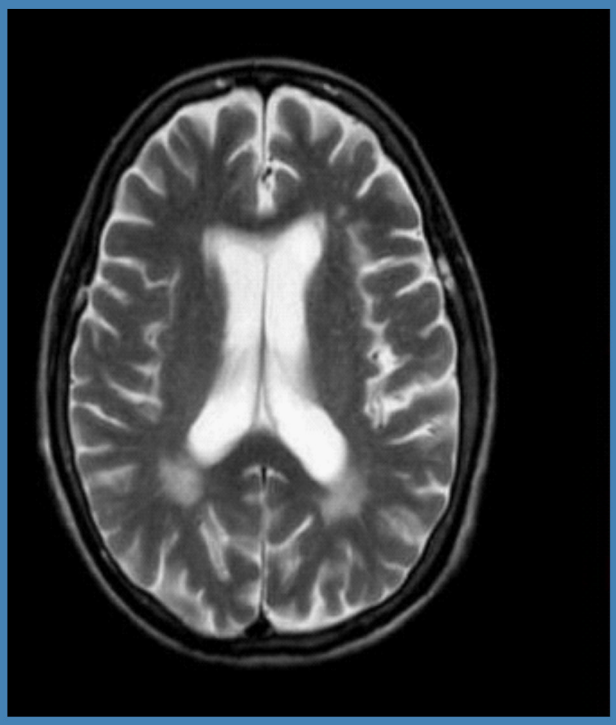

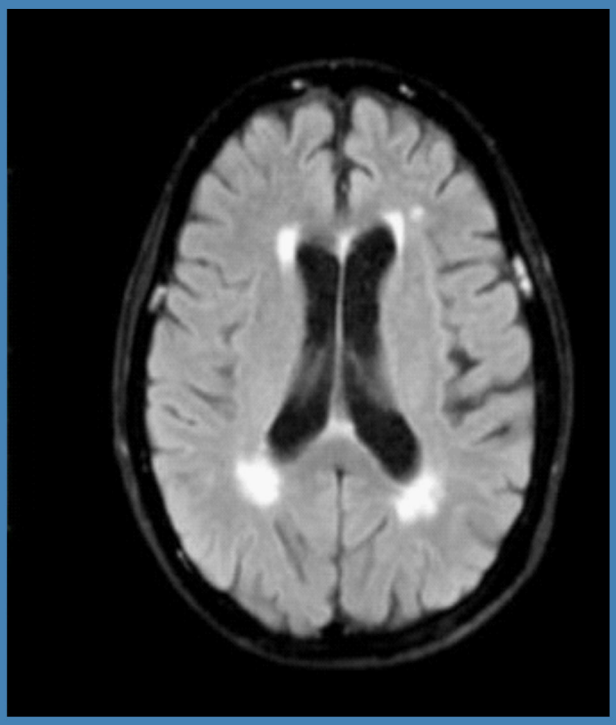

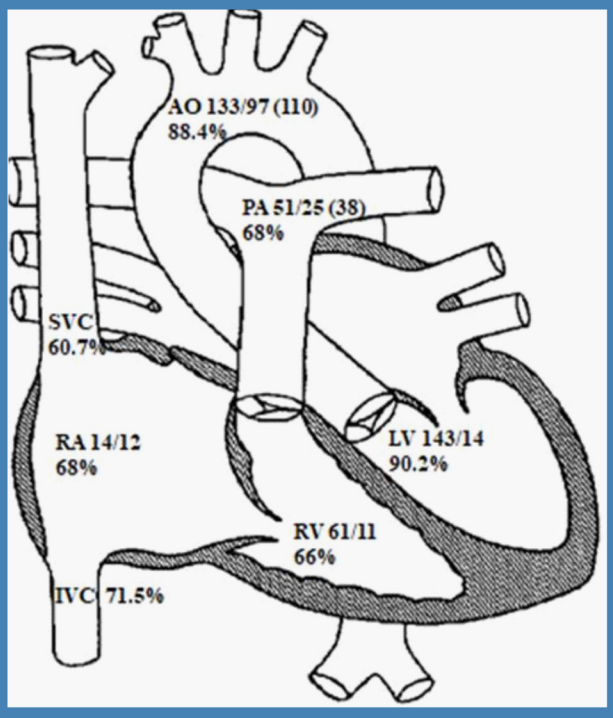

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Effects of 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-chroman-4-one on serum levels of antioxidant enzymes in hyperlipidemic rats

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ABSTRACT

Hyperlipidemia triggers oxidative stress caused by an imbalance between oxidant and antioxidant levels due to the excess production of reactive oxygen species (ROS). The increase of ROS can decrease antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). 7-OH-2-(4-OH-3-Methoxyphenyl)-chroman-4-one is exogenous antioxidants isolated from mahogany seeds (*Swietenia macrophylla* King). This study aimed to evaluate the effects of the 7-OH-2-(4-OH-3-methoxyphenyl)-chroman-4-one on serum levels of SOD, CAT, and GPx in hyperglycemic rats. Thirty-six male Wistar rats (Rattus norvegicus) were divided into the following six groups: (N) normal group, (HL) hyperlipidemia group, (P) hyperlipidemia group with simvastatin, F10, F30, and F90 hyperlipidemia group with 7-OH-2-(4-OH-3-methoxyphenyl)-chroman-4-one 10, 30 and 90 mg/200g body weight (BW), respectively. Hyperlipidemia was induced by feed enriched with cholesterol and cholic acid. Treatments were administered orally by gavages. After 4 weeks of treatments, blood sample was drawn and serum levels of SOD, CAT, and GPx enzymes were analyzed using a spectrophotometric method. Serum levels of SOD, CAT, and GPx in hyperlipidemic rats treated with 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-chroman-4-one at dose 10, 30 and 90 mg/200g BW were higher than HL group. In addition, no significantly different on serum SOD and CAT between group F90 and group P was observed (p>0.05).

ABSTRAK

Hiperlipidemia dapat memicu stress oksidatif yang disebabkan oleh ketidakseimbangan antara senyawa oksidan dan kadar antioksidan akibat produksi reactive oxygen species (ROS) yang berlebih. Kenaikan ROS ini dapat menurunkan enzim antioksidan seperti superoksida dismutase (SOD), katalase (CAT) dan glutation peroksidase (GPx). Senyawa 7-OH-2-(4-OH-3-metoksifenil)-kroman-4-one adalah antioksidan eksogen yang diisolasi dari biji mahoni (*Swietenia macrophylla* King). Tujuan dari penelitian ini adalah mengkaji pengaruh pemberian senyawa 7-OH-2-(4-OH-3-metoksifenil)-kroman-4-one terhadap kadar SOD, CAT dan GPx dalam serum tikus hiperglikemia. Sebanyak 36 ekor tikus wistar (Rattus norvegicus) jantan dibagi menjadi 6 kelompok yaitu (N) kelompok normal, (HL) kelompok hyperlipidemia, (P) kelompok hyperlipidemia + simvastatin, F10, F30, dan F90 kelompok hyperlipidemia + 7-OH-2-(4-OH-3-metoksifenil)-kroman-4-one berturut-turut dengan dosis 10, 30 dan 90 mg/200g berat badan (BB). Tikus hiperglikemia dibuat dengan diinduksi makanan kaya kolesterol dan asam kolic. Enzim SOD, CAT dan GPx dianalisis menggunakan metode spektrofotometri. Kadar SOD, CAT, dan GPx serum tikus hiperlipidemia yang diberi 7-OH -2-(4-OH-3-metoksifenil)-kroman-4-one dosis 10, 30 dan 90 mg/200g BB lebih tinggi dibanding kelompok HL. Kadar SOD dan CAT serum kelompok F90 (dosis 90mg/200g BB) berbeda tidak bermakna dengan kelompok P (p>0,05).

Keywords:
hyperlipidemia:
superoxide dismutase;
catalase;
glutathione peroxidase;
antioxidants

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INTRODUCTION

Hyperlipidemia is a medical condition characterized by an increase in one or all of the lipid or lipoprotein profiles in the blood.[1] These conditions lead to the development of free radicals in the body that cause other pathological diseases. Hyperlipidemia is the most common cause of atherosclerosis which affects more than 3 million adults throughout the United States and Europe. Recently, the incidence of the atherosclerosis is rapidly increasing.[2] The decrease in antioxidants caused by reactive oxygen species (ROS) is a key factor for the initiation of the development of hyperlipidemia-related diseases such as atherosclerosis.[3] An imbalance between ROS production and the endogenous antioxidant systems can cause damage to cellular biomolecules, including lipids, proteins, and DNA.[4]

Several natural antioxidants such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) act as radical scavengers which are biomolecular repair systems damaged by free radicals.[5] These enzymes act as an inhibitor of the oxidation process and also inhibit chain oxidant reactions at small concentrations so they can suppress the potential threat of pathological processes.[6] The SOD enzyme act as the first scavenger by catalyzing the superoxide anion into H_2O_2 and oxygen molecules.[7] The CAT enzyme is a tetrameric ferriheme oxidoreductase which catalyzes H_2O_2 into water and oxygen.[8] In addition, there is a debate on the role of CAT versus peroxynitrite, but recent advances reported the ability of CAT as an ONOO-scavenger.[9] The GPx enzyme is a selenium-dependent oxidoreductase that uses H_2O_2 or organic hydroperoxides as oxidants and tripeptide glutathione (GSH) as electron donors.[10]

Hyperlipidemia conditions can be treated through a pharmacological approach by considering the side effects associated with drugs. Several studies have examined natural ingredients that have active compounds such as polyphenols and flavonoids which have antioxidant and antihyperlipidemic activities.[11]

Mahogany seeds (*Swietenia macrophylla* King) have a variety of isolated pure compounds with a large number of pharmacological activities that have been identified and isolated. Some of these compounds have hypolipidemic and antioxidant activities.[12] One of the compounds that was successfully isolated from mahogany seeds was 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-chroman-4-one which is a compound belonging to the flavonoid class which has many benefits including as antioxidant effect.[13] This study aimed to evaluate the antioxidant effects of 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-chroman-4-one by measuring serum antioxidant enzymes in hyperlipidemic rats.

MATERIALS AND METHODS

Compound tested

7-Hydroxy-2-(4-hydroxy-3-methoxyphenyl)-chroman-4-one was isolated from S. macrophylla King by Dr. Sri Mursiti from the Department of Chemistry, Faculty of Mathematics and Natural Sciences, Universitas Negeri Semarang, Semarang.

Experimental design

Thirty-six male Wistar rats weighing between 150 and 200 g, 10 weeks old, were used in this study. Serum levels of SOD, CAT, and GPx were tested using a post-test only with a normal group design. The research location was conducted in two laboratories: The Biochemistry Laboratory, Faculty of Medicine, Public Health and Nursing,

Universitas Gadjah Mada, and the Food and Nutrition Laboratory, Universitas Gadjah Mada, Yogyakarta, Indonesia. The experiments were carried out according to the guidelines for the use of animals and approved by the Medical and Health Research Ethic Committee, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada (No. KE/FK/08/8/EC/2017).

The rats were divided into 6 groups of experimental with 6 rats in each group with the following distribution: Normal group (N), hyperlipidemia group (HL), hyperlipidemia group with simvastatin 0.18 mg/200 g BW (P), hyperlipidemia group with 10 mg (F10), 30 mg (F30) and 90 (F90) mg/200 g BW 7-OH-2-(4-OH-3-methoxyphenyl) chroman-4-one, respectively. The rats were given AIN 93M standard feed for 5 days for acclimatization. Hyperlipidemia was induced by administering laboratory feed enriched with 10 g/kg cholesterol and 2 g/kg cholic acid for a week. Groups N and HL were given orally by infusion with the same volume of water, while the other groups were given 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-chroman-4-one once daily for 4 weeks. At the end of the experiment, the serum samples were collected for assessment of SOD, CAT, and GPx serum levels.

Serum antioxidant measurement

The serum SOD level was measured by spectrophotometry in percentages. The CAT serum level (U/mL) was measured by spectrophotometry.[14] The GPx serum level (U/mL) was measured spectrophotometrically.

Statistical methods

The data were expressed as the mean ± standard deviation (SD). One-way Anova was used to examine the effects of 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-chroman-4-one on serum levels of SOD, CAT, and GPx. The p value <0.05 was used to determine significant differences between groups. Homogeneous variance with individual comparisons were obtained by Tukey's HSD post hoc test.

RESULTS

Serum level of SOD

The results showed that the cholesterol-induced rats (HL) had lower serum SOD levels than the normal group (N) (FIGURE 1). Serum SOD levels in hyperlipidemic rats that were intervened with 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-chroman-4-one dose 10,30 and 90 mg/200g BW were higher than HL group that was not intervened. Serum SOD levels at the dose of 90 mg/200 gBW (F90) were not significantly different (p>0.05) compared with the simvastatin group (P).

Serum CAT levels

Serum CAT levels after administration of 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-chroman-4-one at doses 10, 30, and 90 mg/200gBW were higher compared to the hyperlipidemic group (HL) (FIGURE 2). Serum CAT levels at a dose of 90 mg/200gBB were not significantly different (p>0.05) compared with the simvastatin group (P).

Serum GPx levels

Serum GPx levels after administration of 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-chroman-4-one at doses 10, 30, and 90 mg/200gBW were higher compared to the hyperlipidemic group (HL) (FIGURE 3).

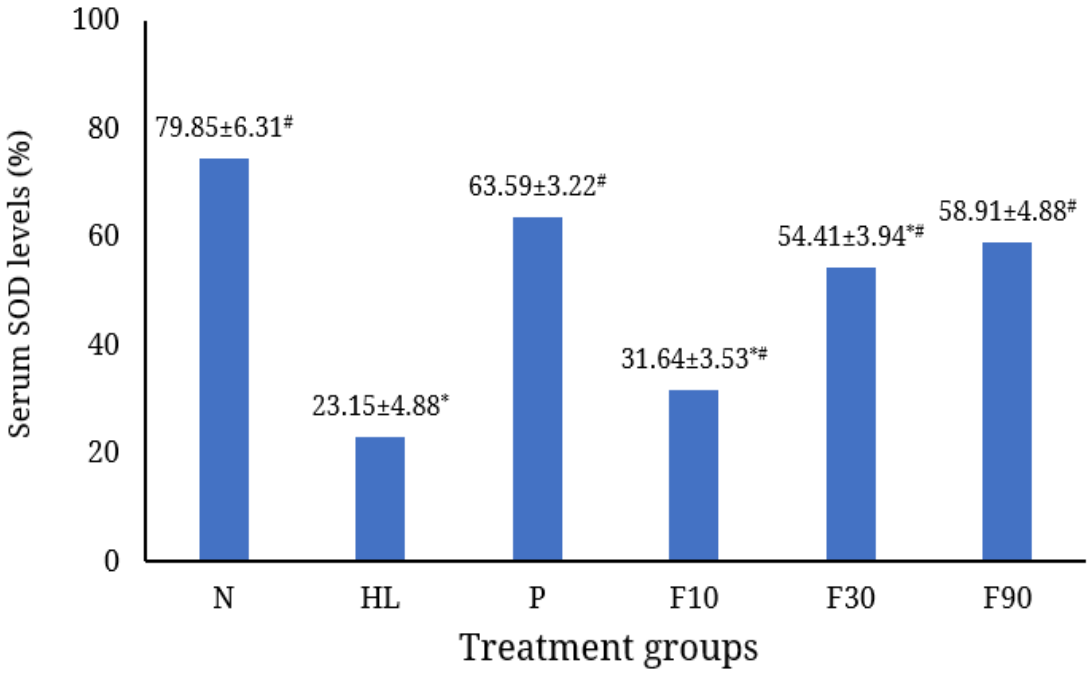

FIGURE 1. Serum SOD levels (%) in hyperlipidemic rats. N: normal, HL: hyperlipidemia, P: HL + simvastatin, F10, F30, F90: HL+ 7-OH-2-(4-OH3-methoxyphenyl)-chroman-4-one 10, 30, 90 mg/200g BW, respectively. Normality test with Shapiro-Wilk; data were tested with Anova test, Notation *: p <0.05 vs P; #: p <0.05 vs HL.

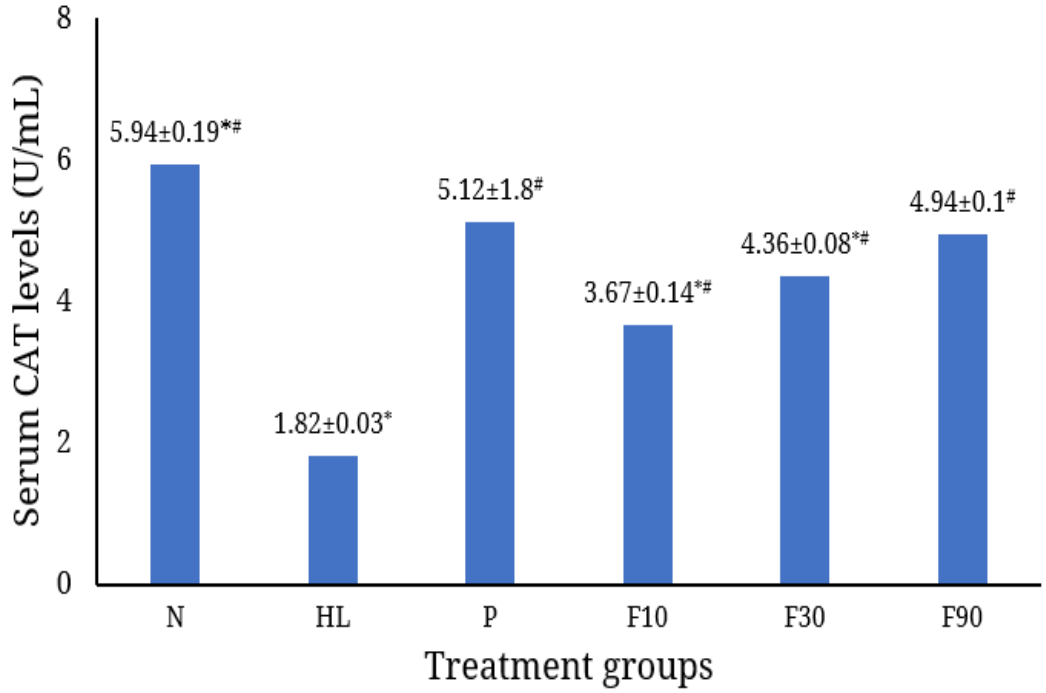

FIGURE 2. Serum CAT levels (U/mL) in hyperlipidemic rats. N: normal, HL: hyperlipidemia, P: HL + simvastatin, F10, F30, F90: HL+ 7-OH-2-(4-OH3-methoxyphenyl)-chroman-4-one 10, 30, 90 mg/200g BW, respectively. Normality test with Shapiro-Wilk; data were tested with Anova, p <0.05. Notation *: p <0.05 vs P; #: p <0.05 vs HL.

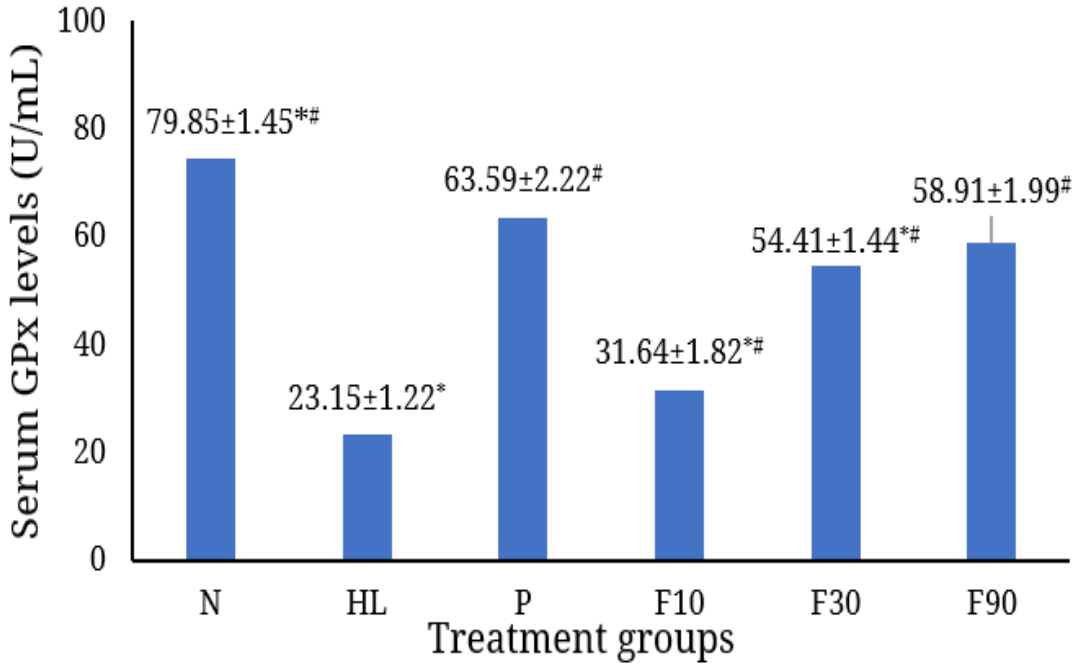

FIGURE 3. Serum levels of GPx (U/mL) in hyperlipidemic rats. N: normal, HL: hyperlipidemia, P: HL + simvastatin, F10, F30, F90: HL + 7-OH-2-(4-OH3-methoxyphenyl)-chroman-4-one 10, 30, 90 mg/200g BW, respectively. Normality test with Shapiro Wilk; data were tested with Anova p <0.05. Notation *: p <0.05 vs P; #: p <0.05 vs HL.

DISCUSSION

The high-fat diet for one week promotes hyperlipidemia as reviewed by Ayunda *et al.*,[15] who reported that cholesterol-induced rats had higher total and low-density lipoprotein (LDL) cholesterol than the normal group. Lipids are very susceptible to damage caused by free radicals which result in lipid peroxidation that causes adverse changes.[16]

High lipid levels change the properties of lipids and activate NADPH oxidase to produce ROS. High levels of fat and LDL can also suppress antioxidant enzymes.[17] This is in line with the results after induction of hyperlipidemia which showed lower serum antioxidant enzymes compared to the normal group. Increased lipid peroxidation and decreased antioxidant activity are the initial events in the development of hyperlipidemia.[18] Low antioxidant enzyme activity can also be associated with enzyme inactivation by ROS which causes damage to proteins.

Simvastatin is clinically proven to reduce blood cholesterol levels.[19] The simvastatin effectively inhibits HMG CoA reductase activity, thereby preventing cholesterol synthesis in the liver. Decreased cholesterol synthesis in the liver will affect the lipid profile in circulation.[20]

Flavonoids can reduce cholesterol levels by inhibiting the absorption of cholesterol in the intestines and can suppress increasing bile formation to be excreted with feces.[21] Both simvastatin and flavonoids have a positive effect on body fat balance. The 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-chroman-4-one is a flavonoid isolated from mahogany seeds which is a class of flavanones. The positive effects of 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-chroman-4-one on antioxidants and the body, especially in serum are reflected in the results of

post-intervention with 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-chroman-4-one for 4 weeks which can increase serum antioxidant enzymes (SOD, CAT or GPx) in various dose groups compared to the hyperlipidemia group.

Serum level of SOD and Catalase at the dose of 90 mg/200gBW (F90) have the same effect with the simvastatin group (P) p>0.05. The increase in serum antioxidant enzymes is in line with the study of Wu *et al.*,[22] who administered extracted flavonoids from *Rhodomyrtus tomentosa* Hassk berries thereby increasing serum SOD and glutathione peroxidase (GSH-Px) levels and suppressing serum malondialdehyde (MDA) levels. Zeng *et al.*,[23] also conducted research related to the increase in serum antioxidants after the flavonoid intervention, which compared six different flavonoids, namely epicatechin, epigallocatechin, procyanidin, quercetin, taxifolin, and rutin given to rats with induced aging by D-galactose.

In addition to increasing antioxidant enzymes such as SOD, CAT, and G-Px, the studied flavonoids also suppress MDA and inflammatory markers such as tumor necrosis factor-alpha (TNF-α), Interleukin (IL)-1β and IL-6 which are caused by oxidative stress. The structural diversity of flavonoids is postulated to be an important element that influences their antioxidant activity.[24] Several previous studies have compared the antioxidant activity of subclasses of flavonoids with different structures and the results reported that: the position and number of hydroxyl groups,[25] degree of polymerization,[26] glycosylated compounds,[27] the combination of carbonyl groups and C2=C3 double bonds[28] affect antioxidant activity.

7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-chroman-4-one belongs to the homoisoflavonoid group which is a naturally occurring oxygen heterocyclic compound having two aromatic rings and an additional carbon between rings B and C on the isoflavonoid framework.[29] The antioxidant activity of similar compounds using nitro blue tetrazolium (NBT) and 1.1-diphenyl-2-picrylhydrazyl (DPPH) which are free radical scavenging methods. So besides being able to encourage the expression of antioxidant enzymes such as SOD, CAT, and GPx, these compounds can also act directly as free radical scavengers.[30] The lack of antioxidant enzymes such as SOD was proven to promote lipid peroxidation and triglycerides in rat livers and fatty liver conditions.[31] The low catalase in circulation is associated with hyperhomocysteinaemia can increase myocardial wall dysfunction under ischemia reperfusion by excessive ROS production by increased lipid peroxidation.[32] The GPx deficiency can accelerate and modify the development of atherosclerotic lesions in mice.[33]

The results showed that the serum levels of SOD, CAT, and GPx in hyperlipidemic rats that were intervened with 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-chroman-4-one were higher than HL group that was not intervened. This finding can prevent the development of other diseases that originate from hyperlipidemic conditions through flavonoids related to the regulation of antioxidant enzymes, and suppression of lipid peroxidation by antioxidant gene expression in circulation.

CONCLUSION

Serum levels of SOD, CAT, and GPx in hyperlipidemic rats that are intervened with 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-chroman-4-one at dose 10, 30, and 90 mg/200gBW are higher than HL group that is not intervened. Group F90 (dose 90 mg/200g BW) and group P (simvastatin) shows no significant difference in results on serum SOD and CAT.

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High resolution ultrasonography of thyroid nodules: can ultrasonographic assessment obviate the need for invasive aspiration cytology in ultrasonographically benign lesions?

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Keywords:
thyroid imaging reporting & data system (TIRADS);
ultrasonography (USG);
Bethesda;
fine needle aspiration cytology (FNAC);
high resolution ultrasonography (HRUS)

ABSTRACT

The use of high-resolution ultrasound (HRUS) thyroid imaging has resulted in a significant revolution in the treatment of thyroid nodules. The enigma of thyroid nodules has been a blind spot for radiologists for a long period. Reporting a thyroid nodule as benign or malignant is quite difficult and many times not accurate. The American Collage of Radiology-Thyroid Imaging Reporting and Data System (ACR-TIRADS) 2017 classification has solved this problem to a large extent. However, the classification needed pathological confirmation for it to be highly accurate. We compared our HRUS-based TIRADS labeling of thyroid nodules with thyroid cytopathology using revised Bethesda classification system. Patients detected with thyroid nodules by HRUS were categorized using ACR-TIRADS and further were taken for fine needle aspiration cytology (FNAC) in our department. The pathological results were compared with the initial TIRADS category of the nodule and the effectiveness of the TIRADS classification in categorizing nodules into benign and malignant was assessed using various statistical variables. The initial USG and the FNAC were performed by a single radiologist with over 10 years of experience. A total of 201 patients underwent HRUS followed by FNAC after obtaining written consent in our department. The thyroid nodules labeled as true benign on ACR-TIRADS (TIRADS 2) were all true benign on Bethesda cytopathology (less than Bethesda III), confirming the high accuracy of HRUS. The diagnostic accuracy of HRUS in cases of ACR-TIRADS 3 nodules was approximately 90.6% with an error rate of 9.4%. Nodules labeled as ACR-TIRADS 4 and 5 had error rates of 47% and 10% in labeling nodules as malignant. The ultrasound-based ACR-TIRADS system can accurately predict the likelihood of specific nodules being benign. There is a strong concordance between Bethesda cytology and ACR-TIRADS classification, particularly for benign nodules. In resource-constrained system like ours, patients with TIRADS 2 and 3 nodules can be safely followed obviating the need for an invasive procedure like FNAC.

INTRODUCTION

Thyroid nodules are quite common and often detected incidentally. The method used to diagnose them has a significant impact on their prevalence rates.[1] Imaging techniques like high-resolution ultrasound (HRUS) show the prevalence rate in the adult population ranging from 20 to 76% as opposed to just 4 to 7% when determined solely by palpation method.[2] Most thyroid nodules are benign but to categorize a nodule as benign or malignant based

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on imaging has been traditionally difficult. The ability to diagnose a nodule as malignant is the ultimate goal of all imaging modalities so that appropriate treatments can be started at the earliest. The incidence of malignancy among thyroid nodules varies based on clinical and radiological assessment.[3] Histopathological assessment, which in the case of thyroid nodules took the form of fine needle aspiration cytology (FNAC), has historically been the solution to clinical and radiological uncertainty. Nevertheless, FNAC only detects malignancy in 4-6% of thyroid nodules.[4] The frequency of incidental diagnoses of thyroid nodules (thyroid incidentalomas) is rising as a result of the frequent use of HRUS and the improved accessibility to cytological analysis through Ultrasound guided FNAC.[5] Therefore the question of their benignity or malignant nature is a big question that needs to be answered. This question has been partially answered by the introduction of the ACR TIRADS system of classification of thyroid nodules.[6] Incidence of these thyroid nodules is more among women and is almost four times than that of men of same age group. This gender difference is thought to be secondary to hormonal effect (both progesterone and estrogen).[7]

Nodules are grouped into their respective TIRADS category based on shape (S), echogenicity (E), margin (M), and echogenic foci (F). The final ACR-TIRADS categories are based on the sum of the scores for each of these categories, which range from 0 to 3.[8,9] The histopathological results of thyroid nodules are classified based on the Bethesda system for reporting thyroid cytopathology (2017) which categorizes the specimens into 6 categories.[10]

Our study was aimed at reaffirming the role of the ACR TIRADS classification in the management of thyroid nodules, especially with regard to benign nodules, so that a large number of invasive procedures (FNAC, biopsies) can be avoided in a resource constrained system like ours. We also sought to put to test the accuracy of TIRADS system to suggest a diagnosis of malignant thyroid nodule and thereby direct early management of these nodules.

MATERIALS AND METHOD

Patients

This study was conducted in the Department of Radio-diagnosis and Imaging Sheri Kashmir Institute of Medical Sciences, Srinagar in collaboration with The Department of Endocrinology and Department of Pathology over a period for 2 years (September 2020 to October 2022) and included patients who had thyroid nodules on high resolution ultrasound imaging. Informed consent was obtained from all participants in this study. Normal thyroid scan (TIRADS 1) and histopathologically documented cases of thyroid malignancies (TIRADS 6) were excluded. The study was approved by the Institutional ethical committee-vide approval no IEC/ SKIMS Protocol # RP 159/2022. A total of 201 patients were included in the final study who underwent USG based TIRADS categorization followed by FNAC at our department. Loco regional lymphadenopathy was also evaluated and recorded. All USG's were done using 12-14 Hz Ultrasound probe of Logic P5 GE Machine by a radiologist with over 10 years of experience. All patients in our study group underwent FNAC as we wanted a complete evaluation of the TIRADS classification including benign appearing nodules.

Protocol of study

A final TIRADS grade was given to the nodule after consideration of the nodule's nature, its morphology, the

presence or absence of calcifications, and any additional thyroidal expansion. All patients with TIRADS 2-5 then underwent FNAC in our department. The patient's coagulation profile and serology were assessed before any intervention. Informed consent was taken from all patients and all patients were cannulated before the procedure. After cleaning the neck with an antiseptic, sterile drapes were placed over the patient. FNAC was done by using 22G or 25G needles based on the nodular characteristic and operator preference. The procedure was done using real time guidance via USG and the aspirate was then flushed onto multiple slides using a 5mL syringe. Slide preparation, fixation and staining were done by an experienced pathologist with over 10 years of experience.

The slides were then evaluated for classification into BETHESDA system based on various characteristics. The pathologist evaluating the slides was kept blinded to the TIRADS grading of the nodule. The histopathological grade of the thyroid nodule was one of the six grades based on BETHSEDA system with the percentages in brackets indicating the likelihood of malignancy: grade I non diagnostic (1-4%), grade II benign (0-3%), grade III atypia of undetermined significance (5-15%), grade IV follicular neoplasm (15-30%), grade V suspicious for malignancy (60-75%) and grade VI malignant (97-99%).

Statistically analysis

The data was collected and evaluated using SPSS 21.0. Descriptive data was analyzed by frequencies and categorical data by percentages and continuous variables by means and standard deviations. Finally the TIRADS grading of the nodule was correlated with the BETHESDA grading and statistically significant concordances were sought with a p value of <0.05 considered statistically significant.

RESULTS

A total of 201 patients were included in this study with proportion of females versus male equal to 4:1. The mean age of the patients included in our study was 45 years. TIRADS3 and TIRADS4 made up the majority of the nodules on ultrasonography in 77.61% (156/201) of the cases. Using HRUS, thyroid nodules were stratified and TIRADS scoring was labeled for each patient. Out of the 201 nodules, 14(6.9%) nodules were categorized under TIRADS2, 85(42%) nodules were classified under TIRADS3, 71(35%) nodules were labeled as TIRADS 4, and 31(15%) were documented as TIRADS 5 (FIGURE 1). The nodules labeled as Bethesda I, II and III pathologically were considered benign while as those with Bethesda IV, V, and VI categorization were labeled as malignant. 120/201 (approximately 59%) were labeled as Bethesda I and II and III with US guided FNAC results. Further 40% (81/201) nodules proved to be malignant (TABLE 1). Out of the 14 TIRADS 2 nodules, all were benign on FNAC results. Among the 85 TIRADS 3 nodules, 62 nodules (72%) were Bethesda II (FIGURE 2) proving efficacy of HRUS for benignity, 7 nodules (8.2%) were Bethesda 1, 8 nodules (9%) were Bethesda III, 2 nodules (2.3%) were Bethesda IV, 3 nodules (2.3%) were Bethesda V, and 3 nodules (2.3%) were Bethesda VI. A total of 102 nodules were classified as TIRADS4 (FIGURE 3) and TIRADS5 (FIGURE 4) on USG and among them 11 turned out to be Bethesda II and 10 turned as Bethesda III. HRUS had approximately drop rate of 1.8% as in classifying the nodules as malignant (TABLE 1).

TABLE 1. Distribution of Bethesda grading of study subjects.

Bethesda grading	Frequency	Percentage (%)
Bethesda 1	14	6.97
Bethesda 2	85	42.29
Bethesda 3	21	10.45
Bethesda 4	24	11.94
Bethesda 5	17	8.46
Bethesda 6	40	19.90
Total	201	100.00

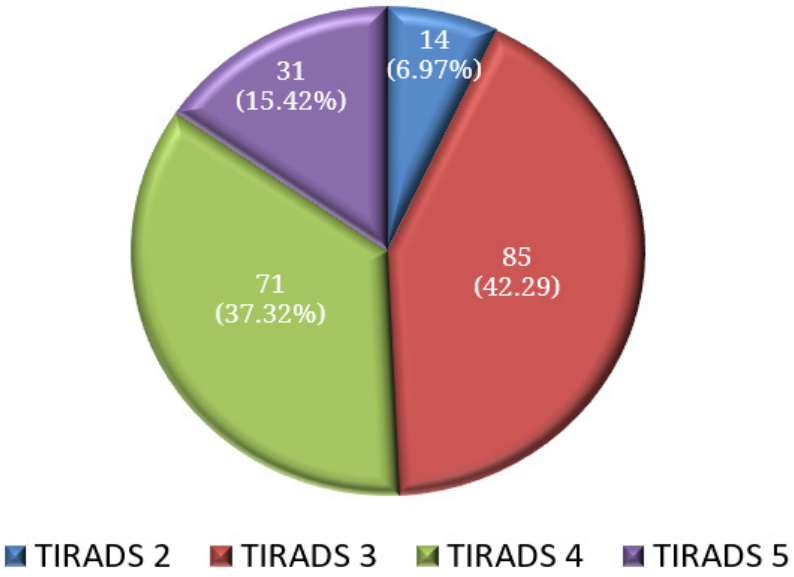

FIGURE 1. Pie chart showing the percentage distribution of thyroid nodules based on the TIRADS categorization on HRUS.

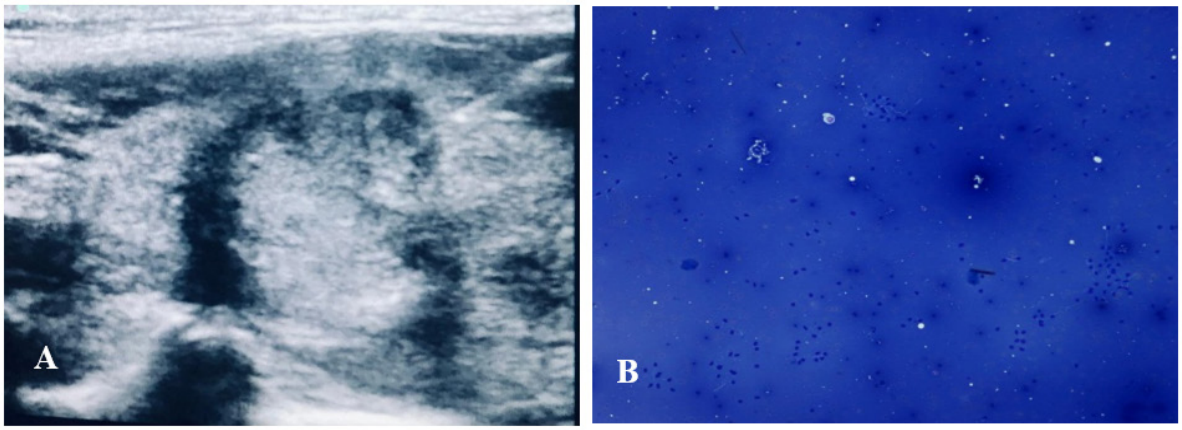

FIGURE 2. Transverse USG scan (A) of left thyroid lobe showing a well defined iso-hyperechoic, solid lesion with no calcifications labeled as TIRADS 3 which on FNAC. (B) came out to be colloid nodule (Bethesda II).

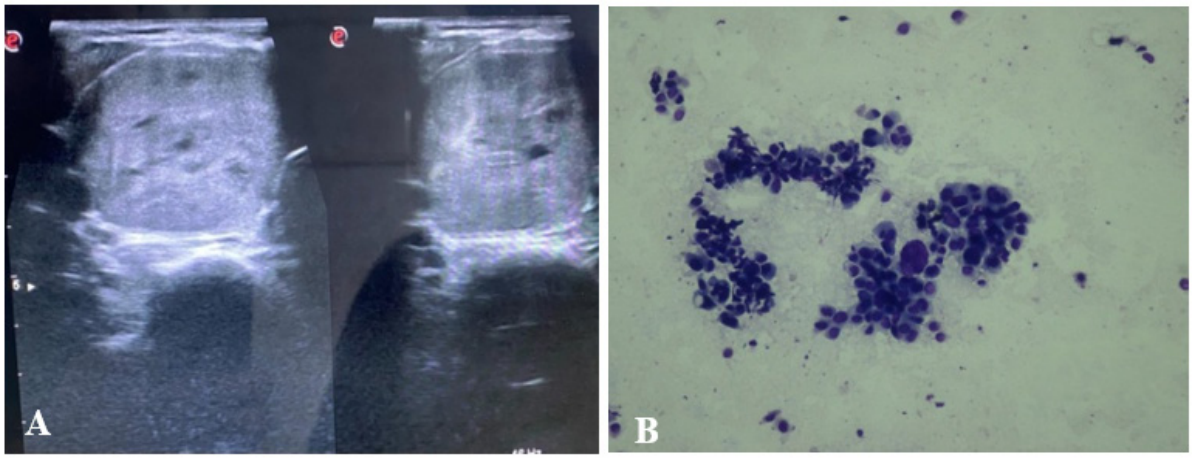

FIGURE 3. Transverse USG images (A) of right thyroid lobe in a 40-year-old female shows well defined, solid, hypoechoic nodule with no calcifications, wider than taller labeled as TIRADS -4 which on FNAC. (B) came out to be medullary carcinoma Thyroid [Bethesda VI].

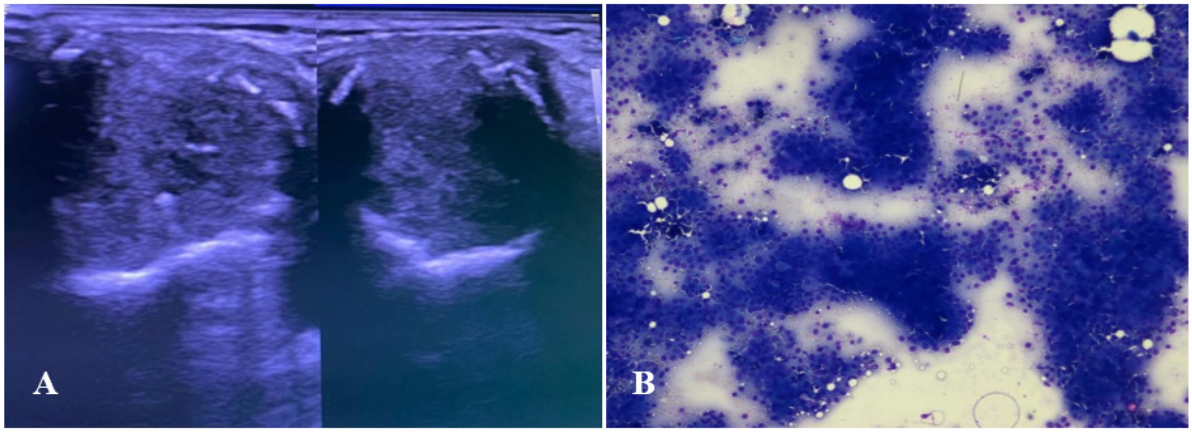

FIGURE 4. (A). Transverse USG images of right thyroid lobe in a 27-year-old female showing well defined, solid, hypoechoic, wider that taller lesion with peripheral calcification labeled as TIRADS 5. (B) came out to be papillary thyroid Carcinoma (Bethesda 6) on FNAC.

Sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), and accuracy were also calculated based on FNAC results. TIRADS4 and 5 were considered positive for malignancy, while TIRADS scores of 1–3 were considered negative for malignancy. Our study showed 86% sensitivity, 84.16% specificity, 84.3% PPV, and 85.9% NPV in labeling thyroid nodules as benign/malignant based on US findings. Significant correlation was seen between ACR-TIRADS and Bethesda system classification with $p<0.001$ (TABLE 2).

TABLE 2. Association of TIRADS classification of thyroid nodules with Bethesda grading

TIRADS	Bethesda grading (n or %)						Total	p
	1	2	3	4	5	6		
	(n=14)	(n=85)	(n=21)	(n=24)	(n=17)	(n=40)		
TIRADS2	2 (14.29)	12 (14.12)	0 (0)	0 (0)	0 (0)	0 (0)	14 (6.97)	<0.001
TIRADS3	7 (50)	62 (72.94)	8 (38.10)	2 (8.33)	3 (17.65)	3 (7.50)	85 (42.29)	
TIRADS4	5 (35.71)	11 (12.94)	10 (47.62)	22 (91.67)	12 (70.59)	11 (27.50)	71 (35.32)	
TIRADS5	0 (0)	0 (0)	3 (14.29)	0 (0)	2 (11.76)	26 (65)	31 (15.42)	
Total	14 (100)	85 (100)	21 (100)	24 (100)	17 (100)	40 (100)	201 (100)	

The efficacy of ultrasound in labeling benign nodule as for TIRADS2, TIRADS3 was 100 and 90.6%. Labeling TIRADS4 and TIRADS5 as malignant were 63.5 and 90% respectively. The risk of malignancy for patients classified as ACR-TIRADS5, ACR-TIRADS4 and ACR-TIRADS3 were in ratio of 10:7:1.

DISCUSSION

Ultrasound should be utilized while assessing the thyroid gland and nodule for the first time. Although guidelines have been put forth for the management and need of FNAC in thyroid nodules, an institutional guideline may differ from the international guidelines based on the availability of resources and the nature of the patients being treated. It is a minimally invasive procedure, but FNAC is an effective and affordable approach for finding thyroid cancer. It is crucial to choose the cases based on their risk of malignancy because it is not cost-effective, nor advisable to do such a test on all thyroid nodules. In an effort to aid in this selection, several classifications based on monographic traits have recently been put forth.[10] The TIRADS system of categorization seeks to correlate cytological classification to sonographic properties. Recent investigations found that 7.3% of malignant nodules lacked ultrasonography evidence of malignancy. The USG characteristics of the thyroid nodule that we considered in classification of nodules as suspicious for malignancy were hypoechogenicity, solid-composition, micro calcifications, taller than wide morphology and irregular margins. It is important to note that the malignancy of the nodule was not correlated with the presence or absence of any one specific ultrasonography characteristic. It is important to always keep in mind that combining at least two ultrasonographic markers will help distinguish between benign nodules and high-risk nodule.

At the end of our study, we have derived the following results after using several ultrasonographic factors to decide the TIRADS scoring of the nodules. The efficacy of ultrasound in labeling benign nodules for TIRADS2, TIRADS3 was 100 and 90.6% and labeling TIRADS4, and TIRADS5 as malignant were 63.5 and 90% respectively. Horvath *et al.*,[9] proposed ten ultrasound features to be seen during the ultrasound examination and nodule classification from TIRADS2–6.[11] They estimated a risk of malignancy of 0% for TIRADS2, 3.4% for TIRADS3, 10–80% for TIRADS4, and 87% for TIRADS5. Kwak *et al.*,[12] gave TIRADS classification used five ultrasound criteria's for thyroid evaluation.[13] The malignant risk of 0% for TIRADS2, 1.7% for TIRADS3, 72.4% for TIRADS4, and 87.5% for TIRADS 5.[14] Similar studies by Indian writers like Srinivas *et al.*,[15] came to the conclusion

that the probability of malignancy for TIRADS categories 1, 2, 3, 4A, 4B, 4C, and 5 was 0, 0, 64, 4.76, 66.67, 83.33, and 100%, respectively. Our study is well correlating with these studies.

CONCLUSION

The need for FNAC in nodules labeled as TIRADS1, 2 and 3 can be obviated considering the high accuracy of HRUS in detecting nodules that are benign especially in a resource constrained system and in patients who are apprehensive of an invasive procedure. With regard to TIRADS4 and 5, the correlation between TIRADS and pathological BETHESDA system is not that strong, so we suggest that FNAC should be performed in all such patients.

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The impact of COVID-19 pandemic on decreasing hospitalization rates and management of acute coronary syndrome: a study from single centre hospital in Yogyakarta, Indonesia

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ABSTRACT

The Corona virus disease-2019 (COVID-19) pandemic has an impact on the medical field, one of which is service for patients with acute coronary syndrome (ACS). Studies in other countries showed a sudden decrease in admission rates, and percutaneous coronary intervention (PCI), one of ACS treatments, has an impact due to this pandemic. This study aimed to ascertain the effect of COVID-19 on the admissions and management of patients with ACS in Yogyakarta, Indonesia. It was an observational single center study conducted by collecting data for ACS patients at Dr. Sardjito General Hospital, Yogyakarta. Admission data for March 2019 to February 2020 were pre pandemic data, while those gathered from March to December 2020 were pandemic data. Data from 864 (pre pandemic period) and 338 patients (during the pandemic period) were further analyzed. The results showed a decrease in ACS patients' admission during the pandemic. The most remarkable reduction occurred in those with ST-segment elevation myocardial infarction (STEMI), followed by non-STEMI (NSTEMI) and unstable angina pectoris (UAP) (63.4, 61.4, and 40.9%, respectively). Furthermore, the PCI procedure decreased compared to the period before the pandemic. No significant differences in patients' characteristics was observed ($p>0.05$), except for the incidence of pneumonia ($p<0.001$). Finally, the mortality rate was higher during the pandemic than before (14.8 vs 13.2%), although it was not significant ($p>0.05$). This study showed that COVID-19 caused a sensible reduction in the admission rates for ACS patients and the number of PCI procedures have been performed. On the other hand, their mortality rate did not increase significantly. However, it is essential to improve healthcare services for ACS patients considering the uncertainty of ending the COVID-19 outbreak.

ABSTRAK

Pandemi penyakit virus Corona-2019 (COVID-19) berdampak pada bidang medis, salah satunya adalah pelayanan kepada pasien dengan sindrom koroner akut (SKA). Studi di negara lain menunjukkan penurunan mendadak dalam tingkat penerimaan, dan intervensi koroner perkutan (PCI), salah satu perawatan ACS, berdampak akibat pandemi ini. Oleh karena itu, penelitian ini bertujuan untuk mengetahui pengaruh COVID-19 terhadap penerimaan dan pengelolaan pasien SKA di Yogyakarta, Indonesia. Penelitian ini merupakan penelitian observasional single-center yang dilakukan dengan mengumpulkan data pasien ACS di Rumah Sakit Umum Pusat Dr. Sardjito, Yogyakarta, Indonesia. Data penerimaan untuk Maret 2019 hingga Februari 2020 adalah data prapandemi, sedangkan yang dikumpulkan dari Maret hingga Desember 2020 adalah data pandemi. Data dari 864 (masa pra-pandemi) dan 338

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COVID-19 pandemic;
admission rates;
management;
acute coronary syndrome

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pasien (selama masa pandemi) dianalisis lebih lanjut. Hasilnya menunjukkan penurunan penerimaan pasien ACS selama pandemi. Pengurangan yang paling luar biasa terjadi pada mereka dengan infark miokard dengan elevasi segmen ST (STEMI), diikuti oleh non-STEMI (NSTEMI) dan angina pektoris tidak stabil (UAP) (masing-masing 63,4%, 61,4% dan 40,9%). Selanjutnya, prosedur PCI menurun dibandingkan periode sebelum pandemi. Tidak terdapat perbedaan yang bermakna pada karakteristik pasien, kecuali pada kejadian pneumonia (p<0,001). Akhirnya, tingkat kematian lebih tinggi selama pandemi daripada sebelumnya (14,8% vs 13,2%), meskipun perbedaannya tidak signifikan secara statistik. Studi ini menunjukkan bahwa COVID-19 menyebabkan penurunan yang masuk akal dalam tingkat penerimaan pasien ACS dan jumlah prosedur PCI yang telah dilakukan. Di sisi lain, angka kematian mereka tidak meningkat secara signifikan. Namun, peningkatan layanan kesehatan bagi pasien ACS sangat penting mengingat ketidakpastian berakhirnya wabah COVID-19.

INTRODUCTION

Acute coronary syndromes (ACS) have become one of the leading causes of death globally, especially in the acute myocardial infarction group with ST-segment elevation (STEMI). The treatment strategy can be carried out through primary percutaneous coronary intervention (primary PCI) or fibrinolysis, which aim to restore blood flow to save the myocardium, reduce infarct area, and extend life expectancy.[1]

Corona virus disease-2019 (COVID-19) pandemic has disrupted the world and impacted health issues. The exponential rise of this virus affects medical personnel in hospitals, with a continuously increasing number of victims. Therefore, the management of several diseases needs to be modified.[2,3] Management strategy for ACS patients needs to be determined by (a) risk stratification and (b) whether the patient has a confirmed case, suspected, or low risk.[2,3] However, it is necessary to understand that this change in management is not based on evidence, but it can be considered to be applied in this COVID-19 pandemic. Accordingly, future evaluations need to be conducted to recognize the potential impact on the outcome of ACS patients.[4]

Before the COVID-19 pandemic, ACS management at Dr. Sardjito General Hospital, Yogyakarta followed the European Society of Cardiology (ESC) or Indonesian Heart Association (*Perkumpulan Kardiologi Indonesia*/ PERKI) guidelines. Furthermore, the reperfusion strategy for STEMI was prioritized for primary PCI when the limit of wire crossing time did not exceed 120 min. Some cases with a crossing time of >120 min have been treated with fibrinolysis. Likewise, the NSTE-ACS case follows ESC guidelines, wherein an invasive strategy was applied, especially in patients with very high or high-risk stratification. Meanwhile, NSTE-ACS patients with low stratification will be first subjected to a non-invasive test. This study aimed to investigate whether the patient needs an invasive strategy or not. During the COVID-19 pandemic, ACS management experienced a few changes due to several considerations.

MATERIALS AND METHODS

Study design and subjects

This was an observational analytic study by obtaining data from the SCIENCE (Sardjito Cardiovascular IntENsive CarE) registry at Dr. Sardjito General Hospital, Yogyakarta, Indonesia. This registry collected data on patients treated in the cardiovascular intensive care unit (ICCU). All ACS patients treated between March 2019 to February 2020 were recorded as data before the COVID-19

pandemic, while those obtained from March to December 2020 were recorded as data during the pandemic. Meanwhile, management and outcomes were recorded during treatment until the patient was discharged. In this study, the primary reported outcome was mortality incidence from any cause.

Data collection

The subjects were sequentially sampled (consecutive sampling). Also, anamnesis, physical examination, 12-lead ECG assessment, and standard laboratory examinations were conducted for patients with ACS as the sample. Furthermore, sampling and data collection were carried out after obtaining ethical clearance from the Medical and Health Research Ethics Committee, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada/Dr. Sardjito General Hospital, Yogyakarta.

Statistical analysis

Categorical data were presented in absolute values or percentages. The data were compared with the Chi-square or Fisher Exact test. Furthermore, continuous data were displayed with the mean ± standard deviation (SD) when the distribution was normal and then compared with Student's t-test. A p value <0.05 was considered to be significant. The IBM SPSS Statistics 24 was used for data analysis.

RESULT

The first positive COVID-19 case in Indonesia was detected on March 2nd, 2020, and it marked the beginning of a pandemic. Over time, the number of cases increased rapidly. At the end of 2020, about 740,000 cases were recorded with a mortality rate of about 22 thousand people. The pandemic impacted the health field against cardiovascular disease, namely ACS. The incidence of ACS (especially STEMI type) in hospitals has markedly decreased in several countries during this pandemic and as well as in Dr. Sardjito General Hospital, Yogyakarta.

Before the pandemic (March 2019 to February 2020), there were 864 ACS cases, consisting of STEMI (70.3%), NSTEMI (20.1%), and unstable angina pectoris (9.6%). During the pandemic (March 2020 to December 2020), the ACS incidence decreased to only 338 cases. Furthermore, over 50% decrease was found in the STEMI and NSTEMI cases, while UAP cases decreased by 40.9%. The largest drop was seen in STEMI cases, namely 63.4% (FIGURE 1).

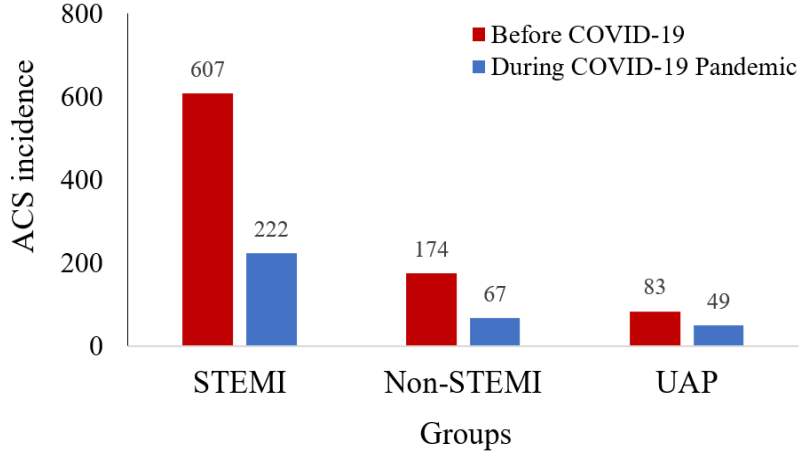

FIGURE 1. ACS incidence in Dr. Sardjito General Hospital before (March 2019 - February 2020) and during the pandemic (March 2020 - December 2020)

The standard of care of STEMI management is through reperfusion, either by fibrinolysis or primary PCI. This procedure has to be performed in a hospital with adequate facilities for both types of reperfusion. Dr. Sardjito General Hospital is one of the hospitals with PCI capable centers in Yogyakarta; hence the primary PCI is among the reperfusion options in the STEMI case.

During the pandemic, the standardized protocols have provoked delays in the treatment of ACS. All patients presenting with ACS should be considered COVID-19 possible, and patients were screened for COVID-19 before admission with an internally developed scoring system. Furthermore, ACS patients with a high COVID-19 probability score were initially hospitalized in the isolation room until the PCR swab results were out. Therefore, when the PCR swab showed negative, the patients were moved to cardiovascular intensive care (ICCU) or inpatient room. Conversely, when the PCR-swab result was positive, the care was maintained in the isolation room for COVID-19 patients.

Among 338 hospitalized ACS cases, 15 had a high probability score of COVID-19, and therefore they had to undergo treatment in the isolation room. However, out of these 15 cases, only one patient showed a positive result from the PCR swab examination (FIGURE 2).

The characteristics of ACS patients before and during the pandemic are presented in TABLE 1. There were no significantly differences in their features, such as age or gender ($p>0.05$). Meanwhile, the comorbidities found in patients, such as pneumonia and urinary tract infections (UTIs), showed a significantly difference ($p<0.05$).

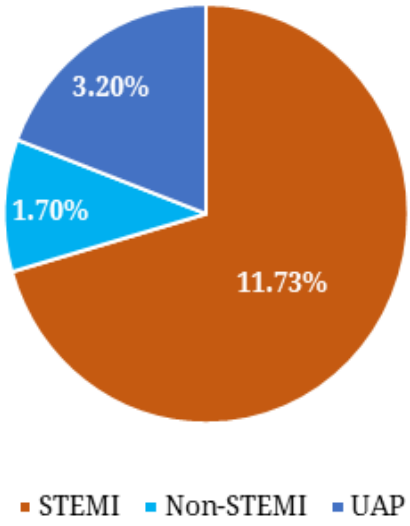

FIGURE 2. Distribution of ACS incidences with high COVID probability scores during the COVID-19 pandemic (March 2020 - December 2020).

TABLE 1. Basic patient characteristics

Parameter	Before COVID-19 (n = 864)	During COVID-19 (n = 338)	p
Age, years [median (range) years]	60 (22 – 95)	61 (24 – 98)	0.926
Sex [n (%)]			
• Male,	694 (80.3)	262 (77.5)	0.278
• Female,	170 (19.7)	76 (22.5)	
ACS type [n (%)]			
• STEMI	606 (70.1)	222 (65.7)	0.049
• Non-STEMI	174 (20.1)	67 (19.8)	
• UAP	84 (9.7)	49 (14.5)	
Killip classification [n (%)]			
• Killip I	690 (79.9)	269 (79.6)	
• Killip II	77 (8.9)	38 (11.2)	
• Killip III	33 (3.8)	11 (3.3)	
• Killip IV	64 (7.4)	20 (5.9)	
Cardiogenic shock [n (%)]	124 (14.3)	57 (16.8)	0.385
Acute heart failure [n (%)]	202 (23.4)	84 (24.9)	0.59
Risk stratification of NSTE-ACS [n (%)]			
• Very high	81 (31.5)	34 (29.3)	0.01
• High	111 (43.2)	50 (43.1)	
• Intermediate	56 (21.8)	18 (15.5)	
• Low	9 (3.5)	14 (12.1)	
Comorbid [n (%)]			
• Pneumonia	60 (6.9)	64 (18.9)	< 0.001
• Urinary tract infection	27 (3.1)	36 (10.7)	< 0.001
• Diabetes mellitus	275 (31.8)	109 (32.2)	0.888
• Hypertension	501 (58)	210 (62.1)	0.189

TABLE 1. Basic patient characteristics
The management of ACS between March 2020 and December 2020 at Dr. Sardjito General Hospital has changed slightly. In the early period between March and May 2020, reperfusion strategy in STEMI patients was prioritized using fibrinolysis compared to primary PCI, especially when the patient had a high probability score. The primary PCI were prioritized when the patient experienced a cardiogenic shock after cardiac arrest or had contra-indications for fibrinolysis. However, between June and December 2020, the strategy in the form of primary PCI began to be carried out by considering the probability score. Likewise, selecting an invasive approach in the management of patients with NSTE-ACS was based on several considerations.

Most STEMI patient management still lies in the primary PCI (61.3%), followed by fibrinolysis and PCI of 21.6% (either rescue PCI or post-fibrinolytic PCI evaluation). Nevertheless, it can be seen that the PCI has decreased significantly by 70.4% compared to the period before the pandemic. This is possibly due to the declining number of STEMI patients presented at the hospital (FIGURE 3).

Meanwhile, NSTE-ACS management before and during the pandemic is presented in FIGURE 4. The invasive

therapy became the management choice for NSTE-ACS patients in the period before the pandemic. Furthermore, the NSTE-ACS patients treated with invasive strategies were 57.9% (for UAP) and 72.4% (for non-STEMI). During the pandemic, invasive strategies were still carried out in NSTE-ACS patients, namely 61.2% (for UAP) and 61.1% (for NSTEMI). It can be observed that management with an invasive strategy remains an option, compared to conservative management.

The comparison of mortality outcomes from ACS management between the period before and during the pandemic is presented in FIGURE 5. The mortality was slightly higher during the pandemic (14.8% of 338 patients) compared before the pandemic (13.2% of 864 patients). However, it was not significantly difference (p=0.468). Therefore, it can be concluded that there is no significant relationship between the mortality rate before and during the COVID-19 pandemic.

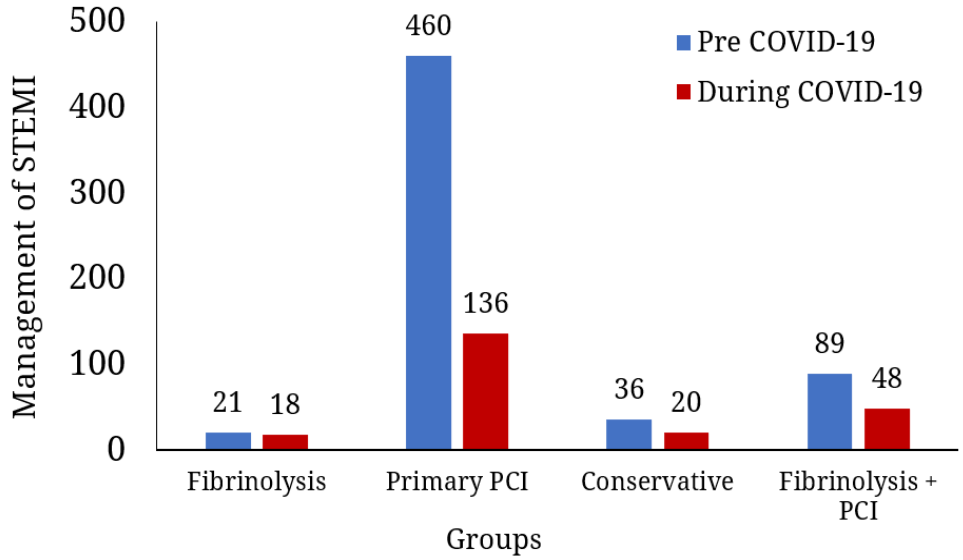

FIGURE 3. Management of STEMI patients at Dr. Sardjito Hospital before and during the COVID-19 pandemic.

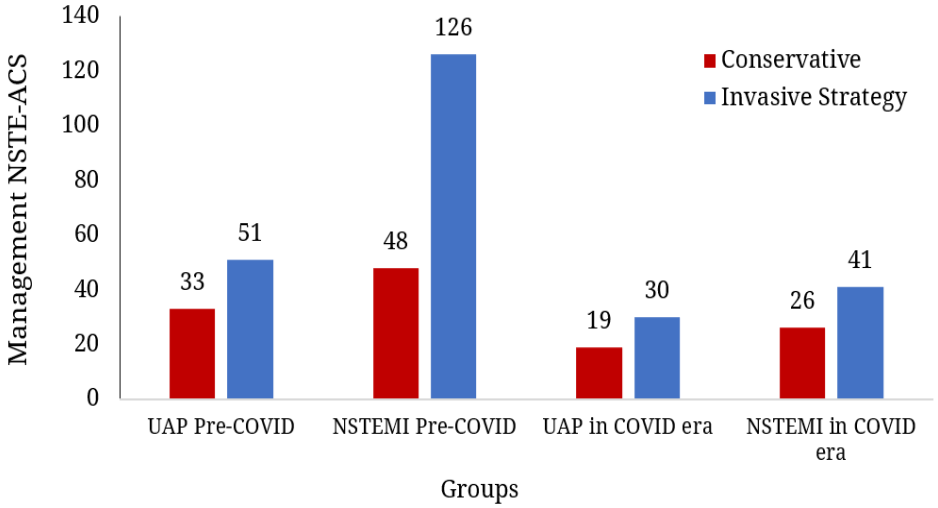

FIGURE 4. Management of NSTE-ACS patients at Dr. Sardjito General Hospital before and during COVID-19

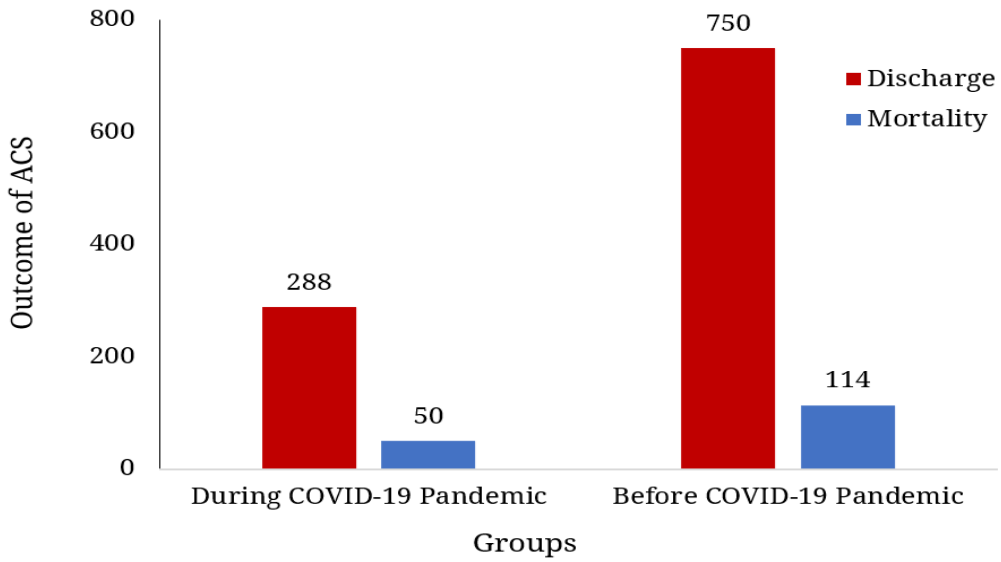

FIGURE 5. The outcomes of ACS patients in Dr. Sardjito General Hospital before and during COVID-19 pandemic

DISCUSSION

The COVID-19 pandemic began with the discovery of the first reported case from the city of Wuhan in China in December 2019. The disease has developed into a pandemic that has infected more than 87 million people and caused more than 1.8 million deaths in early January 2021.[6,7] The COVID-19 outbreak has affected the world of health, one of which is the incidence of ACS.[2,8-12]

This study showed that the treated ACS cases have decreased by 60.8%, i.e. from 864 (March 2019 to February 2020) to 338 cases (March 2020 to December 2020) during the pandemic. Furthermore, the lowest number was observed in the early pandemic period and the end of 2020.

Several factors could be the underlying reasons for the decrease in admissions. First, some suggest that the patients might be afraid of contracting the virus while staying in the hospital due to this hospital's status as the primary referral for COVID-19 patients. Second, referrals from health facilities outside Dr. Sardjito General Hospital, Yogyakarta has decreased during this pandemic. Many of these referral cases are accompanied by a suspicion of being infected by COVID-19 (based on the screening score system developed internally). Meanwhile, the treatment room for COVID-19 patients at the hospital is often full; subsequently, many ACS patients cannot be referred. On the other hand, when they are not suspected of COVID-19, then the referral process can run smoothly because non-COVID treatment rooms are still available.

Another interesting hypothesis proposed by de Rosa *et al.*,[13] is whether the decrease in admissions is related to low physical stress or the condition of people that get a lot of rest during quarantine. Furthermore, lockdown in several countries is a possible trigger for a decrease in acute decompensated episodes of cardiovascular diseases, such as low levels of air pollution, low job stress, or a reduction of work activities. However, this condition is likely to be in contrast to other impacts due to lockdown, such as psychosocial stress caused by social distancing policies, daily routines that are stopped, fear of losing a job, and an uncertain future.[14]

Studies conducted around the world found the same results concerning the admission rate. One of these was a study by Mafham *et al.*,[15] which reported a decrease in admissions in the UK by 40% (95% CI 37-43), from an average of 3017 cases per week in 2019, to 1813 cases in mid-February to late March 2020. In April and May 2020, ACS admissions increased by 2522 cases, or decreased by 16% (95% CI 13-20) when compared to the average admission rate in 2019.

This study showed a decrease in admission rate, especially in the STEMI patients, namely 63.4%, followed by a decrease in the incidence of NSTEMI (61.4%) and UAP (40.9%). Meanwhile, a study by ESC on 141 countries in 6 continents showed that since the COVID-19 pandemic, STEMI admission rates have decreased by> 40%. These STEMI patients appeared to be taking longer to present to the hospital after the onset of chest pain. In addition, as many as >40% visited the hospital beyond the optimal time for reperfusion management, either by primary PCI or thrombolysis, with subsequent impact on mortality. One of the independent predictors of high delay rate from STEMI patients is a change in the structure of cardiac services in the country due to the imposing lockdown policy.[14]

Another study conducted at a multicenter in Italy by obtaining data on acute myocardial infarction (AMI) patients showed a decrease in AMI admissions by 48.4% compared to the same week period in 2019 ($p < 0.001$). Furthermore, a significant decrease was found for both STEMI (26.5%, 95% confidence interval (CI) 21.7 - 32.3; $p = 0.009$) and NSTEMI (65.1%, 95% CI 60, 3 - 70.3; $p < 0.001$) cases. The decrease in STEMI admission rate was found to be more in females (41.2%; p = 0011) than males (17.8%; $p = 0.191$).[13] This is slightly different from the current study, where the proportion of ACS incidence in females was more dominant than males.

The health service policy during the pandemic in Dr. Sardjito General Hospital, Yogyakarta, especially in the emergency room, has changed. Every patient is first screened using an internally developed scoring system. Among 338 admitted patients, 15 (4.43%) had a high probability score of COVID-19. Therefore, the treatment was initially carried out in a particular COVID-19 room until the results of the PCR swab were out. Out of these 15 patients, 11 (70.3%) were with STEMI. Also, reperfusion was performed in 6 patients, either in the form of fibrinolysis (1 patient), primary PCI (2 patients), and fibrinolysis followed by PCI action (3 patients). The remaining 5 underwent conservative management. It turned out that from the PCR- swab examination results, only one patient was confirmed positive for COVID-19.

The characteristics of admitted patients before and during the pandemic were not significantly different. Only other comorbid diseases in the form of infections (pneumonia and urinary tract infections) were observed ($p < 0.001$). The pneumonia incidence during the pandemic has indeed increased. Nevertheless, out of the 338 patients, it was found that only 1 had pneumonia caused by the SARS-Cov2 virus. This study also showed that the presentation of ACS patients with complications like cardiogenic shock or acute heart failure was not significantly different between the time before and during the pandemic.

Matsushita *et al.*,[16] conducted an analysis to determine the characteristics differences between ACS patients before (2019) and during the pandemic. This study obtained data from a hospital in Strasbourg, France. Characteristic data from 174 ACS patients between March 1st to April 20th, 2019 were compared with 106 patients on the same date and month during the pandemic. The results showed no characteristics difference between the population, such as age, gender, and risk factors.

The management of ACS patients is a concern, especially on reperfusion in the STEMI case. Although the primary PCI is an effective reperfusion strategy for STEMI cases, this action is relatively not the main choice. The increased exposure risk to the SARS-Cov2 virus is related to the unavailability of "negative pressure" cardiac catheterization rooms, availability of personal protective equipment (PPE), and the difficulty of manipulating catheters and guidewires. This influences the decision to perform primary PCI in STEMI patients during this pandemic. Consequently, fibrinolysis is the alternative to PCI when there are no contraindications.[5] In the early pandemic (around March-May 2020), fibrinolysis was used as the main choice of reperfusion strategy in STEMI patients that were especially suspected of having COVID-19 comorbid in our hospital. Over time and the formation of a more structured screening system, the primary PCI was carried out with a low probability score. So, the primary PCI procedure was still the main treatment (61.3% of STEMI cases) during the pandemic. This study found that the primary PCI procedure had decreased by 70.4% compared to those before the pandemic. This is probably due to the decreasing number of STEMI admissions.

A study in USA regarding the impact of the COVID-19 pandemic on STEMI services also showed a decrease in the volume of primary PCI actions related to a decrease in the admission rate. Furthermore, the pandemic has affected STEMI services, especially in terms of lengthening the activation time of the catheterization room for primary PCI action.[17,18] This is known as 'wire crossing time' that was also found in this study (average 'wire crossing time' during the pandemic at the hospital was 203.03 min). This is mainly due to the screening process that takes a long time in the emergency room to determine whether a patient has the virus or not. Some of the screening examinations carried out include a chest X-ray or even a lung MSCT. These examinations aim to detect the presence of ground-glass opacity (GGO) image, which is a characteristic sign in COVID-19 patients.

This study showed that an invasive strategy is still an option in NSTE-ACS management. Over 60% of NSTE-ACS patients (both NSTEMI and UAP) underwent an invasive strategy. The number of PCI procedures is indeed less than those before the pandemic. This is because the number of NSTE-ACS patient admissions has decreased. The same result was also found in a UK study, where the PCI procedure for NSTEMI patients decreased by 37%.[15] Likewise, a study in Italy found that the proportion of NSTEMI patients undergoing PCI procedure decreased by 13.3% ($p = 0.023$).[13]

This study showed the mortality rate during the COVID-19 pandemic was greater than that before (14.8% vs 13.2%). However, it was not statistically significant. Furthermore, an increase in the ACS case fatality rate was reported in Italy, namely 13.7% compared to 4.1% before the pandemic (RR = 3.3, 95% CI – 6.6; $p < 0.001$). The STEMI cases increased by 3.3% compared to 1.7% in 2019 (RR = 1.9, 95% CI 0.5 - 6.7, $p = 0.309$) for NSTEMI cases.[13] The increased mortality rates need to be evaluated, whether it lies in the patient's delay in seeking treatment or the provided medical services.

This study has several limitations. First, it was conducted in only one hospital, and therefore, the actual data regarding the ACS incidence and management in the population cannot be generalized. Second, related to the retrospective design of this study, the data affecting the management and outcome of ACS patients are less explored due to limitations in data collection. Third, the PCR swab examination as the gold standard for establishing diagnosis was not carried out in all ACS patients in the

early days of the pandemic. Hence the asymptomatic ones were not detected.

CONCLUSION

The current study reported considerably lower rates of hospitalization for ACS at Dr. Sardjito General Hospital, Yogyakarta. This decrease is caused by multiple factors, both from patients and the change of the healthcare system. The early period of the pandemic is altered the clinical approach of ACS patients. However, as it progresses, improvements have been made in the hospital service system. The mortality rate during the COVID-19 pandemic is not difference compared to before the COVID-19 pandemic. However, it is essential to improve healthcare services for ACS patients considering the uncertainty of ending the COVID-19 outbreak. Hence, further studies need to be conducted by involving hospital networks to determine the actual condition of ACS incidence and management.

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Correlation between the degree of leukoaraiosis and hyperlipidemia in post-ischemic stroke patients

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ABSTRACT

Leukoaraiosis is a neurological imaging in the periventricular area and the centrum semiovale. This condition occurs due to abnormalities in the small blood vessels in the brain that lead to hypoxia. It is often observed in patients with ischemic stroke and accompanied by risk factors for hyperlipidemia. This study aimed to evaluate the correlation between the degree of leukoaraiosis and hyperlipidemia in post-ischemic stroke patients. A cross-sectional study retrospectively was conducted on post-ischemic stroke patients who underwent brain MRI (magnetic resonance imaging) on T2 and FLAIR (fluid-attenuated inversion recovery) sequence at the Department of Radiology, Dr. Sardjito General Hospital, Yogyakarta, from January 2021 to March 2022. A total of 36 patients were involved in this study. The leukoaraiosis of patient was examined by brain MRI. Degree of the leukoaraiosis was determined based on Fazekas classification. Serum cholesterol, HDL (high-density lipoprotein), LDL (low-density lipoprotein), and triglyceride levels of patients were then examined. The data obtained were then analyzed using Spearman correlation test. A positive correlation was observed between the degree of leukoaraiosis and triglyceride level ($p = 0.042$; $r = 0.292$) and age ($p= 0.004$; $r = 0.464$). However, no correlation was observed between the degree of leukoaraiosis and cholesterol, HDL, and LDL ($p>0.05$). In conclusion, the leukoaraiosis degree is correlated with serum triglyceride levels and age in post-ischemic stroke patients.

ABSTRAK

Leukoaraiosis merupakan gambaran neurologis pada daerah periventrikuler dan sentrum semiovale. Leukoaraiosis terjadi akibat adanya kelainan pembuluh darah kecil di otak akibat hipoksia. Leukoaraiosis banyak dijumpai pada pasien stroke iskemik dan yang disertai faktor risiko hyperlipidemia. Penelitian ini bertujuan mengkaji hubungan antara derajat leukoaraiosis dengan hiperlipidemia pada pasien paska stroke iskemik. Penelitian potong lintang secara retrospektif ini menggunakan data sekunder gambaran MRI (*magnetic resonance imaging*) kepala sekuen T2 dan FLAIR (*fluid-attenuated inversion recovery*) pasien paska stroke iskemik di Departemen Radiologi, RSUP Dr Sardjito Yogyakarta periode Januari 2021 sampai Maret 2022. Total sebanyak 36 pasien terlibat dalam penelitian. Leukoaraiosis pasien diperiksa dengan MRI kepala dan derajat leukoaraiosis ditetapkan berdasarkan klasifikasi Fazekas. Data yang diperoleh selanjutnya dianalisis dengan uji korelasi Spearman. Didapatkan hubungan positif antara derajat leukoaraiosis dengan kadar trigliserida serum ($p=0,042$; $r=0,292$) dan dengan umur ($p=0,004$; $r=0,464$). Namun demikian tidak hubungan antara derajat leukoaraiosis dengan kadar kolesterol, HDL dan LDL serum ($p>0,05$). Simpulan, derajat leuokoaraiosis berhubungan dengan kadar trigliserida serum dan umur pada pasien paska stroke iskemik.

Key words:
leukoaraiosis;
hyperlipidemia;
post-ischemic stroke;
correlationp

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INTRODUCTION

Leukoaraiosis is a neurological abnormality in the white matter area that appears as an area of increased intensity on magnetic resonance imaging, especially in the periventricular and centrum semiovale. This disorder is often found among older people. The term was coined by Hachinski in 1987 and derived from the words leuko (white) and araiosis (smooth). Leukoaraiosis may present as subcortical, multifocal, or diffuse periventricular lesions of varying sizes.[1] Leukoaraiosis may be caused by hypoxic ischemia due to small vessel diseases such as thalamostriate and perforated arteries.[2-4]

Decreased blood flow is one of the causes of nerve cell damage.[5] Several studies have investigated blood-brain barrier damage and endothelial dysfunction.[6] Chutinet *et al.*,[7] reported that age and acute ischemic stroke are the strongest determinants of the severity of leukoaraiosis in hypertension patients. Conde *et al.*,[8] revealed that ischemic stroke patients with a history of hyperlipidemia have an increased intensity in the white matter area, which is milder at stroke time. Ke *et al.*,[9] reported that hypertriglyceridemia is associated with the severity of leukoaraiosis and may play a role in small vessel cerebral disease.

Dyslipidemia can manifest as an increase or decrease in lipid fractions, including increased serum cholesterol, LDL (low density lipoprotein), and triglyceride levels and decreased serum HDL (high density lipoprotein) levels. Pathological changes were observed in the white matter area due to lipid accumulation.[10] Elevated of serum cholesterol, LDL, and HDL levels can lead to the development of atherosclerosis, damage to the vascular endothelium, and changes in vascular endothelial permeability.[11] This study aimed to investigate the association between the degree of leukoaraiosis and hyperlipidemia in post-ischemic stroke patients.

MATERIALS AND METHOD

Design and sample

This study used a cross-sectional design with retrospective sampling using secondary data of brain MRI examination results of post-ischemic stroke patients at the Department of Radiology, and lipid profile of the patients at the Clinical Pathology Installation of Dr. Sardjito General Hospital, Yogyakarta from January 2021 to March 2022. The selected sample was part of the population planned to be directly studied.[12] The target population was post-ischemic stroke patients diagnosed with leukoaraiosis through brain MRI examination and found to have hyperlipidemia. Protocol of this study was approved by the Medical and Health Research Ethics Committee, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada/Dr. Sardjito General Hospital, Yogyakarta.

Procedure

Patients who meet the inclusion and exclusion criteria were involved in this study. The inclusion criteria were brain MRI results on T2 and FLAIR sequences with a post-ischemic diagnosis, the presence of leukoaraiosis

images stored on the Picture Archiving and Communication System (PACS) server, and an increase in the levels of cholesterol, LDL, and triglycerides. Patients were excluded when other lesions were found, such as brain infection, hydrocephalus tumor, or bleeding.

The data of brain MRI examination results were displayed on the research computer monitor, and subsequent assessment of leukoaraiosis severity in post-ischemic stroke patients was conducted by a specialist radiologist. During the MRI observation, the examiner was not provided with any information regarding the subjects' identity or clinical data. Degree of the leukoaraiosis was determined based on Fazekas classification. The Fazekas scale classified the white matter area into the periventricular. Each region is graded according to the size and confluency of the lesion. In periventricular white matter (PVWM), 0 is given if no lesion is found; 1 if a "cap" or thin-film image is found; 2 if a "halo" image is found; 3 if irregular periventricular signal extending into the deep white matter is found. In deep white matter (DWM), 0 is given if there is no lesion; 1 if there is a punctate foci; 2 if there is early confluence; 3 if there are large confluent areas.[13]

The lipid profile of the post-ischemic stroke patients was then classified as optimal (LDL <100 mg/dL), above optimal (100-129 mg/dL), borderline high (130-159 mg/dL), high (160-189 mg/dL), and very high (>190 mg/dL), and total cholesterol as desirable (<200 mg/dL), borderline high (200-239 mg/dL), and high (>240 mg/dL). Furthermore, HDL is classified as low (<40 mg/dL) and high (> 60 mg/dL), while triglycerides as normal (< 150 mg/dL), borderline high (150-199 mg/dL), high (200-499 mg/dL), and very high (>500 mg/dL).[14]

Statistical analysis

Data were presented as mean ± standard deviation (SD) or frequency or percentage. Bivariate analysis was applied to evaluate the correlation between leukoaraiosis and hyperlipidemia. A p value < 0.05 was considered to be significant.

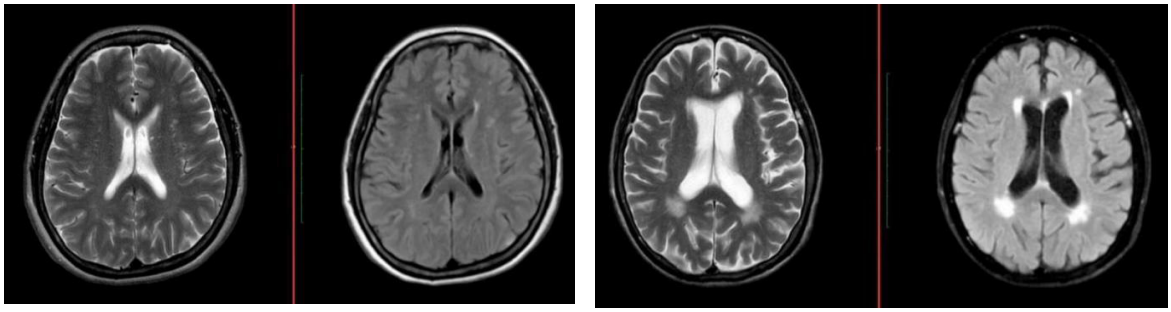
RESULTS

The characteristics of the patients are presented in TABLE 1. A total of 36 post-ischemic stroke patients were involved in this study consisting of 17 (47.2%) male and 19 (52.8%) female with the mean age of 61±11 yo. The mean total cholesterol of all subjects was 199±34 mg/dL, most (58.3%) having cholesterol levels higher than 240 mg/dL (n=21). In terms of HDL levels, the overall mean was 44±14 mg/dL, with most subjects (58.3%) having HDL levels between 40 and 60 mg/dL (n=21), while the mean triglyceride level was 140±67 mg/dL, with almost all subjects (91.7%) having triglyceride levels between 200 and 499 mg/dL. In addition, the mean LDL was 134±31 mg/dL, one-third of which (30.6%) had LDL levels between 100 and 129 mg/dL (n=11). The mean blood pressure was 148±15 mmHg systolic and 85±10 mmHg diastolic, with 58.3% of the subjects classified as hypertension grade 1.

The leukoaraiosis examinations was conducted using 0.4T open MRI. The illustrations of leukoaraiosis lesions obtained from the post-ischemic stroke patients are presented in FIGURE 1.

TABLE 1. Characteristics of patients

Variables	Mean ± SD	n (%)
Age (year)	61 ± 11	
Sex		
• Male		17 (47.2)
• Female		19 (52.8)
Total cholesterol (mg/dL)		
• <200	199 ± 34	15 (41.7)
• 200-239		0 (0.0)
• >240		21 (58.3)
HDL (mg/dL)		
• <40		21 (36.1)
• 40-60	44 ± 14	13 (58.3)
• >60		2 (5.6)
Triglyceride (mg/dL)		
• <150	140 ± 67	3 (8.3)
• 150-199		0 (0.0)
• 200-499		33 (91.7)
• >500		0 (0.0)
LDL (mg/dL)		
• <100		5 (13.9)
• 100-129		11 (30.6)
• 130-159	134 ± 31	10 (27.8)
• 160-189		10 (27.8)
• >190		0 (0.0)
Fazekas scale		
• No lesion		0 (0.0)
• Punctata lesion		18 (50.0)
• Early confluence		15 (41.7)
• Large confluence		3 (8.3)
Hypertension		
• Pre-hypertension		7 (19.4)
• Hypertension grade 1		21 (58.3)
• Hypertension grade 2		8 (22.2)



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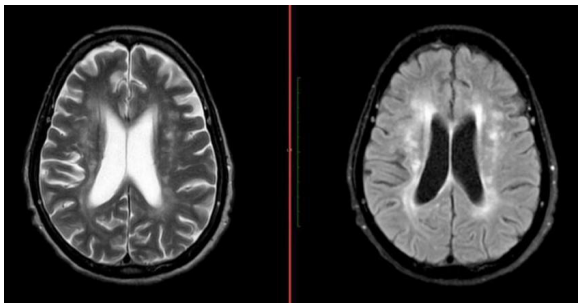

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FIGURE 1. MRI Images A. Leukoaraiosis Fazekas grade 1, illustrated by the presence of punctata lesions in bilateral centrum semiovale B. Leukoaraiosis Fazekas grade 2, illustrated by the presence of hyperintense periventricular confluent lesions on both sides C. Leukoaraiosis Fazekas grade 3, illustrated by the presence of large confluence lesions in periventricular and centrum semiovale on both sides.

TABLE 2 shows the correlation between the degree of leukoaraiosis and cholesterol, HDL, triglycerides, and LDL of the post-ischemic stroke. A significant and positive correlation was observed only between the serum triglyceride levels and the degree of leukoaraiosis (p=0.042; r= 0.292), indicating the patients with the higher degree of leukoaraiosis had the higher serum triglyceride levels. No correlation was observed between the degree of leukoaraiosis and cholesterol, HDL, and LDL levels (p>0.05).

A significant and positive correlation between degree of leukoaraiosis and age of post-ischemic stroke patients was observed (p= 0.004; r= 0.464) indicating that the older age patients had the higher degree of leukoaraiosis (TABEL 3).

TABLE 2. Correlation between the degree of leukoaraiosis and cholesterol, HDL, triglycerides and LDL

Variables	Degree of leukoaraiosis			r	p
	Punctata lesion	Early confluence	Large confluence		
	n (%)	n (%)	n (%)		
Cholesterol					
• <200	6 (33.3)	8 (53.3)	1 (33.3)		
• 200-239	0 (0.0)	0 (0.0)	0 (0.0)	-0.136	0.214
• >240	12 (66.7)	7 (46.7)	2 (66.7)		
HDL					
• <40	7 (38.9)	5 (33.3)	1 (33.3)		
• 40-60	10 (55.6)	10 (66.7)	1 (33.3)	0.079	0.323
• >60	1 (5.6)	0 (0.0)	1 (33.3)		
Triglyceride					
• <150	3 (16.7)	0 (0.0)	0 (0.0)		
• 150-199	0 (0.0)	0 (0.0)	0 (0.0)	0.292	0.042*
• 200-499	15 (83.3)	15 (100.0)	3 (100.0)		
• >500	0 (0.0)	0 (0.0)	0 (0.0)		
LDL					
• <100	3 (16.7)	2 (13.3)	0 (0.0)		
• 100-129	4 (22.2)	5 (33.3)	2 (66.7)		
• 130-159	7 (38.9)	2 (13.3)	1 (33.3)	-0.015	0.465
• 160-189	4 (22.2)	6 (40.0)	0 (0.0)		
• >190	0 (0.0)	0 (0.0)	0 (0.0)		

TABLE 3. Correlation between the degree of leukoaraiosis and age

Variables	Degree of leukoaraiosis			r	p
	Punctata lesion	Early confluence	Large confluence		
	n (%)	n (%)	n (%)		
Age (year)					
• 36-45	3 (100.0)	0 (0.0)	0 (0.0)		
• 46-55	7 (87.5)	1 (12.5)	0 (0.0)	0.464	0.004*
• 56-65	5 (33.3)	8 (53.3)	2 (13.3)		
• > 65	3 (30.0)	6 (60.0)	1 (10.0)		

DISCUSSION

The mean age of post-ischemic stroke patients in this study was 61±11 yo. This results in accordance with the study conducted by Ke *et al.*,[9] which reported that the mean of patients is 60 yo. Furthermore, Ben-Assayag *et al.*,[2] reported that the mean age of the models was 66.4±13.4 yo. Age is the most substantial non-modifiable risk factor for stroke incidence. About three-quarters of all strokes occur in people aged 65 yo or older.[15] Age is reported as a risk factor for ischemic stroke.[16] It can be linked to an increase in leukoaraiosis

in older people due to the thickening and narrowing of blood vessels. This reduced blood flow to the brain is demonstrated by the development of areas of hyperintensity in the periventricular and centrum semiovale. In addition, increasing age can reduce the elasticity of blood vessels.[17]

Leukoaraiosis is expected in the elderly and is associated with recurrent stroke, cognitive decline, gait disturbances, hemorrhagic transformation, and functional abnormalities after ischemic stroke.[18,19] Most studies have investigated the correlation between active stroke and leukoaraiosis severity using computed tomography visual scales or volumetric measurements. Although faster, computed tomography is not as sensitive as T2 and FLAIR. The Fazekas scale allows rapid assessment of severity on T2 and FLAIR sequences.[10]

This study involved 36 ischemic stroke patients consisting of 17 (47.2%) men and 19 (52.8%) women. This number is lower than the sample size in several previous studies, such as Ben-Assayag *et al.*,[2] which involved 170 acute stroke patients, consisting of 104 males and 66 females.[2] A study in China by Ke *et al.*,[9] reported that among 1,270 involving in the study, 66% are men and 34% are women. Another study reported that the incidence of stroke differs between the sexes.[20]

Hypertension is the most common risk factor for stroke. Hypertension was reported in approximately 64% of patients with stroke. Hypertension, blood pressure variability, and leukoaraiosis are risk factors for early adverse events and poor functional outcomes after ischemic stroke. Previous studies have shown different correlation between leukoaraiosis and blood pressure variability, including in ischemic stroke.[8] In this study, over half of the sample (58.3%) had hypertension grade 1.

Hyperlipidemia is known to have a role in the pathogenesis of ischemic stroke. Hyperlipidemia is independently associated with a reduction in the severity of leukoaraiosis in elderly or ischemic stroke patients.[9] In this study, a strong and positive association between the degree of leukoaraiosis and triglyceride levels (p= 0.042; r= 0.292), indicating that patients with the higher the degree of leukoaraiosis have the higher the triglyceride levels. This result is comparable to that of a study conducted by Park *et al.*,[21] that discovered hypertriglyceridemia is associated with a higher incidence of leukoaraiosis.

The radiological examination is conducted using 0.4T open MRI. It is sensitive and specific for leukoaraiosis assessment lower than 1.5T or 3.0T MRI. Thus, the MRI can not compare the result reflecting the effect of triglycerides on the hyperintensity of white matter area lesions in this study. However, the results of this study are in line with study by Ke *et al.*,[9] which discovered a connection between hypertriglyceridemia (1.7 mmol/L) and the severity of leukoaraiosis (p=0.05). The mechanism of the correlation between triglyceride levels and leukoaraiosis remains largely unknown. However, it is thought to have involved myelin in the brain in white matter areas. Myelin contains 70% lipid which could explain the increased levels of triglycerides and cholesterol in ischemic stroke.[9,22]

In this study, no significant correlation was observed between the degree of leukoaraiosis and serum cholesterol level. Previous study by Wiszniewska *et al.*,[6] in Switzerland also reported no significantly difference in the prevalence of hypercholesterolemia in the leukoaraiosis and non-leukoaraiosis groups. However, this study did not use the Fazekas classification and only divided the research subjects into leukoaraiosis and control.

CONCLUSION

In conclusion, there is a correlation between the degree of leukoaraiosis and the serum triglyceride levels on post-ischemic stroke patients. However, there is no a correlation between the degree of leukoaraiosis and the serum cholesterol, LDL, and HDL levels. In addition, age is one of the risk factors for ischemic stroke.

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Relationship of bizygomatic and bigonial breadth with the suitability of surgical masks

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ABSTRACT

Use of masks is mandatory to prevent the transmission of COVID-19. Appropriate masks that match the face size is very important to avoid leakage. This study aimed to evaluate the relationship between bizygomatic and bigonial breadth with the suitability of surgical masks. It was an analytic observational study with a cross-sectional design conducted at the Occupational Medicine Laboratory, Faculty of Medicine, Universitas Trisakti, Jakarta during March to April 2021. A total 132 employees of Faculty of Medicine, Universitas Trisakti aged from 20 to 64 y.o. who meet the inclusion and exclusion criteria participated in this study. No significantly difference in age (p=0.248) and body mass index (BMI) (p=0.226) was observed. However, there was a significantly difference in bizygomatic width (p=0.000) and bigonial width (p=0.001) between men and women. The use of appropriate surgical masks was observed in 89 respondents, but not suitable for 43 respondents. There was no significantly difference between BMI, bizygomatic width and bigonial width with the suitability of surgical masks. However, old age was significantly more appropriate for using surgical masks than young people. In conclusion, BMI, bizygomatic width, and bigonial width are not substantially different with the suitability of surgical masks. However, older age is more suitable for employing surgical masks than younger age.

ABSTRAK

Penggunaan masker diwajibkan untuk mencegah penularan COVID-19. Penggunaan masker yang sesuai dengan ukuran wajah sangat penting agar tidak terjadi kebocoran. Penelitian ini bertujuan untuk mengetahui hubungan antara lebar bizygomatic dan bigonial dengan kesesuaian masker bedah. Ini adalah penelitian observasional analitik dengan dengan rancangan potong lintang dilakukan di Laboratorium Kedokteran Kerja, Fakultas Kedokteran, Universitas Trisakti, Jakarta selama Maret sampai April 2021. Total sebanyak 132 pekerja di Fakultas Kedokteran Trisakti berumur 20 sampai 64 tahun yang memenuhi kriteria inklusi dan eksklusi berpartisipasi dalam penelitian. Tidak dijumpai perbedaan nyata pada umur (p=0.248) dan indeks masa tubuh (IMT) (p=0.226). Namun demikian, terdapat perbedaan nyata pada lebar bizigomatik (p=0.000) dan bigonial (p=0.001) antara pria dan wanita. Pemakaian masker bedah yang sesuai dijumpai pada 89 pekerja dan yang tidak sesuai pada 43 pekerja. Tidak ada perbedaan bermakna antara IMT, lebar bizigomatik, dan bigonial dengan kesesuaian masker bedah. Namun, usia tua secara bermakna lebih sesuai dalam penggunaan masker bedah dibandingkan usia muda. Dapat disimpulkan IMT, lebar bizigomatik, dan lebar bigonial tidak berbeda secara substansial dengan kesesuaian masker bedah. Namun, usia yang lebih tua secara lebih cocok menggunakan masker bedah dibandingkan usia yang lebih muda.

Keywords:
bizygomatic breadth;
bigonial breadth;
surgical mask;
suitability;
age

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INTRODUCTION

Sars-CoV-2 is a new coronavirus strain that is responsible for the respiratory illness named corona virus disease 2019 (COVID-19).[1] This disease is very contagious and caused mortality in more than 2.9 million people worldwide.[2] The transmission of COVID-19 is primarily through the respiratory droplet. Therefore, wearing face masks during the COVID-19 pandemic is mandatory in some coutries.[1] The widespread use of face masks in the community has successfully prevented the spread of Sars-CoV-2 and reduced the incidence of COVID-19.[3] However, wearing face masks could become useless if they are not worn properly and the materials are not suitable to prevent droplets.[4]

One of the recommended face masks for daily use in this situation is surgical masks. According to the American Industrial Hygiene Association (AIHA), a surgical mask is an infection control device designed to prevent the spread of infection from the wearer's exhaled breath to potentially susceptible individuals. It provides a barrier to reduce environmental contamination from materials exhaled by the wearer.[5] Milton *et al*.,[6] proved that surgical masks could reduce the amount of virus on fine particles (< 5mm): OR 2.8 (95% CI 1.5 - 5.2) and on coarse particles (> 5mm): OR 25 (95% CI 3.5 to 180). Overall, the masks can provide 3.4 fold reduction in viral aerosol release (95% CI 1.8 to 6.3).[6]

Two factors that play an essential role in determining the function of a mask. The first one is the efficiency of the filter material, which depends on the particle size, and the second one is the suitability of the mask. Therefore the ineffectiveness of face masks can be influenced by a person's face or facial anthropometry.[7] In this study, two measurements of face anthropometry were carried out i.e. bizygomatic breadth and bigonial breadth. The bizygomatic breadth was obtained by measuring the distance between the most prominent structure of left and right zygomatic bones. The bigonial breadth is the straight distance between the most lateral points of the two mandibular angles.[8,9] There are other face dimensions, but we choose these two dimensions because the two face dimensions show the length of the face and it should be covered when one is wearing a mask. Facial anthropometry not only being influenced by race, but also by age and gender. Omotoso *et al*.,[10] study proved a significant difference in all facial anthropometric measurements except facial width between men and women in the age group of 16-20 yr. The results in the higher age group also got similar results. For age, there was an average increase in all facial sizes and an increase in the age group.

A study examining the connection between the bizygomatic and bigonial breadth and the appropriateness of the surgical mask has not yet been conducted. The aim of this study was to compare the bizygomatic and bigonial breadth and the suitability of the surgical mask. The surgical mask was chosen because they are commonly used. The results of this study are expected to determine the size of surgical masks suitable for Indonesian facial anthropometry so that they can effectively minimize the spread of COVID-19 or other droplet transmission diseases.

MATERIALS AND METHODS

It was an analytic observational study with a cross-sectional design conducted at the Occupational Medicine Laboratory, Faculty of Medicine, Universitas Trisakti, Jakarta during March to April 2021. A total 132 employees of Faculty of Medicine, Universitas Trisakti aged from 20 to 64 y.o. who meet the inclusion and exclusion criteria participated in this study. Subjects with a history of facial trauma, facial aesthetic surgery, facial

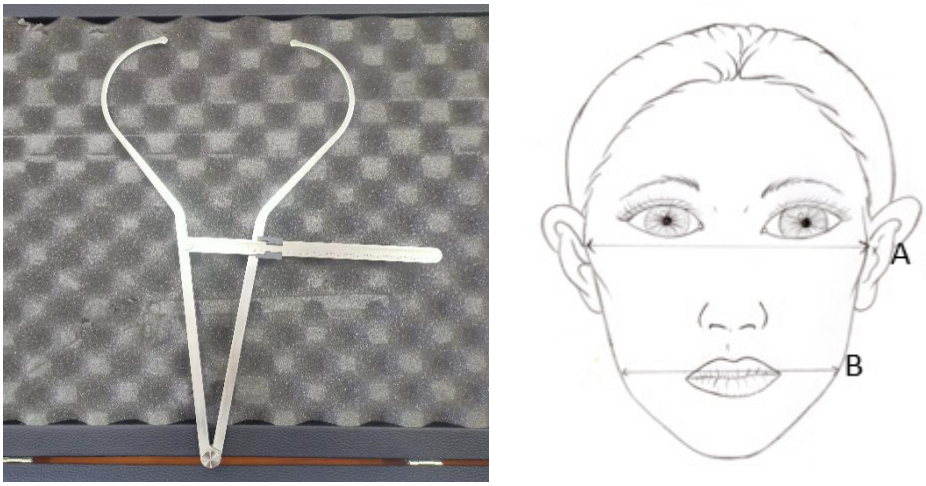
reconstruction and orthognathic surgery as well as orthodontic treatment were excluded in this study.

Measurements

Demographic data, including age and gender, were obtained through interviews. The age of the subjects was life span as measured by the year listed on the identity card. Gender was male or female written on the identity card. Body mass index (BMI) was calculated by dividing a person's weight in kg by their height in square m. Body height was measured using a height measuring device (microtoise).

Bizygomatic and bigonial breadth measurement

Bizygomatic and bigonial breadth measurements were carried out using the Martin GPM Anthropometer Kit. The measurement was conducted under strict health protocols where researchers wore complete personal protective equipment (PPE). Measurements were made using a small spreading caliper (FIGURE 1A) and following the method developed by Farkas (1994).[9] Subjects were in a sitting position, relaxed, with the head in the correct anatomic position (neutral head position). Bizygomaticum breadth measurement was carried out first by determining the most lateral point of the left and right zygomaticum bones and then measuring the distance between those two points. Bigonial breadth measurements were performed by determining the mandibles's left and right most lateral angles and then measuring the distance between those two points (FIGURE 1B). The measurements were made twice by two different researchers and the mean value was taken for further analysis.[9]



A B

FIGURE 1. A) Small spreading caliper (personal property). B) A is bizygomaticum breadth, B is bigonial breadth.[9]

Surgical mask suitability test

The surgical mask suitability test was performed using 3M Qualitative Fit Test Apparatus FT -30 (FIGURE 2A). A head loop surgical mask was provided, and the individual was instructed to wear it. (FIGURE 2B), and then they had to wear a unique head covering. The fit test was carried out by spraying a special liquid with the tip of the spray located approximately 5 cm in front of the mask at a position of 40° downward. After the first spraying, if the subject could feel a

sensation on the tongue and/or throat, the results were non-fit/not passed. If the subject doubted the sensation, the spraying could be repeated up to three times. If it was confirmed that there was no sensation at all, then the examination results was fit/passed and it's called suitability. The masks used were Sensi® three layers surgical masks sized 90 x 175 cm.

A B

FIGURE 2. A) Subject was tested with 3M Qualitative Fit Test Apparatus FT-30 (personal property), B) Surgical mask (personal property)

Statistical analysis

Data analysis in this study was carried out using the Statistical Package for Social Sciences (SPSS) program version 20.0. Normal distribution was determined by the Kolmogorov Smirnov test. Some variables such as body mass index (BMI), bizygomatic and bigonial breadth had normal distributions, while the age variable was not. For the comparison test, variables with normal distribution were analyzed with t test and the age variable was analyzed with Mann-Whitney as not-normal distribution data.

Ethical clearance

This study has been approved by the Health Research Ethics Committee, Faculty of Medicine, Universitas Trisakti (Number 168/KER/FK/XII/2020).

RESULTS

Characteristics of subjects

This study was carried out at the Faculty of Medicine, Universitas Trisakti, Jakarta from March to April 2021 involving 132 subjects. Fifty eight of them were male, and 74 were female. No significant difference in age and BMI between male and female ($p>0.05$). However, the bizygomatic and bigonial breadth of males were significantly wider than females ($p<0.005$). The male bizygomaticum was about 0.6 cm wider than that of the female ($p=0.000$). Likewise, the bigonial breadth was wider in males than females, about 0.5 cm ($p=0.001$) (TABLE 1).

TABLE 1. Characteristics of subjects [(mean ± SD or median (range)]

Variables	Men (n =58)	Women (n =74)	p
Age (year)	41.50 (18-64)#	40 (20-56)#	0.248[1]
Body mass index	25.43 (15.97-42.96)#	26.07 (17.97-37.70)#	0.226[1]
Bizygomaticum breadth (cm)	13.12 ±0.85 (11.3-15.6)	12.51 ± 0.72 (11.0 – 14.2)	0.000[2*]
Bigonial breadth (cm)	11.73 ± 0.94 (9.35-14.95)	11.23 ± 0.73 (9.15-13.90)	0.001[2*]

Note: #median (range); [1]Mann Whitney test; [2]t test; p significant if < 0.05

Comparison age, BMI, bizygomatic breadth, bigonial breadth, and suitability of surgical masks

The surgical mask compatibility test was passed by 89 participants, while 43 were deemed to have failed it. A significant difference between suitability and inappropriateness of surgical masks based on age was observed (p=0.026). However, there were no significant difference based on BMI, bizygomaticum breadth, and bigonial breadth (p> 0.05) (TABLE 2).

TABLE 2. Comparison between age, body mass index, bizygomatic breadth, bigonial breadth [mean ± SD or media (range)] and suitability of surgical masks.

Variables	Men (n =58)	Women (n =74)	p
Age (year)	43.00 (18-64)#	34 (20-54)#	0.026[1]*
Body Mass Index	25.40 (15.97-37.70)#	26.12 (18.74-42.96)#	0.263[1]
Bizygomaticum breadth (cm)	12.74 ±0.82 (11.1-14.8)	12.88 ± 0.85 (11.0-15.6)	0.381[2]
Bigonial breadth (cm)	11.30 (9.15-13.90)#	11.60 (10.3-14.95)#	0.412[2]

Note: #median (range); [1]Mann Whitney test; [2]t test; p significant if < 0.05

DISCUSSION

Characteristics of subjects

The results showed a significant difference between males and females in bizygomaticum and bigonial breadth. In this study, both dimensions were wider in males than in females. Lin & Chen also reported the same result where the average of bizygomatic breadth in males (128.2±6.6 cm) was wider than in females (122.7±7.0 cm) as well as bigonial breadth (males 114.0±8.8 cm vs females 105.5±7.9 cm).[11] The same results were also proved by Vinay *et al.*,[8] their study showed that the average of bigonial breadth in males was 9.45±0.53 cm, which was wider than in females (8.74±0.53 cm). Abitha *et al.*[12] found that the average of bizygomatic measurement in men was significantly wider (10.63±0.78 cm) compared to women (10.37±0.73 cm).

Comparison age, BMI, bizygomatic breadth, bigonial breadth, and suitability of surgical masks

The results of this study showed no relationship between the size of the bizygomaticum and bigonial breadth and the compatibility of the surgical mask, indicating that staff of Faculty of Medicine, Universitas Trisakti could generally use surgical masks without being affected by the width of the bizygomatic and bigonial. Likewise, the BMI did not affect the suitability of the

surgical mask. This could be because the surgical mask is large enough to encompass the face and prevent exhalation leaks.

In comparison to younger subjects, older subjects demonstrated greater surgical mask suitability, suggesting that older individuals are more likely to wear masks correctly and consistently due to their greater awareness of the fact that they face a greater risk of morbidity and mortality from COVID-19 diseases. Education and information about the importance and proper way to wear masks during the COVID-19 pandemic are highly needed these days. Public health education plays a role in effective-hygiene behavioral changes.[13] A surgical mask can effectively reduce droplet transmission up to 80%.[14] Droplets are respiratory particles with a diameter greater than 5 μm and can disperse around 1 m (close contact) to a maximum of 6 feet (1.83 m) in the air before falling.[15,16] However, in order to minimize the transmission of COVID-19, apart from wearing surgical masks, it is necessary to maintain distance and wear effective eye protectors to protect against respiratory tract diseases that are transmitted by droplets.[16,17]

There has never been any research about the relationship between bizygomatic and bigonial breadth and surgical mask suitability. However, a study about respiratory masks found that more subjects with significantly larger facial width, bigonial breadth, and facial length passed the respirator fit test than those who failed the fit test when using cup-shaped respirators.[18] This study with a surgical mask showed no difference between subjects with wider faces and subject with narrower faces. This is because the size of the surgical mask is wider, so it can adequately cover the nose and mouth, both in narrow and wide faces. These results are important for the user of surgical mask, so they don't have to worry about the leakage when the wear the surgical mask. The limitation of this study is that the bizygomatic and bigonial breadth measurements were not carried out by three-dimensional measurements so that accurate measurement may not be obtained.

CONCLUSION

This study proves that there is no relationship between bizygomatic and bigonial size and the suitability of the mask, but there is a relationship between age and the suitability of the mask. Thus, it can be said that currently the surgical masks available on the market still match the face sizes of employees of Faculty of Medicine, Universitas Trisakti, Jakarta.

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The facial measurements in health workers at Dr. Sardjito General Hospital, Yogyakarta

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ABSTRACT

The appropriate mask is based on facial anthropometric measurements that may be affected by sex, race, age, and body mass index (BMI). This study aimed to determine the difference and relationship between the bizygomatic width (BW) and nasion-menton height (NMH) with sex and BMI in health workers. This descriptive-analytical study used a cross-sectional method. The subjects were 39 health workers (nurses and doctors) at Dr. Sardjito General Hospital, Yogyakarta consisting of 15 male subjects and 24 female subjects, aged between 25-55 years old. Anthropometric measurements were performed on the subjects, including body weight, height, NW, and NMH. The data were analyzed using the Shapiro-Wilk test, independent t-test, and Pearson's test. There was a significant difference in the BW between male and female subjects ($p<0.05$), with the males' BW (13.1 ± 0.76 cm) being larger than that of the female subjects (12.35 ± 0.62 cm). There were no differences in the BMI and nasion-menton height between the male and female subjects ($p>0.05$). The Pearson's test results showed no significant relationship between the BW with BMI in both the male subjects ($r=0.351$; $p=0.199$) and the female subjects ($r=0.349$; $p=0.094$), and between the nasion-menton height with BMI in both the male subjects ($r=0.101$; $p=0.721$) and the female subjects ($r=0.390$, $p=0.060$). In conclusion, the males' BW was larger than the female health workers. It is necessary to consider facial anthropometric measurements in face mask manufacturing to provide comfort and good protection.

Keywords:
anthropometry;
bizygomatic width;
body mass index;
health workers;
nasion-menton height

ABSTRAK

Kesesuaian penggunaan masker didasari oleh adanya variasi ukuran antropometri wajah yang dapat dipengaruhi oleh jenis kelamin, ras, usia, dan indeks massa tubuh (IMT). Tujuan penelitian ini untuk mengetahui perbedaan dan hubungan antara ukuran lebar bizigomatik dan panjang menton-nasion dengan jenis kelamin dan IMT pada tenaga kesehatan. Penelitian ini merupakan penelitian deskriptif analitik dengan metode potong lintang. Subjek adalah 39 orang tenaga kesehatan (perawat dan dokter) di RSUP Dr. Sardjito, Yogyakarta yang terdiri dari 15 laki-laki dan 24 perempuan, berusia antara 25-55 tahun. Pada subjek dilakukan pengukuran antropometri meliputi berat tubuh, tinggi tubuh, lebar bizigomatik, dan panjang nasion-menton. Data dianalisis menggunakan uji Shapiro Wilk, uji t independen, dan uji Pearson. Terdapat perbedaan nyata pada lebar bizigomatik laki-laki dan perempuan ($p<0,05$), dengan lebar bizigomatik laki-laki (13,1 ± 0,76 cm) lebih besar dibanding perempuan (12,35 ± 0,62 cm). Tidak terdapat perbedaan antara IMT dan panjang menton-nasion pada laki-laki dan perempuan ($p>0,05$). Hasil uji Pearson menunjukkan tidak ada hubungan yang signifikan antara ukuran lebar bizigomatik dengan IMT pada laki-laki ($r=0,351$; $p=0,199$) dan perempuan ($r=0,349$; $p=0,094$), serta antara panjang menton-nasion dengan IMT pada laki-laki ($r=0,101$; $p=0,721$) dan perempuan ($r=0,390$, $p=0,060$). Dapat disimpulkan bahwa lebar bizygomatic tenaga kesehatan laki-laki lebih besar dibanding lebar bizygomatic tenaga kesehatan perempuan. Ukuran-ukuran antropometri wajah perlu diperhatikan dalam pembuatan masker supaya nyaman digunakan dan dapat memberikan perlindungan yang baik.

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INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is an infectious disease that is caused by a new variant of coronavirus, i.e., Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Health workers as the frontline of COVID-19 are at a higher risk from SARS-CoV-2.[1] One of the efforts to protect and minimize the risks for health workers from COVID-19 is to wear personal protective equipment such as an N95 mask. Nevertheless, prolonged use of the N95 mask may cause discomfort due to mask pressure in the face, difficult movement of facial muscles, and itching.[2] Besides, a mask size problem may also lead to a mask leak.[3] On the other hand, a mask size that fits facial characteristics can provide good protection.[4] Differences in the mask fit are based on different facial anthropometric measurements that may be affected by sex, race, age, and body mass index (BMI).[5,6]

Anthropometry is the measurements of the body dimensions or other physical characteristics of the body that are useful in designing objects that a person wears.[7] Facial anthropometric measurements can be useful in mask manufacturing. There are 12 facial dimensions that are related to the performance of a respirator, including bi-ectoorbital width, bizygomatic width, bigonial width, nasion-menton height, menton-subnasal height, subnasal-nasion height, biocular width, nasal root width, nasal width, lip width, bitragion-menton arc, and bitragion-subnasal arc.[8] Research results showed that bi-ectoorbital width, bizygomatic width, bigonial width, nasion-menton height, lip width, and bitragion-menton arc are good predictors for a respirator mask fit because, based on a mask fit testing, these facial anthropometric measurements affect a respirator leak in the nose, cheeks, and chin.[3,8]

A face shape depends on the structure of hard tissues (bone) and soft tissues. Facial soft tissue thickness is affected by gender, age, race, and nutritional status.[9] The BMI is an important factor that contributes to accurately determining the differences in facial soft tissue thickness among individuals.[10]

Bizygomatic width and nasion-menton height were selected as the dependent variables because some previous studies showed that bizygomatic width and nasion-menton height were good predictors for a respirator fit and there was a significant difference in the bizygomatic width and nasion-menton height of males and females.[8,11]

Based on the above-mentioned description, this study was conducted to determine the differences and relationship between facial anthropometric measurements, i.e., the bizygomatic width and nasion-menton height with sex and BMI. Health workers at Dr. Sardjito General Hospital, Yogyakarta were chosen as the research subject because it is one of the referral hospitals for handling patients with COVID-19 in the Special Region of Yogyakarta. Therefore, the facial anthropometric measurements obtained in this study expectedly can be useful for developing an N95 mask that can provide both comfort and good protection for health workers.

MATERIALS AND METHODS

Subjects

This descriptive-analytical study used a cross-sectional method. The data were the facial anthropometric measurements of the health workers at Dr. Sardjito General Hospital, Yogyakarta in October-November 2021. A total of 39 subjects (15 males and 24 females) included nurses and doctors at Dr. Sardjito General Hospital, Yogyakarta who were between 25-55 years old.

Protocols of study

The inclusion criteria for this study were: having no facial trauma, having no facial surgery, and having willingness to participate in the study. The exclusion criteria for this study were: having a head and facial fracture, having congenital bone diseases, and having a history of vertebral, pelvic, or lower limb fractures. The instruments used were a sliding caliper to measure facial anthropometry, an anthropometer to measure body height, and a body weight scale. Before the measurements were conducted, all the subjects had signed an informed consent form. BMI was determined by the formula of body weight divided by height squared (kg/m^2), with the categories according to WHO.[12] This research was approved by the Medical and Health Research Ethics Committee of the Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia with the approval number KE-FK-1388-EC-2021.

Statistical analysis

The normality of the data was tested using the Shapiro-Wilk method. The hypothesis was tested using the independent t-test to see any differences between the male and female subjects. The Pearson correlation test was used to determine the relationship between gender and with bizygomatic width (BW) and nasion-menton height (NMH).

RESULTS

The frequency distribution of the research subject characteristics based on sex, age, and profession are presented in TABLE 1, whereas the frequency distribution of the research subject characteristics based on BMI categories are presented in TABLE 2. Most of the subjects (16 people or 41%) were categorized as slightly overweight.

TABLE 1. Characteristics of gender, age, and profession in subjects

Characteristics	n (%)
Gender	
• Male	15 (38.5)
• Female	24 (61.5)
Age (years)	
• 25-29	6 (15.4)
• 30-39	20 (51.3)
• 40-49	8 (20.5)
• 50-55	5 (12.8)
Profession	
• Doctor	13 (33.3)
• Nurse	26 (66.7)

TABLE 2. Frequency distribution of BMI category in subjects

Gender	Normal n (%)	Overweight n (%)	Obesity I n (%)	Obesity II n (%)
Male	2 (5.1)	3 (7.7)	9 (23.1)	1 (2.6)
Female	6 (15.4)	4 (10.3)	7 (17.9)	7 (17.9)
Total	8 (20.5)	7 (17.9)	16 (41.0)	8 (20.5)

Based on the normality test using the Shapiro-Wilk method, the data were normally distributed. The results of the independent t-test (TABLE 3) show that there was a significant difference in the BW between the male and female subjects ($p<0.05$), with the BW of the male subjects being greater than that of the female subjects. There was no significant difference in the NMHt and BMI between the male and female groups. The results of the Pearson's correlation test (TABLE 4) show that there was no significant relationship between the BW and the NMH with BMI in both the male and female subjects.

TABLE 3. Mean ± SD of BMI), BW and NMH in subjects

Variables	Male (n=15)	Female (n=24)	Total (n=39)	Independent t-test	
				t	p
BMI (kg/m^2)	25.98 ± 2.90	26.51 ± 4.40	26.31 ± 3.86	-0.455	0.652
BW (cm)	13.1 ± 0.76	12.35 ± 0.62	12.64 ± 0.76	3.348	0.002*
NMH (cm)	11.45 ± 0.54	11.11 ± 0.53	11.24 ± 0.55	1.925	0.062

BMI: body mass index; BW: bizygomatic width; NMH: nasion - menton height; *p <0.05; the data are partly taken from Aliya.[13]

TABLE 4. The correlation coefficient of BW and NMH with BMI in subjects (Pearson's correlation test)

Variable	BMI					
	Male		Female		Total	
	r	p	r	p	r	p
BW	0.351	0.199	0.349	0.094	0.261	0.109
NMH	0.101	0.721	0.390	0.060	0.265	0.103

BMI: body mass index; BW: bizygomatic width; NMH: nasion - menton height; *p <0.05; the data are partly taken from Aliya.[13]

DISCUSSION

The prevalence of overweight (BMI ≥25 kg/m^2) in this study was 61.5%, with the prevalence of overweight in the female subjects (35.8%) being higher than in the male subjects (25.7%). Based on the Basic Health Research in 2018, the prevalence of overweight (BMI ≥25 kg/m^2) in the population aged >18 years old in Indonesia was 26.6% for men and 44.4% for women.[14] Compared to a study by Kunyahamu *et al.*[15] few reports are available on Malaysian health-care workers' obesity and whether different health-care job categories are related to workers' obesity. This study aimed to determine the prevalence of obesity among HCWs and the association between various HCW job categories and obesity. A cross-sectional study was conducted by analyzing secondary data from the 2019 annual cardiovascular health screening program, which included information regarding all government health-care workers in the east coast region of Peninsular Malaysia. The subject's body mass index (BMIconducted on health workers in Malaysia, 33.1% of the study subjects

had a BMI of 25-29.9 kg/m^2 and at a high risk of being overweight. This difference might be due to various factors related to the shift-working conditions that nurses have to undergo that disrupt sleep patterns, dietary patterns, and physical activity.[15]

A study by Adaja and Idemudia[16] conducted on the health workers in Nigeria revealed that based on the classification as set by the World Health Organization,[17] 31.7% of the health workers were overweight (BMI 25–29.9 kg/m^2) and 25.5% were obese (BMI ≥30 kg/m^2), in which the overweight and obese categories were more common in female health workers.[16] Other studies also mentioned that the higher prevalence of overweight and obesity in female health workers is because female health workers perform fewer physical activities than male health workers.[18,19] A high energy intake with minimum physical activity could increase the risk of being obese among health workers.[20] A study by Kit in 2019 revealed that 45.6% of health workers were categorized as physically inactive and had a sedentary lifestyle with a mean daily duration of 5 hours. In addition, vitamin E and zinc deficiency, less than 7-hour sleep duration, and non-smokers are significantly associated with a high body fat percentage.[21]

Based on the result of this study, there was no significant difference in the mean BMI of the male subjects (25.98 ± 2.90 kg/m^2) and the female subjects (26.51 ± 4.40 kg/m^2). This result is in line with a study by Asil *et al.*,[22] showing that there was no difference in the mean BMI based on gender, but there was a significant difference in the mean BMI based on age, education level, marital status, parity, smoking status, and sleep duration. However, these results are different from a study by Xiao *et al.*,[23] showing a significant difference in the mean BMI of the male subjects (21.74 ± 1.74 kg/m^2) and the female subjects (24.39 ± 3.54 kg/m^2).

In fact, muscular people or athletes may have a high BMI due to the volume of muscle mass; women have a higher fat percentage than men; older adults have a higher body fat than young adults.[24] Decreased physical activity, slowing metabolism due to old age, menopause and physiological changes in women can increase body weight.[25] A pregnancy or weight gain due to pregnancy can trigger obesity; even in women with a poor dietary pattern, the BMI can also increase after childbirth.[26,27] The basal metabolic rate of women is 10% smaller than men. Thus, women are likely to turn food into fat, while men are more likely to turn food into muscle and energy reserves. In addition, women have fewer muscles than men. Meanwhile, muscle cells are able to burn more fat than other cells.[28]

In addition, the education level of an individual affects the dietary pattern, where the higher the education level, the lower the BMI. Marriage, divorce, or a loss of a spouse also affects body weight. Unmarried individuals are likely to have a lower BMI than those who are married or have lost a spouse.[22] Smokers have a lower BMI than non-smokers.[22] Smoking can help weight loss by increasing the metabolism rate and suppressing appetite.[29] However, it is necessary to analyze the effect of genetic and environmental factors on obesity to reveal more details about the factors that affect BMI in individuals.[22] But, these factors were not examined in this study.

Sex influences the facial profile because the soft tissues that cover the hard tissues in men are thicker than those in women. In addition, the chin growth in men forms a greater jaw angle than in women, causing women in general to have a more convex facial profile than men.[30] Regarding the facial anthropometric measurements, the results of the study showed that the bizygomatic width of the male group (13.1 ± 0.76 cm) was larger and significantly different than the female subjects (12.35

± 0.62 cm). This result is consistent with some previous studies,[8,11,31] showing that the average BW of males is greater than in females, but the zygomatic bone of females is more prominent than that of males. In addition, there was no significant difference in the NMH of the male subjects (11.45 ± 0.54 cm) and female subjects (11.11 ± 0.53 cm). This is different from some studies,[8,32,33] showing that the average NMH in male subjects is significantly higher than that in female subjects. Various factors cause differences in facial dimensions, including genetics and race. In addition, the hormone testosterone in men can increase the size and mass of muscles and bones, leading to differences in the facial shape between men and women.[33] A higher testosterone to estradiol ratio (T/E ratio) in men is related to the size of the cheekbones, mandible, chin, and face height. Testosterone can affect on facial development through an increased level of growth hormone (GH) which plays an important role in regulating growth, body development, and body composition.[34] A study conducted in Korea showed that there was a significant difference between 11 facial dimensions of men and women, two of which were the BW and NMH.[8] Women have smaller facial dimensions than men, particularly in terms of the bigonial width, BW, and facial height.[11]

The results of the Pearson's test showed no significant relationship between the BM with BMI in both the male (r=0.351; p=0.199) and the female subjects (r=0.349; p=0.094), and no significant relationship between the NMH with BMI in the male subjects (r=0.101; p=0.721) and female group (r=0.390, p=0.060). The insignificant result obtained in this study might be due to the uneven distribution of the BMI categories. In this study, there were 31 subjects (79.4%) who were in the overweight and obese categories, and only 8 subjects (20.5%) in the normal category. The results of this study are different from some previous studies, such as a study by Nádaždyová *et al.*[10] showing that the group with BMI >25.0 kg/m^2 had a larger nasal width, BW, total facial height, mouth width, and morphological facial height compared to the group with BMI of 18.6–24.9 kg/m^2. Facial soft tissues fluctuate according to the nutritional status of a person. The BMI is a key factor in accurately determining the difference in the facial soft tissue thickness among individuals.[35] Additionally, nutritional status also affects cheek width and the relative width of the lower face.[36]

According to a study by Windhager *et al.*,[37] body fat percentage leads to 8.7% variation in facial shape and it has a significant correlation with BMI. Facial width and height are significantly related to BMI, in which an increased BMI has more effect on facial width than on facial height. An increase in BMI leads to a relative widening of the midface and lower face. Someone with a lower body fat percentage tend to have angular face with relatively small cheeks, pointy chin, relatively big eyes, and a pointy nose.[36,37] According to a study by Dong *et al.*,[35] that was conducted using a 3D skull model in North China, the soft tissue thickness is increased along with an increasing BMI, in which the thickest soft tissues were found at landmarks in the cheeks for all the BMI categories in both men and women. Sex affects facial profiles because the soft tissues that cover the hard tissues in most areas of male face are thicker than in female faces.[30,38]

Based on the results of this study, the BW of the male group was greater the female subjects, therefore, it is necessary to consider different N95 mask sizes based on sex. Based on a study conducted by Solano *et al.*,[39] the standard N95 mask size recommended by the Centre for Disease Control and Prevention (CDC) is too big for women, causing a mask leak, especially in the chin. Therefore, women need smaller N95 mask size than men.

CONCLUSION

There is no correlation between the BW and NMH with sex and BMI. However, there are differences in BW between male and female health workers at Dr. Sardjito General Hospital, Yogyakarta. It is crucial to consider facial anthropometric measurements in mask manufacturing to manufacture masks that are both comfortable to wear and provide good protection.

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Reconsidering the limited role of right heart catheterization on severe pulmonary hypertension-due to progressive interstitial lung disease in young male patient: a case report

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ABSTRACT

Pulmonary hypertension (PH)-associated with interstitial lung disease (ILD) develops as a consequence of progressive underlying lung disease or disproportionately to the underlying disease. The PH investigation by right heart catheterization (RHC) for defining PH severity is recommended in patients with ILD who show more severe symptoms than expected from lung disease, appearance of right heart failure, and clinical deterioration not matched by the declining lung function. In patient with progressive ILD, RHC is only considered if it affects the future treatment such as lung transplantation or enrollment in clinical trial/registry. The decision to undertake the RHC in progressive ILD was still fraught with doubts. Here we reported a young adult male patient with ILD whom developed progressive signs and symptoms. By RHC, he had severe precapillary PH with hemodynamic parameters indicated the presence of pulmonary vascular disease. A PH-specific treatment, sildenafil citrate, was administered, and patient responded well and was clinically stable during the addition of sildenafil citrate. This case highlights the clinical implication of performing RHC in progressive ILD, which can change the treatment decision by PH-specific drugs. Therefore, the RHC decision making in patient with progressive ILD need reconsideration.

ABSTRAK

Hipertensi pulmonal (PH)-terkait dengan penyakit paru interstitial (ILD) terjadi sebagai konsekuensi dari penyakit paru-paru progresif yang mendasari atau tidak proporsional dengan penyakit paru-paru yang mendasarinya. Penentuan diagnosis PH dengan kateterisasi jantung kanan (RHC) sebagai standar emas untuk menentukan tingkat keparahan PH direkomendasikan pada ILD dengan gejala yang lebih parah dari yang diharapkan berdasarkan fungsi paru, munculnya tanda gagal jantung kanan, dan perburukan klinis yang tidak diimbangi dengan penurunan fungsi paru. Pada pasien dengan ILD progresif, RHC hanya dipertimbangkan jika mempengaruhi pengobatan seperti transplantasi paru atau pendaftaran dalam uji klinis. Keputusan untuk melakukan RHC pada ILD progresif masih kontroversi. Kasus ini melaporkan seorang pasien pria dewasa muda dengan ILD yang mengalami tanda dan gejala progresif. Dengan RHC, didiagnsosi dengan PH prekapiler yang parah dengan parameter hemodinamik yang menunjukkan adanya penyakit pembuluh darah paru. Pengobatan spesifik PH yaitu sildenafil sitrat diberikan dan pasien merespons dengan baik dan stabil secara klinis selama penambahan sildenafil sitrat. Kasus ini menekankan implikasi klinik melakukan RHC pada penyakit ILD progresif, yang dapat mengubah pengobatan dengan obat spesifik PH. Dengan demikian, pengambilan keputusan untuk melakukan RHC perlu dipertimbangkan kembali pada kasus ILD progresif.

Keywords:
interstitial lung disease;
pulmonary hypertension;
heart catheterization;
pulmonary arterial remodeling;
sildenafil citrate

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INTRODUCTION

Pulmonary hypertension (PH) is defined by mean pulmonary arterial pressure (mPAP) >20 mmHg at rest as measured by the right heart catheterization (RHC).[1] The PH is classified into five clinical groups, one of them is PH due to lung disease and/or hypoxia.[2] In addition to chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD) is one of the most common lung diseases associated with PH.[2] There is an increasing prevalence of PH among patients with progressive and advanced ILD.[3] Pulmonary hypertension-associated with ILD usually mild to the moderate degree with mean pulmonary artery pressure (mPAP) 20-30 mmHg and does not need PH-specific treatment.[3]

Pulmonary hypertension-associated with ILD may develop as a consequence of progressive lung disease and hypoxia (PH group 3 or PH-due to lung disease/hypoxia) or disproportionately to the underlying disease.[4] Several patients experience an out-of-proportion PH, with mPAP ≥35 mmHg but with mild-to-moderate ILD, a term to indicate a disproportionate increase in mPAP that is not suitable with the severity of fibrotic lung disease due to ILD.[3,4] In these populations, the pulmonary vascular remodeling coexists and may predominate the pathogenesis of PH mimicking those of pulmonary arterial hypertension (PAH) in whom the PH-specific treatment will have a beneficial impact.[5] The RHC is the gold standard examination for determining the severity of PH in ILD. However, the current guideline limits the recommended use of RHC for PH-associated with ILD only for patients with more severe signs and symptoms than expected from lung function, the appearance of right heart failure, clinical deterioration not matched by the declining lung function, and candidate of lung transplantation or candidate for enrollment in clinical trial/registry.[2,3] The RHC is considered in patients with chronic lung disease when severe PH is suspected and the result of RHC will likely affect patient treatment.[6] The patient with progressive or advanced ILD is not recommended to get an RHC examination, since RHC may not give effect to severe PH.[6] Here we report a young male progressive ILD patient with severe PH, determined by RHC, and indicated as severe PH due to lung disease/hypoxia or PH group 3. The patient was successfully treated with the addition of PH-specific treatment. This case report aimed to discuss about reconsidering the decision-making to perform RHC in the progressive ILD case, which may alter the management of patients.

CASE

A male patient aged 39 y.o. came to be hospitalized with complaints of increasing shortness of breath, productive cough, and fatigue. The patient was an active smoker with two packs a day of cigarettes on average. No history of cardiovascular and cerebrovascular disease was reported. From the physical examination patient was tachypneic, with a blood pressure of 108/69 mmHg, pulse 102 times per min, respiratory rate 32 times per min, and temperature of 36.6°C. Peripheral oxygen saturation was 89% on nasal cannula 3 L per min. The increased jugular venous pressure (JVP) at 5+3 cmH_2O was observed. Chest examination showed right heart border was enlarged with increased vesicular lung sound and hoarse rhonchi in both lung fields. No parasternal lifts or prominent heart murmurs were detected. No hepatomegaly and ascites in abdominal examination. The extremities were non oedema. There were clubbing fingers.

The electrocardiogram examination showed sinus rhythm and poor R wave progression (FIGURE 1). There was an elevated N-terminal pro B-type natriuretic peptide (NT-proBNP) 2.045 pg/mL. The chest X-rays showed in both lung field the presence of inhomogeneous

opacity in the suprahiller and perihiller region, bilateral paracardial amorphous boundary forms of air-bronchogram, widening of visible intercostal space, and slippery and horizontal contour of right diaphragm; in the heart there was enlargement of right atrium (FIGURE 2). The thorax CT scan indicated an interstitial lung disease with signs of interstitial pneumonia (FIGURE 3). Patients had previously undergone work-up for tuberculosis, HIV, chronic hepatitis and all shown negative result. The work-up for autoimmune diseases yielded negative results. Lung function test showed FVC was 31% predicted and FEV1 was 33% predicted, indicated severe reduced lung function both obstructive and restrictive.

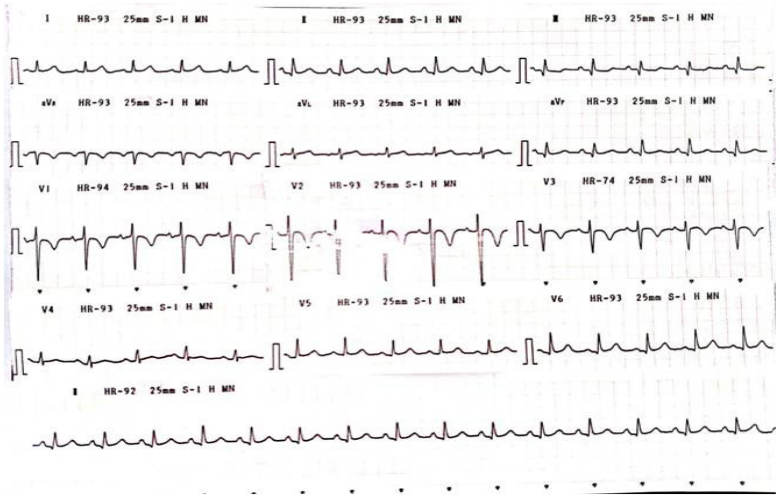

FIGURE 1. An ECG on admission showed sinus rhythm, normoaxis, symmetrical inversion T in the precordial leads, V1 to V3.

FIGURE 2. A Chest X-ray showed AP projections, supine position, asymmetric, inspirational, and sufficient conditions, the results of the two apex pulmo were calm, visible inhomogeneous opacity in the suprahiller, perihiller, and bilateral paracardial amorphous boundary forms of airbronchogram, cephalization (-), no visible widening of the two pleural spaces, visible SIC was widened and the dextra diaphragm was slippery and horizontal, the heart's waist disappeared and enlarged right atrium with CTR = 0.56

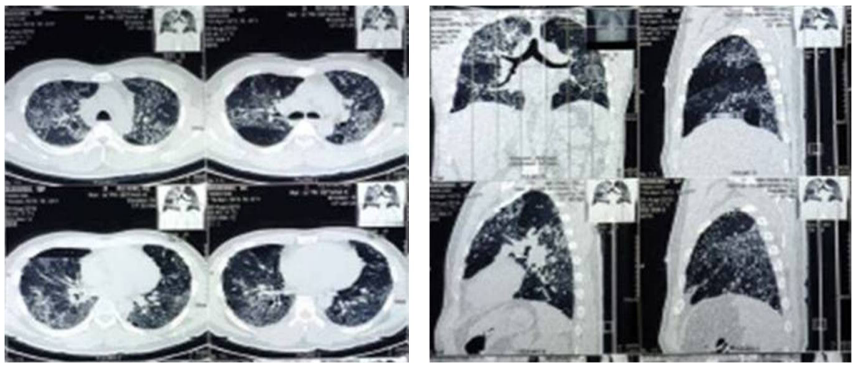

FIGURE 3. A Thorax CT scan showed interstitial pneumonia results in a differential diagnosis of interstitial lung disease with heart size within normal limits.

During the hospitalization, the patient was diagnosed with interstitial pneumonia and progressive hypoxia due to ILD. The internist-pulmonologists took care of the patient in the intensive care unit and internal medicine ward. The patient has undergone antibiotics treatment, antiinflammations (steroids), and continuous oxygen therapy, however during the treatment course little improvement was achieved. The internist-pulmonologists suspected PH as an accompanying disease in the patient and consulted cardiologists for further work-up. The initial work-up of suspicion of PH was performed by transthoracic echocardiography (TTE) and indicated the dilatation of the right atrium and ventricle (diameter of 42 mm and 34 mm, respectively), normal left ventricular (LV) systolic function (with LV ejection fraction of 76%), normal right ventricular systolic function (with tricuspid annular plane systolic excursion (TAPSE) of 23 mm) and tricuspid valve regurgitation (pressure gradient of 48 mmHg and velocity 3.46 cm/s). From the TTE result, the patient was assessed with a high probability of PH (FIGURE 4). Since our center had a long experience with PAH patients,[7] the invasive hemodynamic assessment by RHC was proposed to be completed to determine the severity of PH.

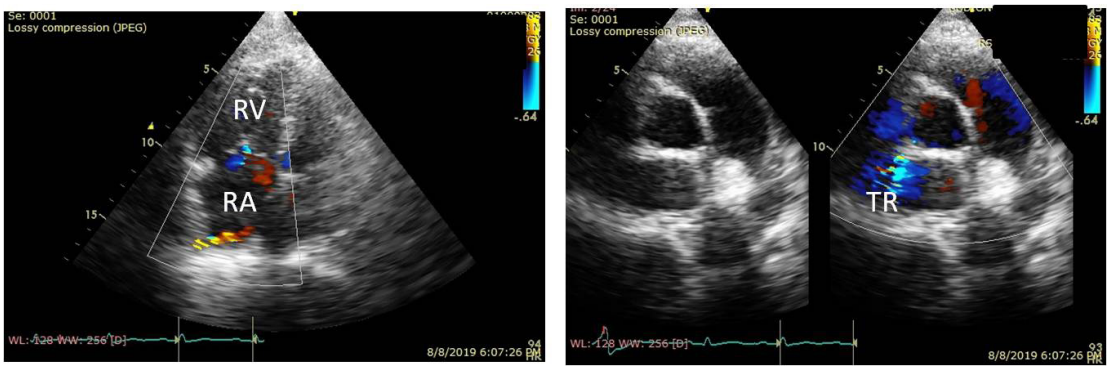

FIGURE 4. A transthoracal echocardiography appeared a jet of tricuspid regurgitation (TR) and right atrial (RA) and ventricular (RV) dilatation, a sign of a high probability of PH.

We proceeded to perform the RHC to measure the hemodynamic and determined severity of PH. The hemodynamics showed the aortic pressure systolic/diastolic (mean): 133/97 (115) mmHg, left ventricle

systolic/diastolic: 143/14 mmHg, right atrium systolic/diastolic: 14/12 mmHg, right ventricle systolic/diastolic: 61/11 mmHg, and pulmonary artery systolic/diastolic (mean): 51/25 (38) mmHg. The oxygen saturation measured in the aorta was 88.4%, the inferior vena cava was 71.5%, the superior vena cava was 60.7%, the right atrium was 68%, the right ventricle was 66%, the pulmonary arteries were 68.1%, and the left ventricle 90.2%. The pulmonary vascular resistance (PVR) index was 8.5 Wood Unit/m^2 and the cardiac index was 1.45 L/min/m^2 (FIGURE 5 and 6). During RHC, pulmonary angiography was also performed to exclude the possibility of chronic thromboembolic pulmonary hypertension or pulmonary artery obstructions. The result indicated there was no stenosis, obstruction, or thrombus in pulmonary artery branches.

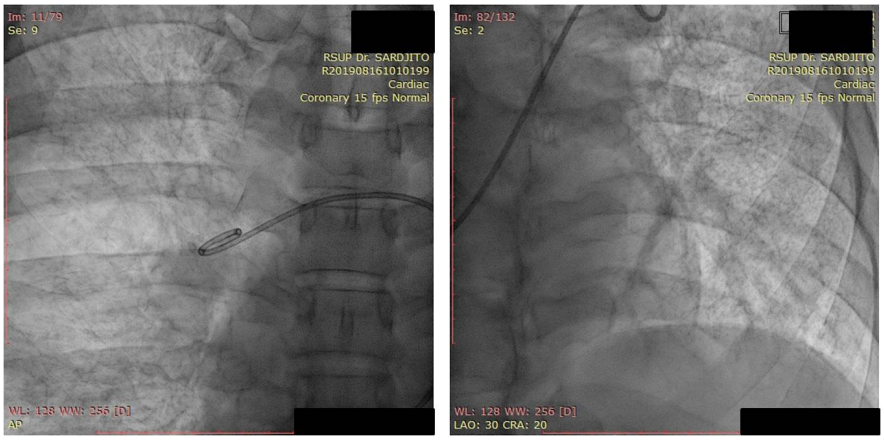

FIGURE 5. A right heart catheterization (RHC) and pulmonary angiography with no visible features of stenosis or thrombus.

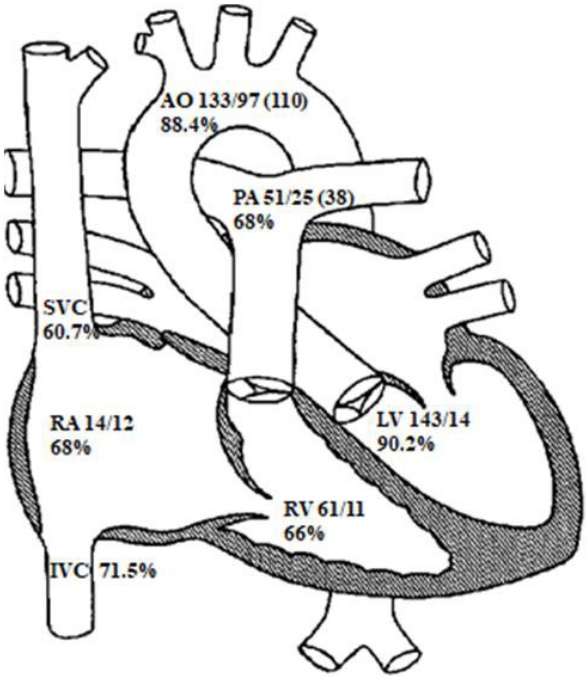

FIGURE 6. A haemodynamic diagram from the RHC indicated the low oxygen saturation and increased mean pulmonary artery pressure.

The patient's mean pulmonary artery pressure (mPAP) was ≥35 mmHg, which indicated a severe form of PH.[5] This was most likely due to the consequence of severe ILD progression or PH group 3 (severe PH-due to lung disease). The patient was decided to be given oral sildenafil citrate starting from 20 mg every 8 hr. We closely monitored him during the first dose of 20 mg oral sildenafil until 4 hr to detect the intolerance or side effects (Emoto, personal communication). The result showed no reduced peripheral oxygen saturation, no increasing dyspnea or tachypnea, and no headache or flushing sensation. We, therefore, continued to give the patients oral sildenafil citrate 20 mg t.i.d. until discharge. During six mo of follow-up, the patients doing well, with no need for continuous oxygen supplementation at home, and still using sildenafil citrate in their daily routine. He recited that daily activity can be performed without significant complaint. Unfortunately, he did not show up for objective evaluation performed routinely in our PH clinic every 6 mo, such as 6 min walking test, TTE evaluation, and NT-proBNP examination.

However, sildenafil citrate was discontinued since March 2020 because the patient did not visit our PH clinic ever since. The patient could not come to our hospital due to the COVID-19 pandemic, therefore he relied on medication from a district hospital that could not provide sildenafil citrate. Since then, the patient had relapsed and was hospitalized for about 3 times in a district hospital due to increased shortness of breath. From the district hospital, he was discharged without sildenafil citrate medication, and at home, the patient still often used supplementary oxygen when the shortness of breath attacked. In August 2020, the patient had a sudden recurrence of shortness of breath while working in the field and was taken to the nearest hospital but experienced respiratory failure and was declared dead.

DISCUSSION

Here we reported a young adult patient with severe PH due to ILD, diagnosed by RHC. The recommendation to perform RHC in chronic lung disease was limited. In general, RHC should be performed when significant PH is suspected and the management will likely be influenced by its results, such as lung transplantation, clinical trials or registry enrollments, or compassionate use of PH-specific therapy.[5,6]

The role of RHC to confirm the diagnosis and determine the severity of PH is recommended especially in ILD patients with (1) more severe symptoms than those expected based on pulmonary function data, (2) appearance of right heart failure signs, and (3) clinical deterioration that is not matched by the decline in lung function test.[3] We decided to perform RHC in this patient because the TTE showed a high probability of PH and the suggestion that we would try to give PH-specific treatment if the patient had severe PH by RHC. The haemodynamic data from RHC of this patient indicated severe PH,[5,6] i.e increased mPAP ≥35 mmHg and PVR index >3 Wood Unit. m^2. Therefore, the use of pulmonary vasodilator such as sildenafil citrate may have a beneficial impact. In this patient, we suspected that the extent of ILD progression was in-line with the increase of mPAP and PVR index, which lead to worsened symptoms. The addition of sildenafil citrate along with optimum therapy for ILD was conducted to keep the patient clinically stable. Therefore, our case indicates that RHC performed in progressive ILD gives a beneficial impact on altering patient management by guiding and administering PH-specific drugs. We suggest that the decision-making on performing RHC needs reconsidering in patients with ILD who

show worsened symptoms even if they are associated with the progressiveness of ILD. The referral to PH-center to perform PH investigation, including RHC, is an important step for specialists or general practitioners while treating progressive ILD patients.

Several studies in patients with chronic lung disease show that up to 90% of patients have mPAP >20 mmHg, with most ranging between 20 and 35 mmHg.[6] Only about 1-5% of patients have higher mPAP >35 mmHg rest, which indicates a loss of flexibility in pulmonary arteries and vascular distensibility.[5,6] This extent of PH impact circulatory impairment that considerably deteriorates exercise capacity already reduced caused by obstructive/restrictive ventilatory impairment.[5] The mPAP cut-off point of 35 mmHg was used to determine the PH severity in ILD, because ILD with mPAP ≥35 mm Hg resulted in significantly reduced lung capacity to diffuse carbon monoxide, lower arterial oxygenation at rest, lower exercise capacity, and decline of arterial oxygenation upon exercise, regardless lung function tests.[5,6] In this case, the mPAP 38 mmHg is parallel with a worsened clinical condition.

The mechanism of the occurrence of PH in patients with ILD is mostly associated with pulmonary fibrosis which involves several types of cells and interactions between various cellular components and mediators that determine the pattern and severity of fibrosis.[8] This mediator induces fibroblast activation by extracellular matrix deposition leading to fibrosis.[9] Pro-apoptotic endothelial cells reduce vasodilators, such as nitric oxide and prostacyclin, and increase vasoconstrictor agents, such as endothelin-1, which lead to an increase in vasoconstriction of smooth muscle cells.[8,9] Apoptotic endothelial cells decrease vascular density, increase the production of vascular growth factors and give rise to the proliferation of resistant endothelial cells so that the lesions become angioproliferative.[9] Therefore, in ILD, the presence of pulmonary vascular remodeling is indicated by the profound increased of mPAP and PVR. In this case, the measured mPAP was 38 mmHg, and calculated PVR index was 8.5 Wood Unit/m^2 which supported the presence of pulmonary vascular disease.

Patients with more severe lung disease (ILD with FVC <70% of predicted or COPD with FEV1 <60% of predicted) and accompanying by less severe PH (mPAP 20–24 mmHg with PVR ≥ 3 WU or mPAP 25–34 mmHg) represent the majority of patients presenting with PH-associated ILD.[6,10] Current data do not support therapy with PH-specific drugs in these patients.[2,6,11] However, patients with more severe lung disease and severe PH as defined earlier (mPAP >35 mmHg and PVR ≥ 3 WU) have a poor prognosis and should be referred to a centre with expertise in both PH and chronic lung disease for individualized patient care.[5,6] The PH-specific drugs in these patients may be beneficial to stabilize and retard the disease progression.[12,13] The decision to use PH-specific treatment shoud be based on hemodynamic parameters by RHC, regardless ILD severity.[14,15] Based on an open-label study, sildenafil citrate improved 6 min walking distance and in a controlled trial among advanced idiopathic pulmonary fibrosis, sildenafil citrate improved arterial oxygenation, lung diffusion capacity of CO, dyspnea score, and quality of life.[5,6] Our patient showed improvement and stabilization of clinical condition during adding sildenafil citrate into his treatment. However, since the advanced ILD is progressive disease, the underlying parenchymal lung disease, along with the unexpected termination of sildenafil citrate, deteriorated patient condition.

CONCLUSION

In conclusion, we reported a young

adult male patient with severe PH-due to ILD (severe PH due to lung disease or PH group 3) diagnosed by RHC. The clinical presentation was consistent with the progressivity of ILD and complicated by severe PH. Based on high-probability PH on TTE examination and clinical decision to guide the PH-specific treatment, we performed RHC in this progressive ILD patient. The adding of PH-specific drug was responded well and clinically stabilized the patient. The reconsideration of performing RHC in advanced or progresive ILD should be suggested since the patient may get a beneficial impact of adding PH-specific treatment. The referral to PH-center to perform PH investigation, including RHC, is an important step to improve the management of ILD-associated PH patients.

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Acute compartment syndrome of the forearm after transradial approach to percutaneous coronary intervention: a case report

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ABSTRACT

Percutaneous coronary intervention (PCI) through transradial pathway is associated with lower risk of severe vascular problems comparing to transfemoral. It is reported that the acute compartment syndrome (ACS) in forearm is significant lower comparing to leg. A 47 y.o. male with ACS following a transradial approach of PCI due to inferior myocardial infarction was reported. The patient experienced pain and swelling in his right forearm for 7 hr after the procedure and was later brought to hospital and treated with emergency of fasciotomy. The patient showed good post-fasciotomy recovery on the first 2 wk and showed good DASH score after 4 wk. Quick diagnosis with prompt treatment makes a better outcome for the patient. Consequently, a high level of awareness to make the diagnosis as quickly and accurately management as possible could prevent morbidity caused by late and unrecognized management compartment syndrome eventually could make a better clinical outcome.

ABSTRACT

Percutaneous coronary intervention (PCI) melalui pendekatan transradial dikaitkan dengan risiko komplikasi vaskular yang lebih rendah di lokasi akses dibandingkan dengan pendekatan transfemoral. Insiden sindrom kompartemen akut di lengan bawah dilaporkan secara signifikan lebih rendah dibandingkan di kaki bawah. Seorang pria 47 tahun dengan sindrom kompartemen akut setelah dilakukan PCI transradial karena infark miokard inferior dipresentasikan dalam laporan kasus ini. Pasien mengalami nyeri dan bengkak pada lengan kanannya 7 jam setelah prosedur dan kemudian pasien dibawa ke rumah sakit kami dan segera dilakukan fasiotomi pada lengan kanan. Pasien menunjukkan pemulihan pasca fasciotomi yang baik pada 2 minggu pertama. Setelah 4 minggu paska operasi, diperoleh skor *disabilities of arm, shoulder and hand* (DASH) yang memuaskan. Diagnosis cepat dengan pengobatan yang tepat dapat mencegah morbiditas yang disebabkan karena keterlambatan penanganan yang dapat memberikan hasil yang lebih baik bagi pasien.

Keywords:
percutaneous coronary intervention;
acute compartment syndrome;
transradial approach;
clinical outcome

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INTRODUCTION

Acute compartment syndrome (ACS) represents a limb-threatening condition that occurs due to increased pressure within a fibroosseous space and ends up in a decreased tissue perfusion condition. Time to diagnosis is a factor in outcome for ACS, which is still a diagnostic problem despite technology advancements.[1,2] Compartment syndrome is defined as the elevation of fascial compartment pressure, which surpasses perfusion pressure leading to irreversible tissue ischemia and necrosis.other less common etiologies such as burns, emboli, and iatrogenic injuries can be equally troublesome and challenging to diagnose. The sequelae of a delayed diagnosis of compartment syndrome may be devastating. All care providers must understand the etiologies, high-risk situation, and the urgency of intervention. Questions/ Purposes: This study was conducted to perform a comprehensive review of compartment syndrome discussing etiologies, risk stratification, clinical progression, noninvasive and invasive monitoring, documentation, medical-legal implication, and our step-by-step approach to compartment syndrome prevention, detection, and early intervention. Methods: A literature search was performed using the PubMed Database and the following search terms: \"Compartment syndrome AND Extremity,\" \"Compartment syndrome AND Gluteal,\" and Compartment syndrome AND Paraspinal.\" A total of 2,068 articles were identified. Filters allowed for the exclusion of studies not printed in English (359

In situations of ACS, fractures account for 75% of cases.[3,4] It occurs primarily because of trauma, especially in the lower leg. However, it can also be triggered by static patient positioning during long surgical procedures such as recreational drugs injection, post-operative bleeding, tourniquet use, injury to blood vessels, rhabdomyolysis, and sports injuries.[5] Compartment syndrome rarely happens as a sequela of trans-radial percutaneous coronary intervention (PCI).

In this case report and literature review, an uncommon case of ACS after PCI was reported. The CARE guidelines and checklist were followed in this study.[6] Furthermore, our patients signed an informed consent form to the publication of their data and clinical photographs.

CASE

A 47 y.o. male arrived at the emergency room (ER) on April 28th, 2019 with the chief complaint of pain and swelling in his right forearm. The patient was referred to the orthopaedic division from another hospital after a transradial approach of primary PCI using the coronary stent because of diagnoses of inferior acute myocardial infarct on April 26th, 2019. Seven hours after the procedure, a swelling and a pale were noted in his right wrist, extending to the fingers and elbow. The patient also complains of paresthesia in the tip of his fingers, and there were no pulses on the radial artery. Blisters started to appear on his right wrist a day after PCI. There was no medical history of hypertension or diabetes. Upon arrival at the ER, he had a 160/80 mmHg systolic blood pressure with oxygen saturation at each right finger ranging from 93-95%. There was swelling and bullae on the right forearm (FIGURE 1). From the examination it was tender to palpation, and there was positive passive stretch pain with a limited range of motion (ROM). The patient had a relatively normal pre-PCI laboratory result aside from the elevation of white blood cells of 14.870/mL and SGOT/SGPT of 98/37 U/L.

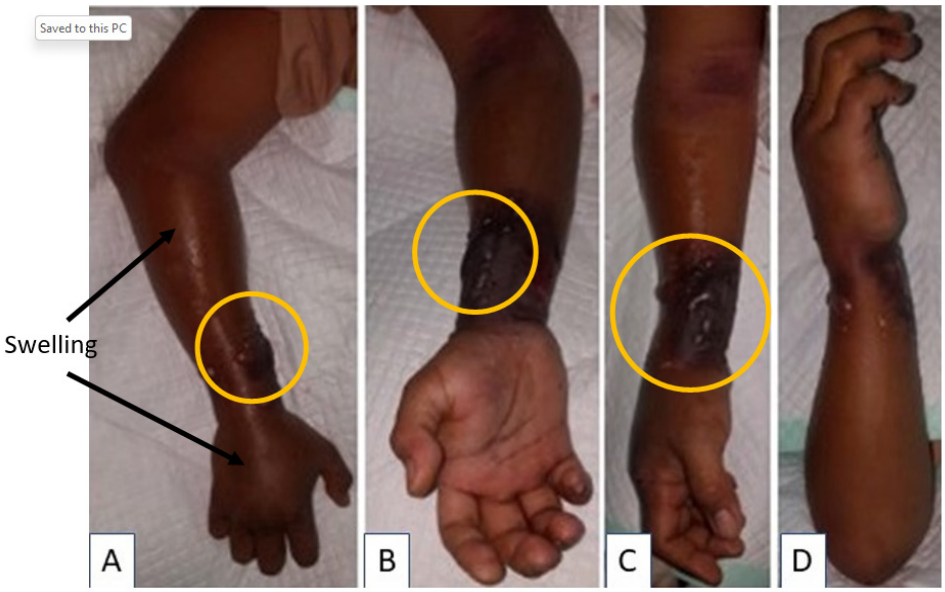

FIGURE 1. The clinical picture of compartment syndrome in right hands. There was swelling and bullae at the right forearm. The circle indicates the presence of a bulla, and black arrows show swelling that occurs in the patient's right hand

From the anamnesis and physical examination, the patient was diagnosed with ACS of the right forearm based on 4 out of 5 cardinal signs and symptoms of ACS that consists of pain, pallor, paresthesia, and pulselessness. Emergency fasciotomy was performed to release the compartment of the forearm with four lines of incisions; one at the volar side of the forearm (FIGURE 2A), one at the volar side of the thenar, and two at the dorsal of the hand (FIGURE 2B). Upon surgical examination, the muscle looks bulging and dark colored (FIGURE 2A). Antibiotic and antitetanic were given, and the patient was also consulted to the cardiology division for post PCI evaluation, especially regarding the reuse of anticoagulants after fasciotomy. Three days after the emergency of fasciotomy, the patient underwent a second-look procedure for redebridement. The patient's outcome is good, with an excellent post-operative follow-up 2 wk and 4 mo after initial admission with a Disability of Arm-Shoulder-Hand (DASH) score of 65 or satisfactory (FIGURE 3).

FIGURE 2. Emergency fasciotomy was performed to release compartment of the forearm. One at the volar side of the forearm and two at the dorsal of the hand.

FIGURE 3. Clinical picture outcome after emergency of fasciotomy and the follow up after four months.

DISCUSSION

Acute compartment syndrome arises when there is an elevation of intercompartmental pressure within a nonexpandable space. The forearm contains three compartments: volar, dorsal, and mobile wad. Pressure elevation in the forearm could result in increased interstitial pressure and progressive tissue oedema, which leads to irreversible muscle and nerve damage.[7]

Acute compartment syndrome is diagnosed clinically based on the prompt recognition of those symptoms, and in cases where the diagnosis is ambiguous, the measurement of compartment pressures may be used to confirm the diagnosis.[8]

The cardinal sign and symptoms of AS involving "5P": pain, paresthesia, pallor, pulselessness, and paralysis. The most frequent and identifying symptom is severe pain. This pain frequently outweighs the obvious damage and is resistant to analgesics. The absence of the other symptoms and signs does not rule out ACS because they are not always present. Paresthesia and paralysis are later symptoms, whereas edema is an early symptom (caused by nerve ischemia).[9]

The incidence of compartment syndrome of the forearm after trans-radial approach is very low with an incidence <0.01%.[10] Another study reported that incidence of ACS on forearm 2 of the 51,296 incidences after trans-radial procedures (0.004%).[71] In the PubMed review, only five cases have been reported. The unrecognized perforation at a distance from the puncture site, unsuccessful compression at the puncture site, or radial artery laceration become possible etiologies.[7]

Our study presents a rare case of ACS in the forearm after the transradial approach PCI. Tizon-Marcos and Barbeau reported two similar cases of acute compartment syndrome in the forearm after the trans-radial approach in 2008.[7] The first case reported differs from our case in the onset of symptoms and treatment, but the outcome of both cases is good. The second case also differs from our case in the onset of symptoms which is three days vs seven hours for our case, and the outcome is better in our case. It was probably because of the active bleeding in the second case, which triggered a rapid increase in intercompartmental pressure and thus made a worse prognosis.[7] Another case reported by Jue *et al.*,[11] presented an ACS of the hand after the transradial approach PCI. In this case, there is a slight difference in the decision of treatment. The case by Jue *et al.*,[11] was initially treated with a conservative measure using inflation of a blood pressure cuff to 15 mmHg below systolic blood pressure over the right brachial artery, the elevation of the arm and placement of a cold pack to relieve symptoms. In contrast, in our case, an emergency fasciotomy was performed promptly upon the patient arrival.[11]

Omori *et al.*,[12] reported 4 cases of compartment syndrome after PCI, but only 1 case used a transradial approach. This case had the quickest onset of all other cases reviewed in this study (30 min), and the compartment syndrome of the arm was induced by hematoma formation because of active bleeding from a branch of the radial artery. An urgent open decompression fasciotomy was also performed in this case, the same as ours, and it results in similarly good patient recovery and full movement of the upper extremity.[12]

The formation of an anticoagulant-related hematoma has also been cited as the cause of compartment syndrome. In addition, patients on anticoagulation are at higher risk of developing compartment syndrome given the propensity to develop hematomas.[1] Moreover, anticoagulation has been reported to be a risk factor for the development of ACS. Although

aspirin and clopidogrel are frequently given for the secondary prevention of atherosclerotic vascular events, a few studies have reported that antiplatelet treatment is associated with an increased incidence of compartment syndrome.[13] There is some literature explaining the effect of using anticoagulant post fasciotomy. They suggested discontinuing warfarin or heparin and switching to heparin with a low molecular weight (LMWH). Consequently, it is crucial that a cardiologist evaluate the patient during the initial 36 hr.[13,14] Furthermore, the cardiologist gives full consideration to the maintenance of post PCI management and the administration of anticoagulants after the emergency in the musculoskeletal area has been resolved.

Lower rates of bleeding and vascular sequelae make transradial approach PCI more popular than the transfemoral approach. Although transradial was superior to the transfemoral approach, it still has complications such as radial artery spasm, occlusion, hematoma, perforation, and pseudoaneurysm.[12] Acute compartment syndrome of the forearm is a rare complication of trans radial approach PCI. Because of its rarity, the diagnosis could be missed in the clinical setting. A high level of awareness must always be done for the sign and symptoms of ACS. A rapid and accurate diagnosis with prompt surgical treatment could decrease the morbidity caused by this limb-threatening condition. In this case, transradial approach of PCI could predispose a patient to a risk of acute compartment syndrome, but whether this risk correlated significantly or not still needs further research.

Almost all four other studies apart from our study reported a good outcome with an emergency fasciotomy. One case was initially treated conservatively but later proceed with fasciotomy and end in an excellent outcome. However, another case showed poor functional outcome because of active bleeding, which rapidly increased the intercompartmental pressure. In line with this study, the patient was diagnosed with ACS according to the AAOS guideline,[15] and as soon as the diagnosis was confirmed, a fasciotomy was performed as soon as possible. In result, the patient had a good outcome.

Despite the quick surgical intervention done to the patient in our case, the DASH score is still only satisfactory. Therefore, this complication must be quickly recognized to preserve the hand function as much as possible. Based on the case in this study and all other reports presenting similar cases, it shows that transradial approach PCI could predispose the patient to a risk of upper extremity ACS. However, it is still cannot be concluded whether it is significantly correlated or not. The study only presents one case and compares it with the other four cases. Our limitation in this study is the rarity of acute compartment syndrome after the upper extremity approach of PCI. A future study with more cases presented is needed.

CONCLUSION

A high level of awareness to make the diagnosis as quickly, accurately, with the best management as possible could prevent morbidity caused by late and unrecognized management compartment syndrome that could make a better clinical outcome.

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Protective role of *Nigella sativa* oil against cisplatin-induced ototoxicity: a literature review

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ABSTRACT

Cisplatin is widely used for the chemotherapy of head and neck cancer. However, it has a significant ototoxicity. *Nigella sativa* has been scientifically proven to have numerous benefits included to prevent adverse effect of a drug. This literature review aimed to evaluate the protective role of *N. sativa* oil against cisplatin-induced ototoxicity. Relevant publications were searched from PubMed and Google Scholar databases within the last 10 years. Ototoxicity due to cisplatin can occur through the intrinsic and extrinsic pathways. Cisplatin causes endoplasmic reticulum stress, DNA damage, increased reactive oxygen species (ROS) and inflammatory processes, resulting in increased apoptosis of cochlear outer hair cells. The active constituents of *N. sativa* including flavonoids, phenolics and thymoquinone can prevent the cisplatin-induced ototoxicity. Examination of endogenous antioxidants, antiapoptotic, and proinflammatory could be used as primary approach to evaluate the protective role of *N. sativa* against cisplatin-induced ototoxicity.

ABSTRAK

Cisplatin digunakan secara luas dalam kemoterapi kanker kepala dan leher. Namun demikian, cisplatin mempunyai efek samping ototoksiknya nyata. *Nigella sativa* terbukti secara ilmiah mempunyai berbagai manfaat termasuk mencegah terjadinya efek samping obat. Kajian pustaka ini bertujuan mengkaji peran efek pencegahan minyak *N. sativa* mencegah ototoksik akibat cisplatin. Publikasi yang relevan dicarik dari database PubMed dan Google Cendekia selama 10 tahun terakhir. Ototoksisitas akibat cisplatin dapat terjadi melalui jalur intrinsik dan ekstrinsik. Cisplatin menyebabkan stres retikulum endoplasma, kerusakan DNA, peningkatan *reactive oxygen species* (ROS) dan proses inflamasi, yang mengakibatkan peningkatan apoptosis sel rambut luar koklea. Senyawa aktif dalam *N. sativa* seperti flavonoid, senyawa fenol dan timoquinon dapat mencegah ototoksisitas akibat cisplatin. Pemeriksaan antioksidan endogen, antiapoptosis dan proinflamasi kemungkinan dapat digunakan menjadi pilihan utama untuk melihat peran protektif *N. sativa* terhadap ototoksisitas akibat cisplatin.

Keywords:
cisplatin;
Nigella sativa;
ototoxicity;
protective role;
side effect

INTRODUCTION

Cisplatin (cis-diamminedichloroplatinum) is a chemotherapy agent that is widely used and effective in the treatment of epithelial malignancies, especially head and neck cancer.[1,2] Despite promising result against cancer, clinical use is hampered by serious side effects such as gastrointestinal, peripheral neuropathic, nephropathic, bone marrow toxicity, and ototoxicity.[3,4] The effect of cisplatin ototoxicity is sensorineural hearing in the two ears, irreversible, starting at a frequency of 6000-8000 Hz, which will ultimately influence lower frequencies

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if the treatment continues, joined by tinnitus.[5,6]

Ototoxicity due to cisplatin is still very high, particularly in children and the elderly. Where the level of ototoxicity due to cisplatin occurs in 75-100% of elderly and 22-70% of children.[7,8] The ototoxic effect of cisplatin are greatest in kids because of the potential for delays in education and psychosocial development.[9,10] To date, the mechanism of cisplatin-induced ototoxicity has not been completely clarified. This mechanism may involve many factors and many substances, so the management of cisplatin-induced ototoxicity remains unsolved.[11] The ototoxicity of cisplatin may occur through an apoptotic cycle driven by increased ROS in the inner ear.[12,13] The body produces endogenous antioxidants to inhibit the increase of oxidative stress induced by cisplatin. However, the production is not enough against very high oxidative stress due to cisplatin.[14,15] Therefore, exogenous antioxidants are needed to prevent cisplatin-induced ototoxicity.

Nigella sativa possesses several biological activities including anti-inflammatory, antibacterial, and antioxidant properties.[16] It contains active ingredients such as flavonoids, phenolics, and thymoquinone.[17] Thymoquinone is an active compound isolated from *N. sativa* which is an antioxidant. It is useful to prevent the drug-induced ototoxicity. Thymoquinones are polar polyphenol compounds that will inhibit the formation of ROS by suppressing xanthine oxidase compounds, then catalyzing the oxidation of hypoxanthine and xanthine into uric acid, while reducing O_2 and H_2O_2.[18] In this literature review, the protective role of *N. sativa* oil against cisplatin ototoxicity was reviewed.

MATERIALS AND METHODS

Literature was searched from PubMed and Google Scholar databases. The keywords used were “hearing loss” OR “ototoxicity” AND “cisplatin” AND “Nigella sativa”. A manual search was also conducted to identify additional key references. Literature searching was limited to publications in English or Bahasa Indonesia with a time limit of the last 10 years.

RESULTS

Cisplatin is an anticancer used to treat various malignancies, such as testicular cancer, ovarian cancer, head and neck cancer, and some pediatric malignancies.[19,20] Compared to other platinum compounds, cisplatin has the highest ototoxicity. Approximately 50% of head and neck cancer patients experience ototoxicity after treated with cisplatin.[21,22]

Ototoxicity is hearing loss because the side effects of certain medication. This condition can result in sensorineural hearing loss, irreversible, bilateral, and typically starts at high frequency, as well as tinnitus.[5] There are several criteria used to determine if ototoxicity has occurred, including the guidelines set by the American Speech-Language Hearing Association/ASHA (TABLE 1).

Since there is no cure for hearing loss caused by ototoxic medications, prevention becomes even more crucial. Preventive measured may include considering the utilization of neurotropic, antiapoptotic, and antioxidant drugs. Given the ototoxicity of cisplatin, antioxidants are the appropriate group of substances to help prevent ototoxicity due to cisplatin (TABLE 2).[21,27]

TABLE 1. ASHA criteria for ototoxicity

Criteria	Description
ASHA	Significant ototoxic change when one of three criteria is obtained: 1. Decrease ≥ 20 dB at least one frequency, 2. Decrease ≥ 10 dB at least two adjacent frequencies, 3. Loss of response on three successive frequencies that are on previous checks are still responding.

TABLE 2. Overview of relevant literature on ototoxicity of cisplatin

Author (year)	Country	Methods	n	Age (yo)	Cumulative cisplatin dose (mg/m^2)	Findings
Hodge *et al.*[23]	USA	Case report	1	29 yo	132 mg/m^2	Cisplatin causes ototoxicity and damage to the cochlea, it is necessary to continue monitoring for hearing damage when cisplatin is given.
Camet *et al.*[24]	United States	Retrospective review	153	3-13 yo	300-480 mg/m^2	Alternative dosing with lower amounts per dose may reduce CDDP accumulation in the cochlea and may potentially lead to less ototoxicity while retaining its anti-neoplastic properties.
Patatt *et al.*[25]	Brazil	Systematic review	634	0-19 yo	45-950 mg/m^2	Auditory changes after the use of platinum-based antineoplastic drugs were found, however, there was an important heterogeneity regarding the frequency of ototoxicity and the cumulative dose of the drugs used.
Clemens *et al.*[26]	Netherlands	Cross-sectional	168	0-17 yo	180–900 mg/m^2	Ototoxicity after platinum treatment may be irreversible and that longitudinal clinical audiological monitoring and care is required in long-term survivors of childhood cancer on a large scale.

DISCUSSION

Molecular mechanism of actions of cisplatin

Cisplatin acts as an anticancer during the S phase (DNA replication). It belongs to the genotoxic chemotherapy category, which causes irregularities in DNA, affecting DNA replication and cancer cell division.[28] Cisplatin is a DNA alkylating agent that works by modifying DNA bases, influencing DNA replication and transcription processes, and causing alterations in DNA.[29] Cisplatin attaches alkyl groups to DNA bases, this alteration of DNA construction can result in DNA fragmentation, caused by the activity of enzymes that cleave or remove the alkylated DNA bases. The activity of these DNA repair enzyme is a natural occurrence in response to DNA damage.[30]

Alkylating agents can increase the occurrence of mispairing of DNA bases, causing DNA alterations. Cisplatin binds to double-stranded DNA bases by forming cross-links between G (guanine) bases, resulting in nucleotides changes. Covalent bonds between guanine bases, mediated by cisplatin, can hinder the DNA replication process, ultimately leading to cell death.[15,31]

Immunological reaction to cisplatin chemotherapy

The activity of chemotherapy relies not just upon its cytotoxic impact on cancer cells, but also on its ability to influence immune cells. Some chemotherapeutic medications can induce damage, leading to protein expression on the cell surface, cytokine release, or plasma membrane disruption and release of the intracellular substance.[32]

The innate immune system

The effects of chemotherapy on macrophages have also been documented. Macrophages can differentiate blood monocytes into two distinct subtypes, namely classically activated (M1) and alternatively activated (M2) which possess effector or suppressive capacities, respectively. Solid tumor infiltrating macrophages (tumor-associated macrophages/ TAMs) share numerous characteristics with M2 macrophages and exert pro-tumorigenic functions based on their direct or indirect immune-suppressive effects (via cytokine production) on NK cells and T cells. In cancer patients, the presence of TAMs promotes cancer progression. Several studies have investigated the impact of chemotherapy in subverting the pro-tumorigenic activity of macrophages.[33]

Chemotherapy affects bone marrow hematopoiesis, unexpectedly influencing myeloid cell activation. Platinum-based compounds, such as cisplatin, have also been reported to modulate the percentage of myeloid cells by increasing dendritic cells and eliminating myeloid-derived suppressor cells (MDSC), thus promoting immune effector responses. A direct immunostimulatory effect of cytotoxic drugs on dendritic cell activity has also been reported. Cisplatin chemotherapy can influence dendritic cell movement likewise through indirect mechanisms.[34]

The adaptive immune system

Intensive chemotherapy treatment in cancer patients leads to profound depletion of all lymphocyte populations, particularly B cells. Cisplatin and low-dose paclitaxel synergize to produce specific CD8 T cells that exhibit strong responses through the release of IL-2 and IFN-γ, resulting in high therapeutic efficacy. Cancer often results in a Th1/ Th2 immune imbalance, which some antineoplastic drugs can help to address. Paclitaxel enhances Th1 cell immunity by increasing the levels of IFN-γ-releasing CD8 T cells and IL-2-releasing CD4 T cells (FIGURE 1).[34,35]

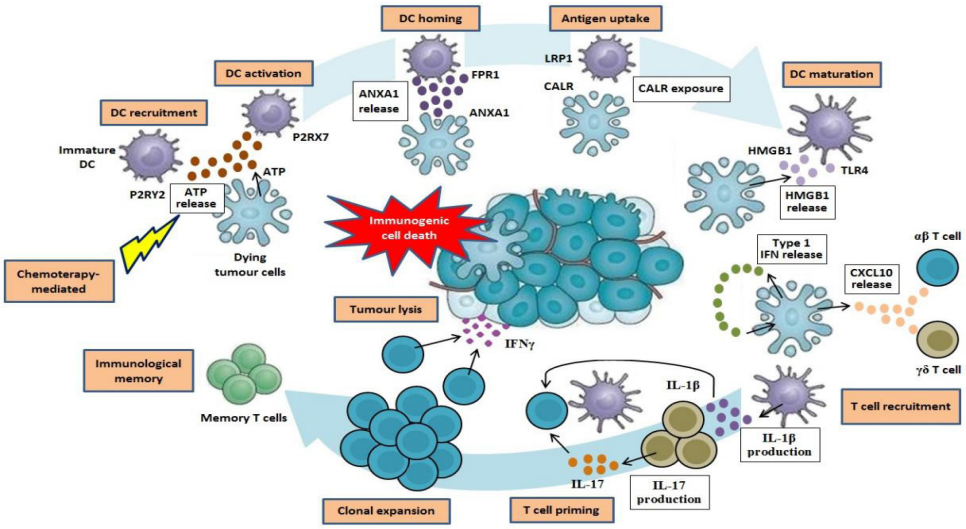

FIGURE 1. Mechanism of immunogenic cell death due to chemotherapy.[35]

Pathobiological mechanism of cisplatin ototoxicity

Cisplatin enters the outer hair cell (OHC) with the help of organic cation transporter-2 (OCT-2) as the vehicle medium. In OHC, cisplatin undergoes 2 pathways: the intrinsic pathway and the extrinsic pathway.[36,37] The intrinsic pathway consists of the mitochondrial pathway and the endoplasmic reticulum pathway. In the mitochondrial pathway, cisplatin causes an increase in oxidative NADPH and DNA damage, which leads to an increase in reactive oxygen species (ROS). DNA damage also results in an increase in p53, further raising ROS levels.[21] Increased ROS in mitochondria causes an increase in oxidative stress in the body, endogenous antioxidants (superoksida dismutase, glutation peroksidase, catalase, glutation reductase) that will protect/repress the increase in oxidative stress. However, due to the extremely high oxidative stress caused by cisplatin, the endogenous antioxidant activity is decreased. an increase in p53 also inhibits the anti-apoptotic Bcl-2 from blocking Bax, a pro-apoptotic protein.[38] Increased oxidative stress and Bax lead to the release of cytochrome-c which activates caspase-9 and caspase-3. In the endoplasmic reticulum pathway, cisplatin causes endoplasmic reticulum stress, resulting in calpain activation and an increase in caspase-12. Initiation of caspase-12 leads to the production of caspase-9 and caspase-3.[39] Caspase-3 induces apoptosis, ultimately causing ototoxicity.[31,40]

The extrinsic pathway, specifically through the death receptor pathway, is another process by which cisplatin induces ototoxicity. Cisplatin binds to death and inflammation receptors on the cell surface. Tumor necrosis factor-α (TNF-α) is an inflammatory mediator and cytokine that triggers apoptosis through death receptors. It associates with Fas protein (CD95). When Fas binds to its ligand, the membrane moves towards the ligand (FasL). At least three FasL molecules join to form the FADD (Fas-associated death domain), which binds to the inactive form of caspase-8, activating it and leading to the production of caspase-3. Caspase-3 induces apoptosis, which resulting in ototoxicity.[37,41] The pathological mechanism of ototoxicity of cisplatin is presented in FIGURE 2.[7,42]

Protective role of *N. sativa* against cisplatin ototoxicity

Nigella sativa is a natural plant that has been scientifically demonstrated to provide numerous benefits when consumed, either as oil or extract. *Nigella sativa* has several biological properties including an antioxidant, analgesic, antiinflammatory and antihistamine and its protective role against cisplatin ototoxicity may be associated with the antioxidant, anti-inflammatory, and immunomodulator activities (FIGURE 3).[43,44] The active compounds, minerals and nutrients contained in *N. sativa* include flavonoids, phenolics, thymoquinone, thymohydroquinone, dithymoquinone, p-cymene, 4-terpienol, carvacrol, t-anethol, sesquiterpene longifolene, α-piene, thymol, alkaloids, proteins, fat, sugars, Cu, P, Zn and Fe.[17,45]

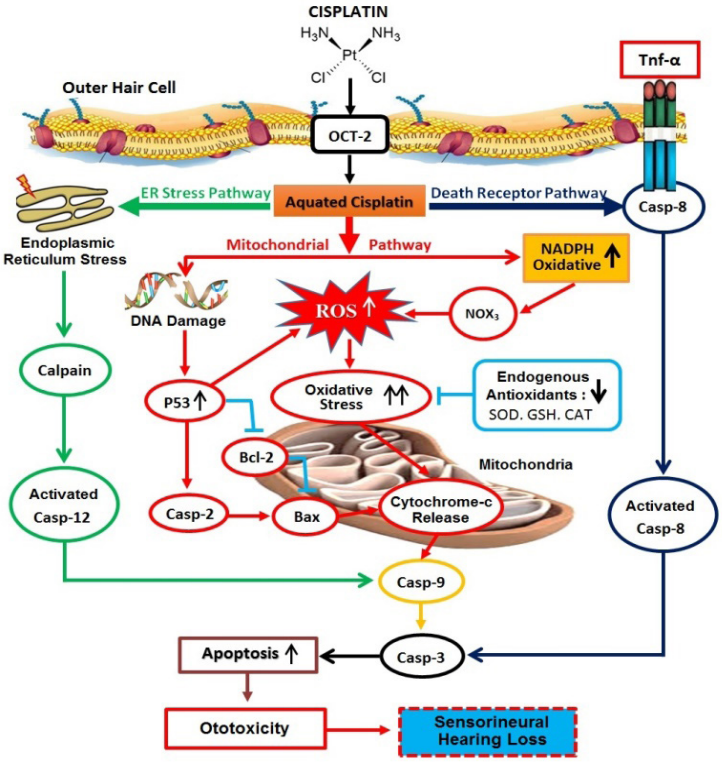

FIGURE 2. Pathobiological mechanism of ototoxicity cisplatin.[7,42]

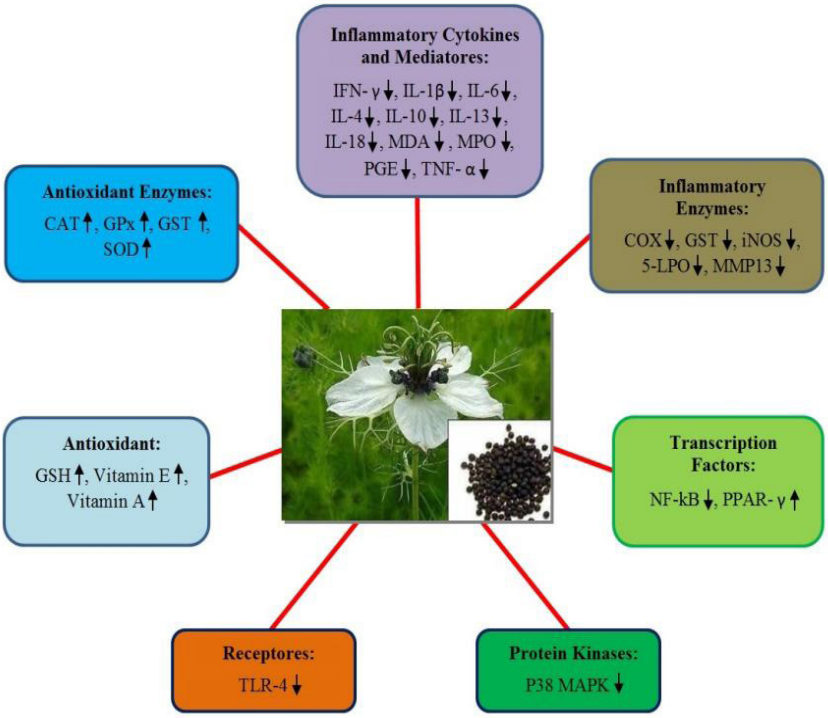

FIGURE 3. The role of *N. sativa* on molecular targets.[43]

Antioxidant

Nigella sativa extract belongs to the group of strong antioxidants, with IC_{50}= 80,433 μg/mL.[46] Flavonoids, phenolics, and thymoquinone are antioxidants that help forestall ototoxic effects. Thymoquinone compounds are polyphenolic compounds (hydroxyl gatherings) that are polar, allowing them to into polar solvents like ethanol, methanol, water, acetone, butanol, dimethyl formamide, and dimethyl sulfoxide. Polyphenols repress the formation of ROS by suppressing the enzyme xanthine oxidase, then catalyzes the oxidation of hypoxanthine and xanthine to uric corrosive while reducing O_2 and H_2O_2. Polyphenols act as antioxidants against oxidative stress, specifically as free radical scavengers, metal chelators in regulating cellular oxidation reactions, and by influencing enzymes involved in oxidative stress and increasing the production of of endogenous antioxidants. The antimicrobial activity of polyphenols works by damaging bacterial cell membranes, inhibiting fatty acid synthesis, and enzyme activity, thereby impeding bacterial growth and development.[18]

Superoxide dismutase (SOD) compounds are metalloenzymes containing copper, zinc or iron particles formed in the cytosol, and manganese-containing compounds formed in the mitochondrial matrix. It works by catalyzing the dismutation of superoxide into hydrogen peroxide and oxygen, with hydrogen peroxide being easy diffused across the plasma membrane. Superoxide dismutase is an endogenous antioxidant enzyme that has a very potent effect and functions as the body's first line of defense against free radicals. Superoxide dismutase activity can be utilized as a reference for measuring oxidative stress in the body.[47,48]

Antiinflammatory

Nigella sativa has anti-inflammatory potential. These effects include the reduction of NO, production of IL-1, cyclooxygenase-1 (COX-1) and COX-2, histone deacetylase (HDAC), as well as other pro-inflammatory mediators such as IL-1β, IL-6, TNF-α, IFN-γ, and PGE_2.[49,50] Thymoquinone, one of the active compounds from *N. sativa*, can attenuate the inflammatory reaction caused by mast cells by blocking the transcription and production of TNF-α through the modulation of the proinflammatory transcription factor NF-Kβ.[51,52]

Tumor necrosis factor-α compound is a proinflammatory mediator that can not only play a role in the mechanism of apoptosis induction but also accelerate cancer progression. Some studies have concluded that TNF-α produces ROS and RNS, leading to DNA damage and promoting proliferation, invasion, and increased chemotherapy resistance by activating MCF-7 cells.[36]

Immunomodulator

The components of *N. sativa* have also been proven to strengthen and stabilize the body's immune system by increasing the ratio between T-helper and T-suppressor cells by 55%, with an average natural killer cell activity achievement of 30%.[49] Thymoquinone, as an active compound of *N. sativa*, also plays a role in diminishing cytokines produced by Th2, in particular, IL-4, IL-5, and IL-13, as well as decreasing serum IgE. A reduction in serum IL-4 and IgE can help prevent the inflammatory response and mucosal edema.[52]

CONCLUSION

Cisplatin-induced ototoxicity is still exceptionally high, particularly in children and the elderly. Cisplatin

causes ototoxicity through two pathways namely the intrinsic and extrinsic pathway. Cisplatin leads to endoplasmic reticulum stress, DNA damage, increased ROS, and inflammatory processes, resulting in an increase in apoptosis of the outer hair cells of the cochlea. *Nigella sativa* oil has a protective effect against cisplatin-induced ototoxicity through its biological activities as an antioxidant, immunomodulator, and antiinflammatory agent.

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Health-related quality of life of the elderly after natural disasters: a scoping review

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ABSTRACT

Every nation on earth is experiencing an increase in the number and proportion of elderly people. This vulnerable population may experience a decline in health-related quality of life (HRQOL) following a natural disaster. This scoping review aimed to have a better understanding on the elderly's HRQOL following natural disasters, its influencing factors, and the state of the research on this topic. A literature search was conducted using four databases (PubMed/MEDLINE, Cochrane Library, Science Direct, and ProQuest) for the last 10 years (2013–2022). The summary of the selected relevant articles and analysis data were used to present the findings. There were seven articles included in our review. One article was about floods and the rest was about earthquake. Two out of the six earthquake articles involved tsunamis. All of the studies were conducted during the recovery phase and revealed that the elderly had poor HRQOL after natural disasters. Several aspects, including demographics, physical, psychological, social, and environmental factors, were identified as having impacts on the elderly's HRQOL following a disaster. The relocation had a significant negative impact on the mental health of the elderly, with a mean difference of -3.69 (-5.60, -1.77). In conclusion, the HRQOL of the elderly after a natural disaster is low and affected by several factors. To improve it, a stronger research agenda and disaster management programs that take these factors into account are required.

ABSTRAK

Setiap negara di dunia mengalami peningkatan jumlah dan proporsi lanjut usia. Populasi rentan ini dapat mengalami penurunan kualitas hidup terkait kesehatan setelah bencana alam. Tinjauan pelingkupan ini bertujuan untuk lebih memahami kualitas hidup terkait kesehatan lansia (HRQOL) setelah bencana alam, faktor-faktor yang mempengaruhinya, dan gambaran penelitian tentang topik tersebut saat ini. Penelusuran literatur dilakukan menggunakan empat database (PubMed/MEDLINE, Cochrane Library, Science Direct, dan ProQuest) selama 10 tahun terakhir (2013–2022). Penyajian temuan pada studi ini menggunakan ringkasan artikel terpilih dan analisis data yang relevan. Terdapat tujuh artikel yang disertakan dalam tinjauan ini, yaitu satu artikel tentang banjir dan enam tentang gempa bumi, dengan dua dari enam artikel gempa yang disebutkan melibatkan gempa bumi yang diikuti oleh tsunami. Semua studi dilakukan selama fase pemulihan bencana dan mengungkapkan bahwa lansia memiliki HRQOL yang buruk setelah bencana alam. Beberapa aspek, termasuk faktor demografi, fisik, psikologis, sosial, dan lingkungan memiliki dampak terhadap kualitas hidup terkait kesehatan lansia setelah bencana. Relokasi memiliki pengaruh negatif yang signifikan terhadap kesehatan mental lansia, dengan selisih rerata -3,69 (-5,60, -1,77). Dapat disimpulkan, kualitas hidup terkait kesehatan lansia pasca bencana alam tergolong rendah dan dipengaruhi oleh beberapa faktor. Untuk memperbaikinya, diperlukan penelitian-penelitian berikutnya dan program penanggulangan bencana yang mempertimbangkan faktor-faktor tersebut.

Keywords:
disaster;
elderly;
quality of life;
relocation;
review

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INTRODUCTION

The Centre for Research on the Epidemiology of Disasters (CRED) defines a disaster as a situation or event that overwhelms local capacity, necessitating a request at the national or international level for external assistance; an unforeseen and often sudden event that causes great damage, destruction, and human suffering.[1] The international classification of disasters distinguishes two generic categories for disasters (natural and technological). The natural disaster category is divided into six sub-groups: biological (e.g., epidemic), geophysical (e.g., earthquake), climatological (e.g., drought, wildfire), hydrological (e.g., flood, landslide); meteorological (e.g., storm), and extraterrestrial (e.g., impact, space weather).[1,2] In 2000—2019, CRED's Emergency Events Database (EM-DAT) recorded 7,348 natural disaster events which claimed approximately 1.23 million lives and affected a total of over 4 billion people, many on more than one occasion.[3] These numbers represent a sharp increase compared to 20 years ago.[3]

Meanwhile, every country in the world is experiencing growth in the number of the elderly people.[4] In between 2017 and 2050, the global population aged 60 or over is expected to increase from 962 million to nearly 2.1 billion.[4] As a result, to ensure that health and social systems are prepared for this demographic shift is one of the global key concerns,[5] including disaster response.[6] Considering the importance of this topic, some review articles have been published, such as one about the post-disaster elderly's health needs[7] and resilience.[8] To the authors' knowledge, no review articles have looked into the health-related quality of life (HRQOL) of the elderly following natural disasters.

Health-related quality of life is an individual or group's perceived physical and mental health over time.[9] The inquiries about HRQOL focus on physical, mental health, and function, have grown to be a crucial component of health surveillance and may provide a complete picture of the burden of diseases, injuries, and impairments.[9,10] The HRQOL is widely regarded as a reliable indicator of service needs and intervention outcomes.[9,10] In the case of a disaster, research on HRQOL may offer specific insights and practical knowledge that might improve healthcare services, psychological support programs, disaster preparedness, policies, and management.[11]

The elderly are more vulnerable to a decreasing HRQOL following a natural disaster, they are likely facing challenges as a result of physical impairments, decreased mobility, and impaired cognitive abilities.[12-14] Chronic diseases, psychological problems, specific nutritional demands, social isolation, and disruptions in health care access and services are other factors that increase the vulnerability of the elderly.[5,6] Minor aging-related deficits in the intrinsic capacity that were previously compensated may suddenly become a significant burden in the event of a disaster.[5]

This scoping study was conducted to find out more about the state of research on the health-related quality of life of the elderly following natural disasters as well as its affecting factors.

MATERIAL AND METHODS

A scoping review was conducted to quickly map the core concepts that underpin the research field as well as the main sources and types of evidence available. The advantages of this approach can be used to assess the extent, range, and nature of research activity, determine the value of undertaking a full systematic review, summarize and disseminate research findings, or

identifying research gaps in the existing literature.[15] The review objective served as the foundation for the PICO elements' formulation. Our research question was "in the elderly population (P), what is the effect of natural disaster (I) on their health-related quality of life (O)?". This PICO would be used for developing search strategies and selecting the studies. The synthesis of the findings was undertaken through an iterative process by three reviewers.

Data sources

On May 21, 2022, medical and health science electronic databases (PubMed/MEDLINE, Cochrane Library, Science Direct, and ProQuest) were searched for the period of 2013-2022 for the purposes of this review. Hand-searching of relevant journals from the reference lists of those obtained in the initial search was undertaken for additional references.

Search strategy

The following key concepts were used to develop a search strategy: natural disasters, elderly people, and health-related quality of life. Using the advanced search, data were limited to title, abstract, and keywords (TABLE 1).

TABLE 1. Search term used in PubMed/MEDLINE, Cochrane Library, Science Direct and ProQuest

Category	PubMed/MEDLINE, Cochrane Library, Science Direct and ProQuest strategy
Natural disasters	"disaster" OR "earthquake" OR "flood" OR "hurricane" OR "tsunami"
Elderly	"elderly" OR "older" OR "aged"
Health quality of life	"quality of life" OR "health-related quality of life"

Eligibility criteria

Articles linked with the HRQOL of the elderly people following natural disasters were included in this review. Articles must also be original research published in English to be considered for inclusion. In this review article, studies were limited to natural hazard-related disasters, excluding biological and extraterrestrial disasters, as in the report of CRED and United Nations Office for Disaster Risk Reduction's (UNDRR).[1,3] Articles that did not focus addressing the elderly population (aged ≥60 years) and HRQOL were excluded. The age of 60 is the threshold age for defining the elderly, as used by the United Nations (UN) and the World Health Organization (WHO) in their previous reports.[4,5]

RESULTS

Through the database search, 149 articles were identified. After removing duplicates, 125 articles were screened. Based on the abstract screening, 109 articles were excluded because they were irrelevant to the research question. Sixteen articles were selected for full article evaluation, with 9 of them failing to meet the eligibility criteria. Thus, the final sample for the review was seven articles (FIGURE 1).

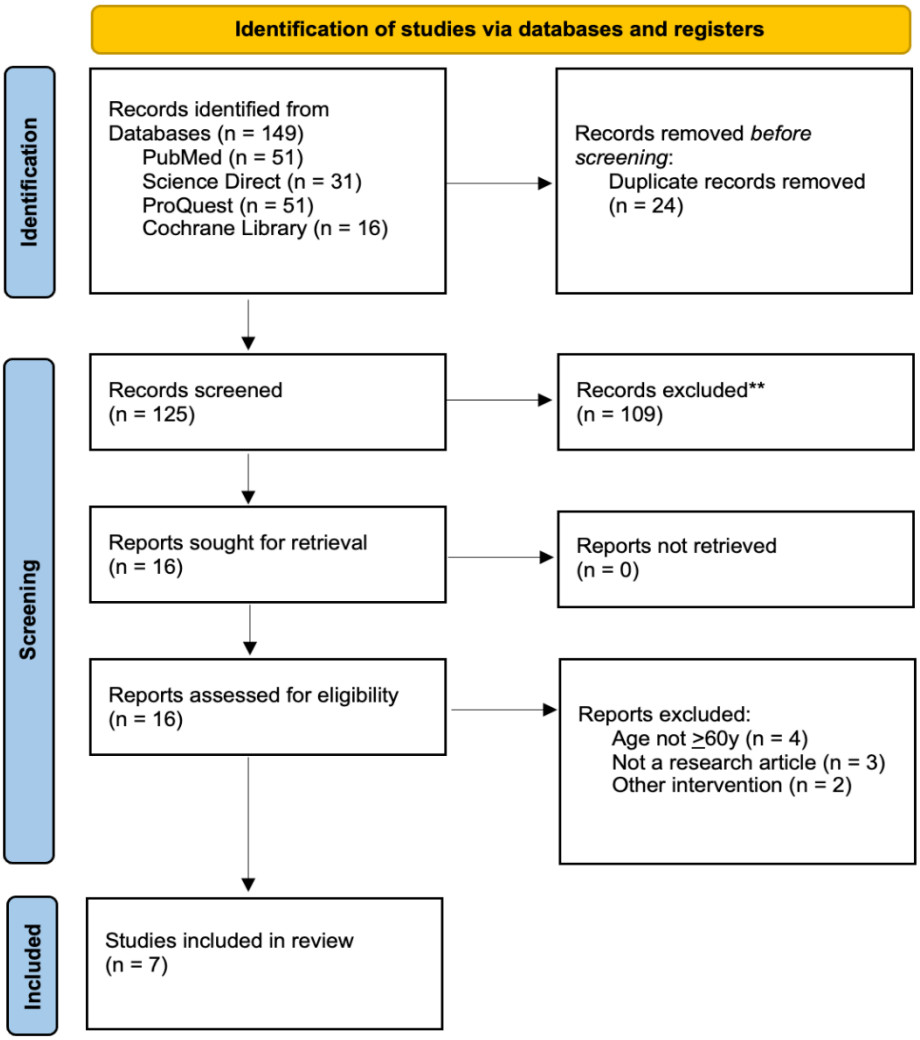

FIGURE 1. PRISMA flow diagram
**records excluded based on the abstract screening

To determine which variables to extract from the included research, a data graphing form was created.[16] This review is focusing on: 1) the study of descriptive characteristics, such as the authors' names, year of publication, article type, type of disaster, study location, and time of data collection (years after the disaster), 2) sample size and demographic characteristics (age and gender); 3) HRQOL instruments; 4) results summary; 5) factors influencing HRQOL; and 4) other outcomes that were examined in the study. The data were retrieved and entered into a spreadsheet to be compiled and synthesized.[17] (TABLE 2)

TABLE 2. Findings of the included studies

Study's descriptive characteristics	Number of subjects & demographic characteristics	HRQOL instrument	Results summary	Factors affecting HRQOL	Other outcome (s)
Moriyama *et al.*,[18]; earthquake followed by tsunami; Japan; 3 yr	128 subjects: 64 temporary housing group: 45 females; mean age female 76.4 ±7.3 yr; mean age male 78.1±6.9 yr 64 control group: 31 females; mean age female 74.6± 6.9 yr; mean age male 75.1±6.1 yr	SF-36v2	Prevalence of low PCS (%) Men: temporary housing group: 36.8 (19.2–59.0); control group: 30.3 (17.4–47.3) Women: temporary housing group: 20.0 (10.9–33.8); control group: 41.9 (26.4–59.2) Prevalence of low MCS (%) Men: temporary housing group: 36.8 (19.2–59.0); control group: 30.3 (17.4–47.3) Women: temporary housing group: 28.9 (17.7–43.4); control group: 38.7 (23.7–56.2)	Gender and Residency Women in the temporary housing group had lower prevalence of a low PCS ($p < 0.05$) and higher bodily pain score (72.0; 95% CI: 61.0–84.0) than women in the control group (62.0; 95%CI: 52.0-84.0) $p<0.01$.	• Physical activity • Timed Up and Go Test • Grasping power
Cao *et al.*,[19]; earthquakes; China; 5 yr	268 subjects (relocated: 112 nonrelocated: 1560; mean age: 72 yr; gender: 50.7% female	SF-36	PCS score: nonrelocated: 51.92± 8.53; relocated 47.80± 8.62; t or Z: 3.87 ($p <.001$) MCS score: nonrelocated 55.36±7.18; relocated 51.93± 8.96; t or Z: -3.33 ($p <.001$)	4 predictors for poor PCS (adjusted $R^2= 0.304$, $p < .001$): 1) older age ($\beta=-0.31$; $p< 0.001$); 2) relocation ($\beta=-0.25$; $p < 0.001$); 3) chronic illnesses ($\beta=-0.23$; $p= 0.003$) 4) educational level ($\beta=0.23$; $p=0.002$) 6 predictors for poor MCS (adjusted $R^2= .373$; $p < .001$): 1) older age ($\beta=-0.20$; $p=0.001$); 2) relocation ($\beta=-0.21$; $p< 0.001$); 3) the death of a spouse ($\beta = -0.20$; $p<0.001$); 4) educational level ($\beta=0.19$; $p=0.004$); 5) the loss of family members ($\beta=-0.16$; $p<0.005$); 6) chronic illnesses ($\beta=-0.14$; $p<0.002$)	Psychological distress
Yabuki *et al.*,[20]; earthquake followed by tsunami, Japan, 1.5 yr	71 subjects: assembled group (in temporary housing):60; individual group (in their residence):11 Mean age: 75.9 yr; gender: 77.5% female	SF-36	PCS score: overall: 40.6 ± 15.9*; individual group (nonrelocated): 28.5±17.9; assembled group (relocated): 42.9±14.5 MCS score: overall: 51.7 ± 10.4; individual group (nonrelocated): 57.1±10.1; assembled group (relocated): 50.7±10.3 Overall subscales: physical functioning: 36.9±17.6*; role physical: 41.8±15.6*; body pain: general health: 46.5±10.3*; vitality; social functioning: 45.9 ± 11.9*; role emotional: 44.1±14.8*; mental health: 46.3±10.8*; *($p < 0.01$) lower than national standard	Temporary housing. If compared to the assembled group who live in temporary housing, the individual group had significantly lower scores in physical functioning (18.8 ± 20.0**); role physical (29.7 ± 19.3***); Social functioning (40.0 ± 9.7***); physical component summary (28.5 ± 17.9***); **($p < 0.01$); ***($p < 0.05$)	• Chronic pain • Activity

TABLE 2. Findings of the included studies (cont.)

Study's descriptive characteristics	Number of subjects & demographic characteristics	HRQOL instrument	Results summary	Factors affecting HRQOL	Other outcome (s)
Wagle *et al*.,[21]; earthquakes; Nepal; 1.5 yr	362 subjects, Mean age 70 y Gender: 53% female	SF-12v2	Overall score: 46.55±14.74; 59% poor HRQOL (score <50) PCS: 45.92±17.80; 54.4% poor PCS (score <50) MCS: 47.18±15.25; 44.8% poor MCS (score <50) Subscales: physical functioning: 47.99±30.59; role physical: 49.10 ±23.11; bodily pain: 54.41±29.26; general health: 32.18±21.70; vitality: 43.02±24.14; social functioning: 48.96±23.32; role emotional: 47.51±24.84; mental health: 49.24±18.33.	Age (β = –0.116, p< 0.001); injury (β = –0.104, p= 0.014); distance to health care facility (β = –0.101, p= 0.026); access to safety information related to an earthquake (β=0.134, p=0.007); social support (β=0.120, p=0.019); chronic disease (β = –0.168, p< 0.001); PTSD (β = –0.225, p< 0.001); functional status (β = 0.295, p< 0.001); difficulty of accessibility to health care services (β = –0.177, p< 0.001).	• PTSD and depression • Functional ability • Coping strategies • Social support • Resilience
Wu *et al*.,[22]; flood; China; 1 yr	1183 subjects : mean age: 69 yr; gender: 41.2% female	SF-36	Overall score median: 64.5 (IQR: 53.3- 74.2); PCS score median: 64.2 (IQR: 51.2-75.3); MCS score median: 64.9 (IQR 53.1-77.1) Subscales scores: physical functioning: 62.5 (48.5-79.0); role physical: 62.5 (35.0-87.5); bodily pain: 78.8 (61.3-93.8); general health: (57.0 (46.5-67.5); vitality: 59.0 (47.0-73.0); social functioning: 76.3 (58.8-92.5); role emotional: 76.7 (43.3-100.0); mental health: 62.0 (48.0-78.0) All dimension scores among Bazhong elderly were significantly lower than the rural elderly	Physical domain: older age: OR 2.331 (1.535 ~ 3.539) p<0.001; marital status: married OR 0.403 (0.276 ~ 0.590) p<0.001; sleep patterns: moderate sleep pattern 0.456 (0.310 ~ 0.670) p<0.001; good 0.393 (0.256 ~ 0.603) p<0.001); no chronic diseases: OR 0.606 (0.416 ~ 0.884) p<0.001; no hospitalization in the past year: (0.597 (0.383 ~ 0.931) p<0.05); living with spouse: OR 0.475 (0.264 ~ 0.856) p<0.05. Mental domain: older age: OR 2.536 (1.610 ~ 3.994) p<0.001; female: OR 1.754(1.232 ~ 2.499) p<0.01; marital status: married OR 0.225 (0.152 ~ 0.333) p<0.001; sleep patterns: moderate OR 0.442 (0.291 ~ 0.672) p<0.001) and good OR 0.368 (0.231 ~ 0.586) p<0.001; no illness in the past two weeks: OR 0.392 (0.265 ~ 0.578) p<0.001; no chronic diseases: OR 0.512 (0.345 ~ 0.761) p<0.001; no hospitalization in the past year: OR 0.597 (0.383 ~ 0.931) p<0.05; living with spouse: OR 0.319 (0.169 ~ 0.603) p<0.001. Other: correlations between physical and mental health were significantly found in both genders (male: r = 0.612, p < 0.001; female: r = 0.600, p < 0.001, respectively)	Health status (two-week healthcare-seeking rate & chronic disease prevalence)

TABLE 2. Findings of the included studies (cont.)

Study's descriptive characteristics	Number of subjects & demographic characteristics	HRQOL instrument	Results summary	Factors affecting HRQOL	Other outcome (s)
Xie *et al.*,[23] earthquake; China; 1 yr	191 subjects Mean age: 74y Gender: 62% female	WHOQOL-BREF	Physical domain 56.2±20.3*; psychological domain 45.7±12.1**; social relationship domain 64.2±15.0; environment domain 52.9±14.0. *p<0.001 significantly lower compared to national standard **p<0.001 significantly lower compared to national standard	Physical domain: IADL (β =–0.479, p< 0.001); interest/ hobbies (β = 0.194, p= 0.002); family function (β = 0.134, p= 0.028) Psychological domain: depression (β= –0.255, p<0.001); family function (β= 0.220, p= 0.001); IADL (β = –2.835, p= 0.005) Social relationship domain: subjective support (β = 0.373, p< 0.001); family function (β = 0.225, p= 0.002). Environment domain: depression (β= –0.211, p= 0.002); subjective support (β= 0.162, p=0.017); ADL (β=–0.208, p= 0.003); chronic conditions (β=0.183; p= 0.007)	• Social support • Depression • Activity of Daily Living • Family function
Kim *et al.*,[11]; earthquake; Korea; 2 yr	312 subjects: Mean age: 78 yr Gender: 69.6% female	WHOQOL-BREF	The mean overall HRQOL score: 51.39±14.60; physical health 49.85±18.07; psychological health 50.16±18.75; social relations 61.93±19.20; environment: 49.53±16.37; general quality of life: 53.44±20.00; general health state: 43.42±26.91.	Depression: significant negative direct (β = – 2.21; p < 0.001), indirect (β =–0.23; p< 0.001), and total effects on HRQOL (β =– 2.44; p < 0.001). Community resilience: significant direct and total effects on HRQOL (β =6.05; p= 0.001) Social support: significant direct and total effects on HRQOL (β = 0.12, p = 0.008) Disaster preparedness: significant indirect and total effects on HRQOL (β = 0.40; p < 0.001 and β = 0.69, p = 0.031, respectively)	• Depression • PTSS • Community resilience • Social support • Disaster preparedness

Effects of relocation

It was found three studies that compared the effects of disaster-related relocation and temporary housing on elderly people's HRQOL.[18-20] It was unlikely to synthesize the data in the Moriyama *et al.*,[18] study because they were presented as medians and interquartile ranges. The data from the studies conducted by Cao *et al.*,[19] and Yabuki *et al.*,[20] was presented using a forest plot. The mental component summary score indicated a significantly poorer psychological condition of the elderly living in a relocation area with a mean difference of -3.69 (-5.60, -1.77) (FIGURE 2). Meanwhile, physical component summary scores revealed inconsistent findings. Cao *et al.*,[19] found that relocated elderly had lower scores than non-relocated elderly, while Yabuki *et al.*,[20] found the contrary to be the case (mean difference: 4.29 (-13.78, 22.36)) (FIGURE 3).

Study or Subgroup	Relocated			Non-relocated				Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
	Mean	SD	Total	Mean	SD	Total	Weight		
Cao *et al.*,[19]	51.93	8.96	112	55.36	7.18	156	91.3%	-3.43 [-5.44, -1.42]	
Yabuki *et al.*,[20]	50.7	10.3	60	57.1	10.1	11	8.7%	-6.40 [-12.92, 0.11]	
Total (95% CI)			**172**			**167**	**100%**	**-3.69 [-5.60, -1.77]**	

Heterogeneity: $Chi^2 = 0.73$, df = 1 (P = 0.39); $I^2 = 0\%$

Test for overall effect: Z = 3.77 (P = 0.0002)

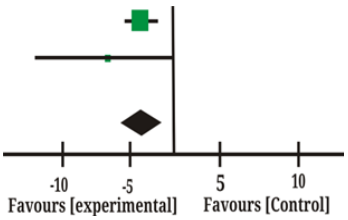

FIGURE 2. Effects of relocation on mental component summary score

Study or Subgroup	Relocated			Non-relocated				Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
	Mean	SD	Total	Mean	SD	Total	Weight		
Cao, *et al.*,[19]	47.8	8.62	112	51.9	8.53	156	54.6%	-4.12 [-6.20, -2.04]	
Yabuki, *et al.*,[20]	42.9	14.5	60	28.5	17.9	11	45.4%	14.40 [-3.20, 25.60]	
Total (95% CI)			**172**			**167**	**100.0%**	**4.29 [-13.78, 22.36]**	

Heterogeneity: $Tau^2 = 154.61$ $Chi^2 = 10.6$, df = 1 (P = 0.001); $I^2 = 90\%$

Test for overall effect: Z = 0.47 (P = 0.64)

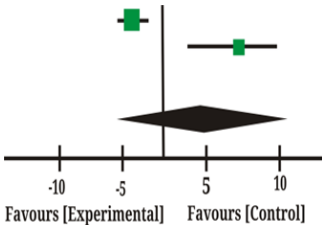

FIGURE 3. Effects of relocation on physical component summary score

DISCUSSION

This scoping review examined the elderly's HRQOL and its factors following a disaster. We also reviewed common research settings and HRQOL instruments that were used. Notably, Wu *et al.*[22] discovered that the elderly in Bazhong after the flood had considerably poorer HRQOL ratings across all dimensions than the overall elderly population as a reference in Sichuan province and other regions of China.[22] In general, the elderly had poorer HRQOL after disasters, which is consistent with the previous studies.[12-14]

Factors affecting HRQOL

Based on the gathered studies, a number of variables that have a substantial impact on elderly HRQOL after a disaster have been found. These variables are categorized into four categories: demographic, physical, psychological, and social-environmental factors.

Demographic factors

Demographic factors that affected elderly HRQOL after disasters were gender, age, marital status, and education level.[20-30]

Gender

Moriyama *et al.*,[18] and Wu *et al.*,[22] revealed that elderly women had lower levels of HRQOL. It could happen may be due to the fact that women frequently endure more mental stress and trauma than male participants following disasters.[24] In a healthy elderly population, women reported lower levels of HRQOL, and these differences were

statistically significant between the ages of 66 and 75.[25] Another study, however, found that when the other factors were taken into account, gender disparities in HRQOL disappeared.[26]

Age

Age may determine the physical and mental health of older victims' HRQOL.[18,21,22] In the general elderly population, there is a steady drop in HRQOL related to age, with a significantly more profound decline in the physical domain than in other domains.[27,28] Among the general elderly population, the lowest HRQOL was observed in the group of people over 80 years old.[25] We were unable to acquire comparable information addressing age group comparisons of elderly HRQOL in a post-disaster setting.

Marital status

According to Wu *et al.*,[22] married couples had considerably greater HRQOL than singles during the flood disaster in Sichuan, China, as a result of the couples' shared emotional and physical support.[22] This outcome was also discovered in a study of elderly Iranians.[27] However, a prior study indicated that among healthy senior populations, marital status had no discernible impact on HRQOL.[25] Wu *et al.*,[22] also revealed that older people who live with their spouses have higher HRQOL than those who live alone or with other family members or relatives after a disaster. Low HRQOL in the elderly who live alone may be impacted by other factors such as chronic illness, limited income, and rural residence.[29]

Education level

Higher education among older persons was associated with greater HRQOL in both the mental and physical domains, according Cao *et al.*,[19] This finding is consistent with earlier research, which revealed that education significantly improved overall HRQOL.[25,27,30] Education has an indirect impact on elderly people's quality of life by affecting their nutritional intake,[30] income,[29] and social support.[29] Lower levels of education were linked to worsening life quality, strained social connections, dissatisfaction, and sensory issues.[30]

Physical factors

Physical factors that had a negative impact on the elderly HRQOL after a disaster were chronic illness,[18,22,23] hospitalization within the previous year,[21] illness within the last two weeks,[21] and injury,[22] Multimorbidity in elderly may have an impact on the reduced ability to carry out daily tasks, increased social isolation, and reduced well-being.[31,32] Chronic medical issues in older individuals necessitate ongoing support from the healthcare system.[33] Since this system is disturbed both during and after disasters, the elderly are in greater danger.[33,34] The elderly are more at risk since this system is disrupted both during and after disasters.[33,34] Elderly people who have certain pre-existing medical conditions, such as dementia, electrolyte imbalances, diabetes, visual or hearing impairment, mobility issues, dialysis patients, and those who require prescription medications or depend on others for daily activities, are particularly vulnerable.[33,35]

Psychological factors

Psychological problems such as depression and post-traumatic stress disorder (PTSD) had a detrimental impact on HRQOL levels in the elderly victim, according to Kim *et al.*,[11] Wagle *et al.*,[21] and Xie *et al.*[23] Previous studies discovered that the elderly who had survived a disaster had higher rates of

depression,[36,37] PTSD,[36,37] and adjustment disorders.[36] Depression or other mental illnesses may affect HRQOL by impairing one's willingness to seek treatment, changing how one response to difficult external circumstances, and impairing one's capacity for decision-making.[33] Furthermore, it has been noted that a large number of disaster victims do not ask for help, and that only a small proportion of people with serious mental problems receive treatment.[38]

Social-environmental factors

Social-environmental factors which were associated with HRQOL include relocation status,[18-20] social support,[11,21,23] community resilience,[11] disaster preparedness,[11] and accessibility to health care services.[21] According to research by Cao *et al*.,[19] and Yabuki *et al*.,[20] elderly people who had relocated had significantly lower mental component scores, with a mean difference of -3.69 (-5.60, -1.77). These results were in line with Uscher-Pines' systematic review.[39] The physical component summary scores, however, showed contradictory results. Relocated elderly had lower physical component scores than non-relocated elderly, according to Cao *et al*.,[19] while the opposite was discovered by Moriyama *et al*.,[18] and Yabuki *et al*.[20] Although there are few studies on the physical health effects of relocation, researchers have shown that relocated elderly had more severe physical health effects over time.[39,40] However, Moriyama *et al*.,[18] and Yabuki *et al*.[20] found that the relocated group had better physical component scores, particularly in women. They proposed that the elderly support groups and social gatherings in the relocation area may account for their maintenance of HRQOL.[18] Additionally, the elderly who have not relocated may have lower physical component scores due to their decreased level of activity.[20]

In the event of a disaster, social isolation and decreased social support may increase the elderly vulnerability and decrease their HRQOL.[23] A previous study showed that increased pre-disaster social support has been correlated with less psychological distress related to hurricanes.[41] It is expected that social support and community resilience will improve elderly victims' HRQOL by easing personal psychological and financial burdens.[21,42,43]

HRQOL was also favorably correlated with disaster preparedness, which includes disaster risk reduction efforts and health-protective behaviours.[44] The elements of the disaster management strategy should take older persons' particular needs in disaster situations into account.[6,34] On the other hand, the elderly could contribute as population-specific experts.[34]

Difficulty accessing health care services was significantly associated with HRQOL among the elderly.[21] According to a prior study, those who resided further from medical facilities reported lower health outcomes than those who did.[45]

Research settings

Studies on HRQOL in the older population after disaster are frequently conducted in the aftermath of earthquakes. There were seven articles included in our review: one about floods and six about earthquakes[11,18-21,23] with two out of the six earthquake articles cited involving earthquakes followed by tsunamis.[19,20] Other natural disaster settings that researchers sought for analyzing HRQOL in the general population, but not notably the elderly, were hurricane,[46,47] tsunami,[48] and wildfire.[49] In general, earthquakes continued to be the subject of most investigation. The discovery that earthquakes were discussed in 6 out of 7 articles demonstrates that they are the most well-studied disaster setting and highlights a need for greater research

on various types of disasters with an emphasis on the elderly population.

The recovery phase is when all investigations were completed. All of the selected studies were conducted between one and five years after the disaster. It was not surprising, however, because the recovery phase entails damage assessment, rehabilitation, and reconstruction in order to improve living conditions in the impacted areas.[50] Conducting randomized or prospective cohort studies that capture the before, during, and after phases of a disaster is frequently problematic due to its unpredictable nature.[51]

HRQOL measures

In the included studies, the SF-36, SF-12, and WHOQOL-BREF were the instruments utilized to assess HRQOL. The SF-36 has a total of 36 items over eight different quality-of-life domains: physical functioning (10 items); role limitations due to physical illness (4 items); bodily pain (2 items); general health perceptions (5 items); vitality (4 items); social functioning (2 items); role limitations due to emotional problems (3 items); and mental health (5 items).[52] Physical functioning, role limitations due to physical illness, bodily pain, and general health perceptions reflect the physical component summary (PCS) score.[52] Vitality, social functioning, role limitations due to emotional problems, and mental health reflect the mental component summary (MCS) score.[52] Each SF-36 domain's score was linearly translated into a standard score between 0 and 100, with a higher score indicating greater self-perceived health.[52] Due to the high homogeneity of SF-36 components and reliability, the SF-36 questionnaire was the most widely used questionnaire in groups of the elderly.[25] The SF-36 is available in more than 50 different languages and has been extensively tested for cultural equivalence.[53-55]

The SF-12 questionnaire consists of 12 questions that evaluate one's general quality of life as well as physical and mental health.[56] Since it is a condensed version of the SF-36, the PCS and MCS are scored similarly.[56] The scores range from 0 to 100, with 0 denoting the lowest level of health determined by the scales and 100 denoting the highest level of health.[56] This instrument generally showed acceptable validity and reliability to measure the quality of life among older people.[56]

WHOQOL-BREF, a condensed version of the 100-item World Health Organization Quality of Life Scale, consists of 26 items.[57] The WHOQOL-BREF comprises two individual items about subjective quality of life and health conditions in addition to domains measuring physical health, psychological health, social relationships, and environmental factors.[57] A Likert scale with five points was used to score the responses.[57] Higher scores correlate with higher quality of life.[57] WHOQOL-BREF may be more useful to evaluate changes in the elderly's quality of life than SF-36 since it prioritizes responses to aging and avoids emphasizing impairment.[58] However, the WHOQOL-BREF examines overall quality of life, while the SF-36 assesses specifically HRQOL.[59] Before deciding which instrument to use, clinicians and researchers should define their study questions carefully.[59] We proposed using a standardized instrument with a uniform data presentation to have a better indicator to compare HRQOL scores.

CONCLUSION

HRQOL of the elderly after natural disaster is low and affected by several factors such as demographic (gender, age, marital status, and education level), physic (chronic illness, hospitalization, illness within the last two weeks, and injury), psychology (depression

and PTSD), and social environment (relocation status, community resilience, disaster preparedness, and accessibility to health care services). Post-disaster relocation had a significant negative impact on the mental health of the elderly. A stronger research agenda and disaster management programs that take these factors into account are needed to improve elderly HRQOL following disasters.

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