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The Role of Angiotensinogen rs699 in Diabetic Nephropathy Among Type 2 Diabetes Mellitus Patients with Uncontrolled Postprandial Glucose Levels

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A B S T R A C T

Diabetic Nephropathy (DN) is the most common complication of Type 2 Diabetes Mellitus (T2DM), leading to the highest mortality rate of DM complications. However, its etiology is still questionable. Hyperglycemia, hypertension, and particular genetic susceptibility are associated with DN. Not all patients with uncontrolled hyperglycemia suffer DN. Thus, genetic susceptibility may be a risk factor for DN. The genetic variant of angiotensinogen rs699 is known to be associated with the risk of DN with inconsistent results between ethnicities. This study aims to reveal the correlation between the AGT rs699 with the incidence of diabetic nephropathy among type-2 diabetes mellitus patients with uncontrolled postprandial glucose levels in the Jambi Malay ethnicity. This study was observational analytic research with a cross-sectional design. It used 48 DNA samples from type-2 diabetes mellitus patients with uncontrolled postprandial glucose levels. The authors took 24 DNA samples from patients with DN and 24 without DN (as a control group). The genotyping method used ARMS-PCR specific for AGT rs699. Subjects with the CT genotype had a lower risk for diabetic nephropathy than the CC genotype, but it was not statistically significant ($p=0.247$; $OR=0.508$; $95\%CI=0.160-1.607$). In addition, subjects with the T allele ($p=0.331$; $OR=0.621$; $95\%CI=0.237-1.630$) had a lower risk for diabetic nephropathy than the C allele, but it was not statistically significant. In conclusion, Angiotensinogen rs699 is not a risk factor for diabetic nephropathy among type-2 diabetes mellitus patients with uncontrolled postprandial glucose levels in the Jambi Malay ethnicity.

INTRODUCTION

According to the International Diabetes Federation (IDF), the prevalence of Type 2 Diabetes Mellitus (T2DM) has increased from the previous year, and the estimation will continue to grow (International Diabetes Federation, 2019). This phenomenon also occurs in Indonesia, especially Jambi Province (Kementerian Kesehatan Republik Indonesia, 2018). Increased incidence of T2DM can lead to complications, one of which is Diabetic Nephropathy (DN). In Jambi Province, DN is the most common complication in individuals with diabetes. The prevalence is approximately 35-45% of individuals with T2DM. In addition, DN has the highest mortality rate compared to other diabetic complications (Bistara and Rusdianingseh, 2019).

The causes of diabetic nephropathy in T2DM are multifactorial and occur due to interaction between genetic and environmental factors. Hyperglycemia, hypertension and genetics are risk factors for DN (Xue *et al.*, 2017). However, previous studies found that uncontrolled blood glucose levels or hyperglycemia were not significantly correlated with an increased risk of DN in individuals with T2DM

(Elfiani *et al.*, 2020). It certainly indicates the possibility of other risk factors more involved in developing DN, one of which is genetic factors.

Genetic variations in the renin-angiotensin-aldosterone System (RAAS) play a role in developing diabetic nephropathy in T2DM patients. Angiotensinogen (AGT) rs699 is one of them. T allele of this genetic variation is associated with an increased risk of DN through increased plasma angiotensinogen levels, blood pressure, and insulin resistance in various tissues (Rahimi, 2016; Ramalingam *et al.*, 2017; Yako *et al.*, 2018). AGT rs699 gene variant is located on the long arm of chromosome 1 (1q41-q45) in the form of a T to C substitution in exon 2, resulting in a functional exchange of methionine (M) to threonine (T) at codon 268 (M268T). It is related to the variability of plasma and tissue levels of the encoded protein (Yako *et al.*, 2018).

Studies reported that the AGT rs699 was significantly associated with DN in T2DM patients in Turkish, Tunisian, and Indian populations (Rahimi, 2016; El-garawani *et al.*, 2021). However, the AGT rs699 did not correlate with diabetic nephropathy among people in Caucasians, Mexican Americans, subgroups of Asians, and Indians (Ahluwalia *et al.*, 2009; Rahimi, 2016; Tziastoudi, Stefanidis and Zintzaras, 2020). Controversial results regarding the association between genetic variation of AGT rs699 and diabetic nephropathy among the population of Jambi Malay ethnic are undoubtedly intriguing to investigate. This study aims to reveal the correlation between the AGT rs699 with the incidence of diabetic nephropathy among type-2 diabetes mellitus patients with uncontrolled postprandial glucose levels in the Jambi Malay ethnicity.

METHOD

Study design

This study was observational analytic research with a cross-sectional design. It used 48 DNA samples from type-2 diabetes mellitus patients with uncontrolled postprandial glucose levels. The authors took 24 DNA samples from patients with DN and 24 without DN (as a control group). The inclusion criteria were DNA samples that fulfilled standard quality and quantity based on a nanodrop index of at least ~ 1.8 for genotyping. The exclusion criteria were DNA samples that were not successfully genotyping using the ARMS-PCR method specific for AGT rs699 and DNA samples that did not have complete demographic data. All subjects signed informed consent forms after receiving a detailed explanation of the study objectives and design. The Faculty of Medicine and Health Sciences, Universitas Jambi Ethics Commission approved this study with certificate number: 2136/UN21.8/PT.01.04/2021.

Blood pressure and laboratory measurements

We measured respondents' blood pressure twice in a seated position after 5 minutes of rest using a calibrated sphygmomanometer. Then, we recorded the mean value of those measurements. In addition, we drew 5 milliliters of blood from respondents' antecubital veins after eight to ten hours of fasting to evaluate the serum creatinine and DNA extracted. The Prodia laboratory measured serum creatinine levels using enzymatic colorimetric Jaffe methods. Serum creatinine levels measure the estimated glomerular filtration rate (eGFR) based on Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

In addition, we took 3 milliliters of blood from a peripheral vein after respondents ate to measure 2-hour postprandial glucose levels. *Perkumpulan Endrokrinologi Indonesia* (PERKENI) guideline 2015 categorizes 2-hour postprandial glucose levels ≥ 180 mg/dL as uncontrolled postprandial glucose levels. Furthermore, we calculated the albumin creatinine ratio (ACR) based on the ratio of quantitative creatinine to albumin from a random spot urine sample. The DN is diagnosed when $ACR \geq 30$ mg/g. Moreover, enzymatic colorimetric methods measure quantitative urine creatinine, and immunoturbidimetric evaluate quantitative urine albumin.

Genotyping

The Deoxyribonucleic Acid (DNA) was extracted from peripheral blood leucocytes using a commercial DNA extraction kit (Macrogen^R). Nanodrop was used to measure the quality and quantity of DNA yielded in the extraction process. We genotyped using the Amplification Refractory Mutation System-Polymerase Chain Reaction (ARMS-PCR) method for angiotensinogen rs699. The primary design in this paper was adapted from El Garawani et al (El-garawani *et al.*, 2021). Table 1 shows primary sequences and their product sizes.

Table 1. PCR primers and the product sizes

Primers	Product sizes or Fragment
Outer Forward	5'TGCGCACAAGGTCCTGTCTG3'
Inner Forward / T allele	5'ATGGAAGACTGGCTGCTCCCTTAT3'
Outer Reverse	5'GTCACCAGGTATGTCCGCAGG3'
Inner Reverse / C allele	5'GCTGTCCCACTGGCTCACG3'

The PCR mixture was 10 μ L of PCR master mix (GoTaq Green), 9 μ L of Nuclease Free Water (NFW), 1 μ L for each specific primer AGT rs699 and DNA template 2 μ L. The thermocycler condition was 95°C for 7 minutes as initial denaturation and 1 minute as denaturation. Then, 60 °C for 1 minute as annealing. Next, 72 °C for 1 minute as an extension and 7 minutes as a final extension. The PCR product was then visualized with 1.5% agarose gel for 35 minutes with 100 mV. The PCR product results obtained 197 bp DNA fragments for the T allele and 295 bp DNA fragments for the C allele.

Data Analysis

Data analysis used the Shapiro-Wilk test to test the normality of data with a continuous scale. Normally distributed data were analyzed using an independent t-test and presented as mean (\pm SD). Data not normally distributed were analyzed using Mann-Whitney and presented as median (min-max). The Chi-square test analyzed the correlation between angiotensinogen rs699 and the incidence of diabetic nephropathy. Then, the authors calculated the Hardy Weinberg equilibrium. P-value $>$ 0.05 indicated that allele frequency was concordant with the Hardy Weinberg equation.

RESULT

Baseline Subject Characteristics

This study used a matching method in age and gender between case and control groups. In addition, subject grouping was based on urine ACR value, with urine ACR value \geq 30 mg/gr Cr for the case group. Table 2 indicates the baseline subject characteristics in this paper.

Table 2. Baseline subject characteristics

Characteristics	DN (n=24)	Non DN (n=24)	<i>p</i>
Age (Years)	51 (29-60)	50.5 (22-60)	0.869 ^b
Gender			
Male	10 (41.7%)	10 (41.7%)	1.000
Female	14 (58.3%)	14 (58.3%)	
Systolic Blood Pressure (mmHg)	140.83 \pm 17.17	121.38 \pm 11.04	$<$ 0.001 ^a
Diastolic Blood Pressure (mmHg)	80 (60-100)	80 (70-90)	0.361 ^b
Postprandial glucose (mg/dL)	249 (180-358)	222 (180-456)	0.375 ^b
Urine ACR (mg/g Cr)	377.30 (32.16-5237.69)	12.03 (3.84-26.26)	$<$ 0.001 ^b
eGFR (mL/minute/1.73 m ²)	66.73 \pm 31.58	94.03 \pm 22.83	0.001 ^a

Statistically significant, $p <$ 0.05, ^aThe Independent t-test, ^bThe Mann-Whitney test

Due to the matching method, there were no significant differences between the mean value of age and gender between the case and control groups. The mean value of systolic blood pressure in the case group was statistically higher than in the control group. However, both groups had no statistically significant difference in the mean of diastolic blood pressure and postprandial glucose. The urine ACR mean in the case group was significantly higher than the control group. Still, the eGFR mean was statistically more elevated in the case group.

Genotyping Results of Angiotensinogen rs699

Figure 1 shows the polymerase chain reaction (PCR) product visualization. The T allele was a 197 bp DNA fragment, and the C allele was a 295bp DNA fragment, with the main band being a 448 bp DNA fragment.

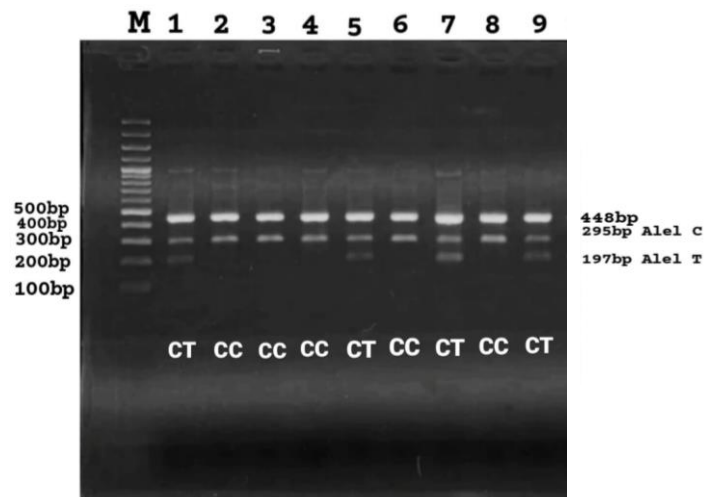


Figure 1. ARMS-PCR results of Angiotensinogen rs699. The CC genotype was marked by the appearance of the C allele and main band in 295 bp and 448 bp DNA fragments. The CT genotype was characterized by the C and T alleles in 295 bp and 197 bp fragments and the main band in the form of 448 bp DNA fragments. M as a marker.

Table 3. Genotype distribution and Hardy Weinberg equation

Genotype	Observed value	Expected value	X ² (Df)	<i>p</i>
TT	0	3		
CT	22	17	4.2425	0.00001
CC	26	29		

MAF=0.34; DF=1; statistically significant, $p>0.05$

The genotype distribution found that the CC genotype was reported as wild type in the respondents, and the T allele was the minor allele. The MAF value of this SNP was around 0.34 in the SNPedia database. Our studies' proportion of genotype frequency deviated from the Hardy Weinberg equation (Table 3).

The Correlation between Angiotensinogen rs699 and the Incidence of Diabetic Nephropathy

The bivariate analysis revealed that Angiotensinogen rs699 showed a higher frequency distribution in the CC genotype than the CT genotype in the diabetic nephropathy group. Thus, subjects with CT genotype had a lower risk for DN than CC genotype. The CT genotype acted as a protective factor against the incidence of diabetic nephropathy, but it was not statistically significant (OR=0.508; 95% CI= 0.160 – 1.607; $p= 0.247$) (Table 4).

Table 4. The bivariate analysis between Angiotensinogen rs699 and the incidence of diabetic nephropathy

Genotype	DN (n=24)	Non DN (n=24)	P value ^a	OR (95% CI)
Additive model				
CT	9 (40.9%)	13 (59.1%)	0.247	0.508 (0.160-1.607)
CC	15 (57.7%)	11 (42.3%)	ref	
Allele				
T	9 (40.9%)	13 (59.1%)	0.331	0.621 (0.237-1.630)
C	39 (52.7%)	35 (47.3%)	ref	

^aChi-Square test; DN refers to diabetic nephropathy; ref refers to reference genotype/allele.

In addition, the frequency distribution of the C allele was higher than the T allele in the diabetic nephropathy group. Thus, subjects with the T allele ($p=0.331$; $OR=0.621$; $95\%CI=0.237-1.630$) had a lower risk for diabetic nephropathy than the C allele. The T allele was a protective factor against diabetic nephropathy but was not statistically significant ($OR=0.621$; $95\% CI=0.237 - 1.630$; $p= 0.331$) (Table 4).

DISCUSSION

Baseline Subject Characteristics

This paper showed no significant differences between the mean value of age and gender between the case and control groups (Table 2). It may be due to the matching method between both groups (DN and non-DN) to minimize confounding factors contributing to diabetic nephropathy. Based on Basic Health Research in 2013, previous epidemiology reported that older age and male T2DM patients contributed increased risk of DN (Mihardja *et al.*, 2018).

In addition, our findings found that the DN group (case group) had statistically higher mean systolic blood pressure than the non-DN (control group) (Table 2). Meanwhile, the diastolic blood pressure was not statistically different between the two groups. A prior study in Slovenia also reported similar results (Makuc *et al.*, 2017). Increased blood pressure in diabetic nephropathy patients is associated with increased activity in the sympathetic nervous system due to insulin resistance in patients with diabetes mellitus. High renal sympathetic nerve tone stimulates renin release and increases sodium reabsorption in renal tubules. In addition, increased renin release will increase cardiac output and peripheral vascular resistance, leading to increased blood pressure (Maqbool, Cooper and Jandeleit-Dahm, 2018; Ohishi, 2018).

Furthermore, this research reported that postprandial glucose levels in the DN group did not have a statistically significant difference compared to the non-DN group (Table 2). However, theory explains a contradiction in the association between blood glucose and DN. Hyperglycemia in T2DM patients leads to insulin resistance and impaired β cell function. The failure of the feedback function between insulin action and insulin secretion causes abnormally increased blood glucose levels. Dysfunction of β cells and reduced insulin secretion leads to impaired blood sugar regulation. As a result, insulin does not work optimally, leading to the pancreas compensates by producing more insulin. However, when β cell is no longer adequate to produce insulin as compensation for increased insulin resistance, blood glucose levels will increase and lead to chronic hyperglycemia. Hyperglycemia increases extracellular matrix (ECM) expression, leading to renal function deterioration (Decroli, 2019; Galicia-Garcia *et al.*, 2020).

ACR and eGFR are clinical assessments of renal function in T2DM. The ACR is a parameter for diagnosing DN. Meanwhile, the eGFR monitors renal function relating to end-stage renal diseases

complication (ESRD). This investigation revealed that the mean urine ACR value in the diabetic nephropathy group was statistically higher than the control group (Table 2). We used urine ACR levels ≥ 30 mg/gr Cr as the parameter for diabetic nephropathy diagnosis. Urinary ACR value can identify albuminuria by calculating the ratio of urine albumin to urine creatinine. The urine ACR in this study was calculated using random spot urine sampling. It is because a previous study reported that this sampling was more representative and practical in assessing albuminuria associated with complications of diabetes mellitus than a 24-hour urine sample (Elfiani *et al.*, 2020). Albuminuria in patients with diabetes mellitus provides an early indication of kidney damage (Seidu, Barrat and Khunti, 2020). Increased urinary albumin excretion in diabetic nephropathy occurs due to intraglomerular hyperfiltration or hypertension (Umanath and Lewis, 2018). Albuminuria in DN patients is also associated with a decrease in podocyte density, causing the loss of barrier to preventing urinary protein loss (Podgórski *et al.*, 2019).

Moreover, the mean value of the Estimated Glomerular Filtration Rate (eGFR) in the DN group tended to be statistically lower than the control group (Table 2). eGFR is calculated from serum creatinine concentration as a marker of endogenous glomerular filtration (Seidu, Barrat and Khunti, 2020). The hyperglycemia will induce media and intima layer thickening in afferent arterioles. Then, it causes decreased elasticity of blood vessels and control of glomerular pressure. In addition, hyperglycemia causes afferent arteriolar dysfunction. Next, it leads to increased glomerular pressure, hyperfiltration, and reduced serum creatinine levels. High glomerular pressure will result in proteinuria. In addition, it can decrease the glomerular filtration rate due to mesangial denaturation or glomerular necrosis. Finally, it leads to end-stage kidney damage (Ohishi, 2018; Yamazaki, Hitomi and Nishiyama, 2018).

The Correlation between Angiotensinogen rs699 and the Incidence of Diabetic Nephropathy

This research reported that the population's CC genotype was wild-type, and the T allele was minor. In addition, our studies' proportion of genotype frequency deviated from the Hardy Weinberg equation, which may be due to the small number of samples (Table 3). Furthermore, there was no correlation between Angiotensinogen rs699 and the incidence of diabetic nephropathy in this paper (Table 4). Studies in Slovenian, Caucasian, Mexican Americans and subgroups of Asian populations also revealed similar results (Rahimi, 2016; Makuc *et al.*, 2017; Tziastoudi, Stefanidis and Zintzaras, 2020). However, Several studies in Indian, Turkish and Tunisian populations showed an association between angiotensinogen rs699 and the risk of diabetic nephropathy in individuals with type 2 diabetes mellitus (Ahluwalia *et al.*, 2009; Rahimi, 2016). The different results in various populations may be due to ethnic heterogeneity and sampling method (Makuc *et al.*, 2017).

In addition, the CT genotype acted as a protective factor against the incidence of diabetic nephropathy but was not statistically significant (Table 4). However, a study in India showed that CT genotype was a risk

factor for diabetic nephropathy and CC genotype was a protective factor. In addition, this study found that the T allele acted as a protective factor against diabetic nephropathy and the C allele acted as a risk factor among type-2 diabetes mellitus patients with uncontrolled postprandial glucose levels in the Jambi Malay ethnicity. Still, it was not statistically significant (Table 4). Research in the Slovenian population also reported that T and C alleles of angiotensinogen rs699 did not associate with the risk of diabetic nephropathy (Makuc *et al.*, 2017). However, a study in India indicated that the T allele acted as a risk factor for diabetic nephropathy, and the C allele is a protective factor (Ahluwalia *et al.*, 2009).

Some genotype and phenotype studies reported the association between Angiotensinogen rs699 and ESRD. A prior study in Egyptian reported that the T allele of rs699 was associated with an increased risk of ESRD (El-garawani *et al.*, 2021). The review article on the role of the RAAS gene in DN reported that the TT genotype was associated with susceptibility and faster progression to ESRD in T2DM patients (Rahimi, 2016).

The authors used ARMS-PCR specific for angiotensinogen rs699 in this investigation. The ARMS-PCR method is faster, more reliable, and affordable than other methods. The method is appropriately performed with limited laboratory resources (Puspasari *et al.*, 2021). In addition, primer angiotensinogen rs699 was adapted from El-Garawani *et al.* (El-garawani *et al.*, 2021). We performed In Silico analysis to measure the primer sequence and PCR product size. Furthermore, PCR conditions optimization was adapted to our laboratory resources.

The limitations of this study were the relatively small number of samples and no conformational sequencing. However, the sample number in this study was proper with the minimum number of samples size. In addition, we did an in-silico analysis to measure the primer sequence and PCR product specific for angiotensinogen rs699.

CONCLUSION

Angiotensinogen rs699 is not a risk factor for diabetic nephropathy among type-2 diabetes mellitus patients with uncontrolled postprandial glucose levels in the Jambi Malay ethnicity. Further study should use a larger sample and analyses other genetic variations.

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The Correlation Between the Type of Occupation Toward Blood Pressure and Cholesterol Levels in Individuals with Hypertension

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A B S T R A C T

Daily activities and occupation can significantly influence health conditions, so a health assessment related to occupational factors is essential to reduce the risk of the disease. One of the leading causes of mortality from cardiovascular disease worldwide is hypertension. This study aims to determine the correlation between the type of occupation toward blood pressure and cholesterol levels in individuals with hypertension. This paper was an analytical observational study with a cross-sectional approach. The population was individuals with hypertension at Depok 2 Public Health Centre, Sleman Regency, Special Region of Yogyakarta. In addition, the sample was 121 respondents with consecutive sampling. The independent variable was the type of occupation, and the dependent variables were blood pressure and cholesterol levels. Instruments were a questionnaire to evaluate the characteristics of respondents and the type of occupation, a digital sphygmomanometer to examine blood pressure, and cholesterol test kits to assess cholesterol levels. The data analysis used the Chi-Square test with $\alpha=0.05$. Most respondents were female (59.5%) and aged 60-69 years old (47.1%). They worked in the informal sector (81.2%). In addition, they had grade 1 hypertension (52.1%). There was no significant correlation between the type of occupation and blood pressure in individuals with hypertension ($p=0.248$). In addition, most respondents had high cholesterol levels (50.4%). Furthermore, there was no significant association between the type of occupation and cholesterol levels in individuals with hypertension ($p=0.128$). In conclusion, the type of occupation is not a risk factor for increased blood pressure and cholesterol levels in individuals with hypertension.

INTRODUCTION

Hypertension is the leading cause of death from cardiovascular disease worldwide (Zhou *et al.*, 2018). In 2019, hypertension patients aged 30-79 reached 626 million women and 652 men (Zhou *et al.*, 2021). In Indonesia, hypertension has become one of the health problems in non-communicable diseases commonly found in the community (Balgis and Sumardiyono, 2019). Based on data from Basic Health Research in 2013, hypertension in Indonesia reached 25.8% population. Furthermore, its prevalence increases in young people (Balgis and Sumardiyono, 2019). Some risk factors for hypertension include an unhealthy diet consisting of a diet high in sodium and low in potassium, obesity, alcohol consumption, and lack of physical activity (Mills, Stefanescu, and He, 2020).

Based on Basic Health Research in 2018, hypertension in the Special Region of Yogyakarta reached 11.01% of the population, higher than the national prevalence (8.8%) (Dinas Kesehatan Yogyakarta, 2021). The estimated number of hypertension patients in the DI Yogyakarta province aged 15 years was 210,112 cases in 2020 (Dinas Kesehatan Yogyakarta, 2021). A survey in Indonesia found several risk

factors for hypertension, such as age, obesity, education level, lack of fruit and vegetable consumption, lack of physical activity, and anxiety levels. (Defianna *et al.*, 2021).

Hypertension can lead to stroke, coronary heart disease, and heart and kidney failure (Nugroho and Fahrurrodzi, 2020). One factor predisposing hypertension is cholesterol levels (Ulfah, Sukandar, and Afiatin, 2017). Usually, cholesterol is essential to form corticosteroids, sex hormones, and bile acids (Ulfah, Sukandar, and Afiatin, 2017). However, high cholesterol levels can interfere with vascular endothelial function by reducing vasodilating ability and causing blockage of the blood vessel walls (Otsuka *et al.*, 2015). In addition, increased cholesterol levels can cause insulin resistance and increased catecholamine levels. Then, it results in hyperinsulinemia (Mahmuda *et al.*, 2018). Increased catecholamines will interfere with the renin-angiotensin-aldosterone system, which controls blood pressure (Mahmuda *et al.*, 2018). As a result, there is an increase in vasoconstriction and fluid and salt retention in the body, developing into hypertension (Mahmuda *et al.*, 2018).

Daily activities and occupation can significantly influence health conditions, so a health assessment related to occupational factors is needed to reduce the risk of the disease (Stanaway *et al.*, 2018). According to a systemic analysis based on the Global Burden Study from 2007 to 2017, there was an increase in metabolic factors associated with socioeconomic status (Stanaway *et al.*, 2018). Socioeconomic status can influence biological, psychosocial, and behavioral factors that increase the risk of cardiovascular and metabolic diseases. Lower socioeconomic status predisposes poorer health outcomes (Schultz *et al.*, 2018). In addition, an increasingly heavy workload with low levels of physical activity can increase the risk of cardiovascular disease, especially in workers with low cardiorespiratory fitness (Holtermann *et al.*, 2016). Occupational not following the body's circadian rhythm can also increase the risk of cardiometabolic disease. Thus, it is necessary to analyze occupations that potentially pose the illness (Berkman *et al.*, 2015). This study aims to determine the correlation between the type of occupation toward blood pressure and cholesterol levels in individuals with hypertension at Depok 2 Public Health Centre, Sleman Regency, Special Region of Yogyakarta.

METHOD

This paper was an analytical observational study with a cross-sectional approach. The population was individuals with hypertension at Depok 2 Public Health Centre, Sleman Regency, Special Region of Yogyakarta. In addition, the sample was 121 respondents with consecutive sampling. The inclusion criteria were more than 20 years old, communicating well in Indonesian in writing or orally, and signing informed consent. Meanwhile, the exclusion criteria were sick or hospitalized individuals and respondents with an inadequate diet. This research received ethical approval from the Ethical Committee of Universitas Islam Indonesia with certificate 28/Ka.Kom.Et/70/K.E./XII/2020. The independent variable

was the type of occupation, and the dependent variables were blood pressure and cholesterol levels. Instruments were a questionnaire to evaluate the characteristics of respondents and the type of occupation, a digital sphygmomanometer to examine blood pressure, and cholesterol test kits to assess cholesterol levels. The classification of hypertension based on the Joint National Committee was prehypertension (120-139/80-89 mmHg), grade 1 hypertension (140-159/90-99 mmHg), and grade 2 hypertension (160-179/100-110 mmHg) (Chobanian *et al.*, 2003). In addition, cholesterol levels classification was normal (total cholesterol <200 mg/dL), borderline (200-240 mg/dL), and high (\geq 240 mg/dL) (National Cholesterol Education Program (US). Expert Panel on Detection, 2002). This study categorized normal and borderline total cholesterol as normal cholesterol levels. Then, the data analysis used the Chi-Square test with $\alpha=0.05$.

RESULT

Characteristics of respondents

Table 1 indicates that almost half of the respondents are 60-69 years (47.1%). In addition, most respondents are female (59.5%).

Table 1. Characteristics of respondents

Characteristics of respondents		Frequency (Percentage)
Age	20-29 years old	1 (0.9%)
	30-39 years old	1(0.9%)
	40-49 years old	11 (9%)
	50-59 years old	24 (19.8%)
	60-69 years old	57 (47.1%)
	70-79 years old	23 (19%)
	80-89 years old	4 (3.3%)
Sex	Male	49 (40.5%)
	Female	72 (59.5%)

Most respondents worked in the informal sector (81.2%). In addition, they had grade 1 hypertension (52.1%). Respondents who worked in the informal sector mostly had grade 1 hypertension (38.8%). In addition, respondents who worked in the formal sector also mostly had grade 1 hypertension (13.2%). Thus, there was no significant correlation between the type of occupation and blood pressure in individuals with hypertension ($p=0.248$) (Table.2).

Table 2. The bivariate analysis between the type of occupation and blood pressure in individuals with hypertension

The type of occupation	Blood Pressure			Total	<i>p</i>
	Pre-Hypertension	Grade 1 hypertension	Grade 2 hypertension		
Formal sector	5 (4.1%)	16 (13.2%)	3 (2.5%)	24 (19.8%)	0.248
Informal sector	26 (21.5%)	47 (38.8%)	24 (19.8%)	97 (81.2%)	
Total	31 (25.6%)	63 (52.1%)	27 (22.3%)	121 (100%)	

Most respondents had high cholesterol levels (50.4%). Respondents who worked in the formal sector mostly had normal cholesterol levels (10.7%). Meanwhile, respondents who worked in the informal

sector mostly had high cholesterol levels (50.4%). However, there was no significant correlation between the type of occupation and cholesterol levels in individuals with hypertension ($p=0.128$) (Table.3).

Table 3. The bivariate analysis between the type of occupation and blood pressure in individuals with hypertension

Occupation	Cholesterol Levels		Total	<i>p</i>
	Normal	High		
Formal sector	13 (10.7%)	11 (9.1%)	24 (19.8%)	0.128
Informal sector	36 (29.8%)	61 (50.4%)	97 (80.2%)	
Total	49 (40.5%)	72 (59.5%)	121 (100%)	

DISCUSSION

This study found that most respondents were female and aged 60-69 years old (Table 1). Prior research also revealed that individuals with hypertension were female and more than 60 years old (Ulfah, Sukandar, and Afiatin, 2017; Umar and Mariana, 2021). Women have a higher risk of hypertension and hypercholesterolemia and a higher risk of mortality due to cardiovascular disease than men (Colafella and Denton, 2018). Moreover, women after menopause will have an increased risk of hypertension and hypercholesterolemia due to decreased hormone estrogen. Thus, women need special attention as a risk factor for cardiovascular disease, especially postmenopausal women (Agarwala *et al.*, 2020).

Our findings indicated that most respondents worked in the informal sector (Table 2). Several work conditions can increase risk factors for hypertension in workers (Ribeiro Junior and Fernandes, 2020). A study by Hrehova and Ziara (2021) of 16,713 workers from various countries in the European Union found that work-related factors such as level of satisfaction, opportunity to develop new skills, adequate salary, and gain recognition from the workplace were associated with the incidence of hypertension (Hrehova and Ziaran, 2021). In addition, the type of work is a predisposing factor for metabolic syndrome (Sara *et al.*, 2018). In a study by Cho and Koo (2018), women with informal jobs had a higher prevalence of metabolic syndrome, regardless of differences in the characteristics of age, smoking, drinking habits, physical activity, body mass index, levels of stress or depression (Cho and Koo, 2018). Research conducted by Mello *et al.* (2021) also showed that informal employment with active smoking habits had a more significant prevalence of cardiovascular disease than the formal workgroup, unemployed, homemakers, and students (Mello *et al.*, 2021). Detecting occupational disease is essential to evaluate job safety and quality of life in daily activities (Halshka *et al.*, 2021).

In addition, most respondents in this paper had grade 1 hypertension (Table 2). Hypertension is a risk factor for cardiovascular diseases such as coronary heart disease and stroke. In addition, high systolic and diastolic blood pressure in individuals with hypertension affects poor health outcomes. (Hussain *et al.*, 2016; Flint *et al.*, 2019). In addition, a study by Junior and Fernandes (2020) showed that inadequate

physical activity (once per week or not at all) was a risk of high blood pressure. Furthermore, other risk factors were male, overweight, and aged more than 31 years (Ribeiro Junior and Fernandes, 2020).

Furthermore, this research indicated that most individuals with hypertension had high cholesterol levels (Table 3). Cholesterol levels in hypertension can affect endothelial function. When cholesterol levels increase, it will cause an inflammatory reaction by macrophages and endothelial dysfunction of blood vessels, resulting in damage to target organs such as the heart and brain (Zhou *et al.*, 2016). In addition to the damage to endothelial function, high cholesterol levels can increase the regulation of the hormone angiotensin I and increase the release of angiotensin II, which interacts with cholesterol through macrophages, leading to the accumulation of foam cells (Borghi, Urso, and Cicero, 2017). Thus, managing blood pressure and cholesterol levels can reduce the risk of cardiovascular disease (Gupta *et al.*, 2018). However, a study by Saputra *et al.* (2019) showed no association between cholesterol levels and blood pressure (Saputra *et al.*, 2019).

Our findings found no significant correlation between the type of occupation and blood pressure in individuals with hypertension (Table.2). It is in line with a study by Chasanah and Syarifah (2017). The study showed no correlation between work on the severity of hypertension (Chasanah and Syarifah, 2017). However, the findings of Rengganis *et al.* (2020) showed that stress levels at work increased blood pressure in workers (Rengganis, Rakhimullah, and Garna, 2020). Several work-related factors, such as overwork, a decreased number of employees, and an unfavorable work environment, also could affect increasing blood pressure (Trudel *et al.*, 2016). Work-related hypertension is multifactorial, so further monitoring is crucial to prevent hypertension (Munakata, 2018) (Bistara and Kartini, 2018).

This paper also revealed no significant correlation between the type of occupation and cholesterol levels in individuals with hypertension (Table.3). It is in line with a meta-analysis by Nyberg *et al.* (2013). The meta-analysis revealed no association between job strain and blood lipids. However, a study by Hansun *et al.* (2017) showed an association between work and the risk of cardiovascular disease, one of which was due to high cholesterol levels (Nyberg *et al.*, 2013; Hanson *et al.*, 2017). The unbalanced work potentially results in poor health outcomes, especially hypercholesterolemia (Schmidt *et al.*, 2015). The effect of occupation on cholesterol levels is multifactorial. Thus, assessing risk factors and managing work-related hypercholesterolemia is essential (Hwang and Lee, 2014).

This study has several limitations. One of them was limited samples due to the short duration of the study. In addition, this paper did not include other essential variables, including body mass index, physical activity, diet, educational level, and stress.

CONCLUSION

In conclusion, the type of occupation is not a risk factor for increased blood pressure and cholesterol levels in individuals with hypertension. Further research could evaluate work-related factors such as stress levels and social security such as insurance toward blood pressure and total cholesterol levels in individuals with hypertension.

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Dupilumab Efficacy and Safety as an Add-On Therapy in Uncontrolled Asthma Patients: A Systematic Review

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KEYWORDS

Dupilumab; Uncontrolled asthma patients; The annualized rate of severe asthma exacerbation; FEV1; Anti-IL-4; Anti IL-13; Monoclonal antibody

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ABSTRACT

Asthma is a heterogeneous chronic inflammatory condition affecting the lung. Standard treatment, a high-dose inhaled corticosteroid (ICS) and long-acting bronchodilator (LABA), effectively manages asthma in most individuals. However, 5%-10% of individuals with asthma were ineffective with those treatments. Recent RCTs suggested that Dupilumab posed potential as an add-on therapy. This systematic review aims to support the efficacy (the annualized rate of severe asthma exacerbation and increase in FEV1) and the safety of Dupilumab as an add-on therapy in uncontrolled asthma patients. We used "(Asthma) AND (Dupilumab)" as keywords on PubMed and ScienceDirect. We included only RCT design studies comparing the efficacy and safety of Dupilumab with a placebo in uncontrolled asthma patients. The placebo was ICS and LABA or oral glucocorticoids. This paper included five RCTs with 3400 participants, and their quality was assessed using Critical Appraisal Tools Program (CASP) tools. We conducted a meta-analysis to calculate the pooled risk ratio (RR). In addition, we used Mantel-Haenszel with 95% confidence intervals for dichotomous data. Furthermore, we used a random-effects model to count for interstudy heterogeneity. Then, we processed data using Revman 5.4. Dupilumab as an add-on therapy significantly showed a consistent effect in lower the annualized rate of severe asthma exacerbation (RR= 0.46; 95% CI 0.36- 0.58; p=0.007) and increased FEV1 compared to placebo. In addition, the most common adverse effect of using Dupilumab were injection site reaction, upper respiratory tract infections, and eosinophilia. In conclusion, Dupilumab is safe and well-tolerated as moderate-to-severe uncontrolled asthma add-on therapy

INTRODUCTION

Asthma is a heterogeneous chronic inflammatory affecting the airways caused by airway hyperresponsiveness after exposure to triggers or allergens. It results in bronchoconstriction and airflow obstruction. Its symptoms are breathlessness, chest tightness, wheezing, and cough (Farne *et al.*, 2017; Harb and Chatila, 2017; GINA, 2021). Symptoms due to airflow obstruction may resolve either spontaneously or with asthma therapy. However, patients can experience exacerbations, an increase in the severity of a disease or its signs and symptoms in a certain period (Rothe *et al.*, 2018). Based on World Health Organization (WHO) survey data from 2002 to 2003, the prevalence of asthma patients among young adults (18-45 years old) in 70 countries was 177,496 (Global Asthma Network, 2018; Syfridiana and Herawati, 2021). Furthermore, asthma is still one of Indonesia's top ten diseases causing illness and death. Based on Basic Health Research in 2018, the prevalence of asthma in Indonesia was 2.4% of the total population of Indonesia. The highest asthma prevalence was in DI Yogyakarta (4.59%), East Kalimantan (4.0%), and Bali (3.9%) (Kemenkes RI, 2019).

The long-term goals of asthma management are symptom control and risk reduction. The treatment includes medication, risk factors modification, and non-pharmacological therapies. Controller medication is vital in controlling asthma and preventing exacerbation in chronic asthma. There are five steps of treatment for chronic asthma. The higher the step, the more medication to manage chronic asthma (Fig.1) (GINA, 2021).

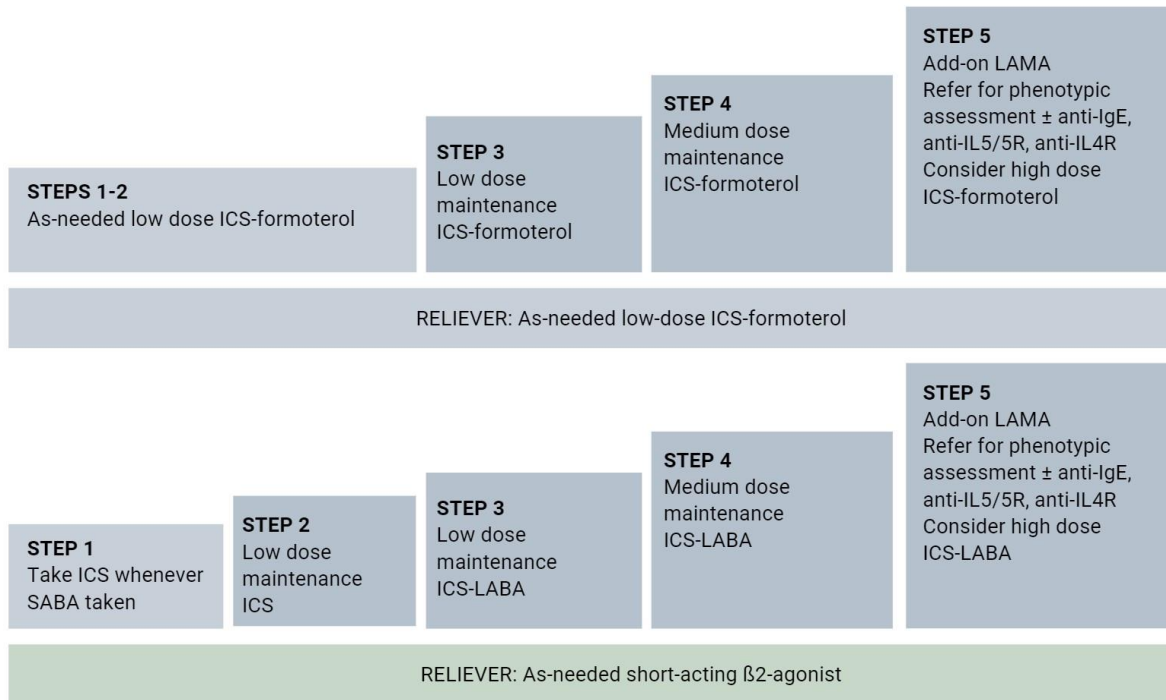


Figure 1. Asthma treatment strategy adapted from Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2021

Standard treatment, a high-dose inhaled corticosteroid (ICS) and long-acting bronchodilator (LABA), effectively manages asthma in most individuals. There were no data in Indonesia, but to the authors' knowledge, 5%-10% of individuals with asthma were ineffective with those treatments. They require add-on therapy (in step 5; Fig.1). Patients with severe uncontrolled asthma tend to have a poor quality of life (QOL), more extended hospitalization, and impaired lifestyle compared to well-controlled asthmatic patients. In addition, they experience adverse effects from oral corticosteroids (Rogliani *et al.*, 2020; Ricciardolo, Bertolini, and Carriero, 2021).

In the last decade, advanced research has led to new asthma treatments. This new therapy is a biological therapy indicated for uncontrolled severe asthma patients. Most of these therapy target inflammation molecules from the type two inflammation pathway (Rogliani *et al.*, 2020). There is currently a limited medication option in step 5 for uncontrolled, moderate to severe asthma patients. Omalizumab is an anti-IgE available in Indonesia, but only for persistent asthma patients with a positive skin test or reactive to perennial aeroallergen (in vitro) (FDA, 2017b). Also, Dupilumab is

the first biological therapy to target IL-4 and IL-13 type 2 cytokines. As a result, it reduces eosinophil levels.

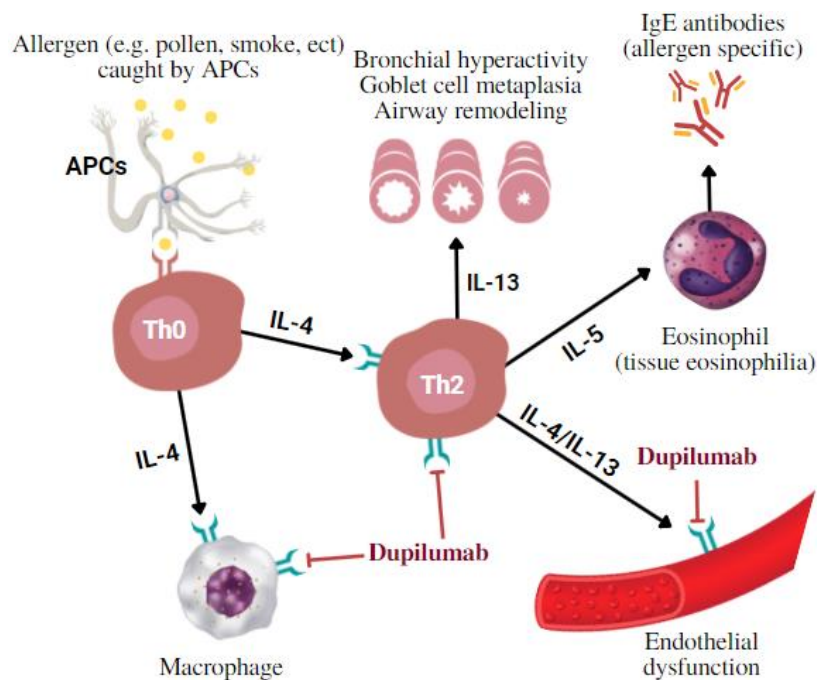


Figure 2. immunopathological pathway of Th-2 mediated asthma (modified from Hammad *et al.* (2021)(Harb and Chatila, 2017; Papi *et al.*, 2018)

T-helper2 (Th-2) lymphocytes can mediate the Th-2 immune response that precipitates asthma. Evidence states that elevated expression of Th2 cytokines, such as IL-4, IL-5, and IL-13, can drive allergic asthma (Ricciardolo, Bertolini, and Carriero, 2021). IL-4 promotes the synthesis of IgE and primes blood vessels for eosinophil extravasation by acting on IL-4R (Papi *et al.*, 2018). Meanwhile, IL-13 induces the production of iNOS in airway epithelial cells and metaplasia of goblet cells. In addition, it causes bronchial hyperactivity (Fig.2) (Papi *et al.*, 2018). Therefore, these molecules are essential for managing T2 allergic asthma (Ricciardolo, Bertolini, and Carriero, 2021). Preliminary simulation of Th-2 lymphocytes with the aid of several inflammatory cytokines, causing the expression of the CCR-4 chemokine receptor and secretion of different inflammatory interleukins, such as IL-4, IL-5, IL-9, and IL-13. As Th-2 lymphocytes migrate from surrounding lymph nodes to the airways, they induce chemotaxis and activation of inflammatory cells. In addition, it causes mast cells and eosinophils production that are liable for bronchial asthma symptoms over a long period (Zayed *et al.*, 2019). The prevalence of eosinophilic asthma is about 50% in asthmatic adults. In addition, recent findings suggest that patients with corticosteroid withdrawal also have eosinophilic inflammation. Therefore an IL-4/IL-13 inhibitor that can lower the eosinophilic levels is essential to target therapy (Papi *et al.*, 2018).

Dupilumab is a monoclonal antibody derived from humans, acting as an IL-4/IL-13 inhibitor. It targets the α subunit of the IL-4 and IL-13 receptors. It forms a high affinity to IL-13- and IL-4-binding type II heterodimeric complex (Fig.2) (Harb and Chatila, 2017, 2020). Thus, it blocks the signal transduction of the Th-2-mediated immune response (Ricciardolo, Bertolini, and Carriero, 2021).

A systematic review and meta-analysis of randomized clinical trials conducted in 2018 supported Dupilumab use in patients with uncontrolled asthma (Zayed *et al.*, 2019). The addition of Dupilumab in moderate-to-severe asthma therapy was associated with a reduced risk of asthma exacerbation and improved FEV₁ without an increased risk of an adverse event (Zayed *et al.*, 2019). Dupilumab injection was approved by the US Food and Drug Administration on Mar 28, 2017, to treat adults with uncontrolled moderate-to-severe eczema (atopic dermatitis) (FDA, 2017a). Dupilumab is available in Indonesia. Therefore, updated evidence with more recent trials is required to support its use in uncontrolled asthma therapy.

In this systematic review, we updated published systematic reviews and meta-analyses (Zayed *et al.*, 2019). This paper analyzes the efficacy (the annualized rate of severe asthma exacerbation and increase in FEV₁ from baseline) and safety of Dupilumab as an add-on therapy compared to a placebo in patients with moderate-severe uncontrolled asthma.

METHOD

Literature search, data source, and selection of study

Electronic literature searching was performed independently and separately by two authors (EE and PBD) using PUBMED and ScienceDirect with keywords (Asthma) AND (Dupilumab). The authors searched studies conducted from January 2013 to Feb 15, 2022. Collected studies were screened, and duplicates were removed using Mendeley Reference Manager. All included studies met the inclusion criteria: RCTs that compare the efficacy and safety of Dupilumab with a placebo in uncontrolled asthma patients with inhaled ICS and LABA or requiring oral glucocorticoids to control their symptoms. We excluded post hoc analysis and non-RCT studies.

Article quality assessment

Two authors (EE and PBD) assessed the studies' quality using the Critical Appraisal Program (CASP) tools (CASP, 2020) and journal reputation. The CASP checklist contains three parts consisting of several questions. Part A assesses the validation of research results. In addition, part B assesses research results. Furthermore, part C assesses whether the research results can be applied or used by readers. For the CASP checklist, articles were considered good quality because there were at least ten "yes" answers.

Outcomes

The primary efficacy outcome was the annualized rate of severe asthma exacerbations with criteria: a reduction of $\geq 30\%$ in morning peak expiratory flow (PEF) from baseline on two consecutive days, at least six additional reliever inhalations (salbutamol or albuterol or levalbuterol) in 24 hours relative to baseline on two consecutive days, asthma exacerbation requiring systemic glucocorticoid treatment, an increase in inhaled glucocorticoids of at least four times the most recent dose, or hospitalization for asthma. The secondary outcome was the change in forced expiratory volume at 1s (FEV₁) between baseline and the most prolonged follow-up duration (12–24 weeks).

The authors also assessed safety outcomes and adverse events. Furthermore, we analyzed descriptively and narratively all included studies.

Statistical Analysis

We conducted a meta-analysis to calculate the pooled risk ratio (RR). In addition, we used Mantel-Haenszel with 95% confidence intervals for dichotomous data. Furthermore, we used a random-effects model to count for interstudy heterogeneity. Then, we processed data using Revman 5.4.

Ethical Clearance

This systematic review extracted data from accessible published articles, so ethical clearance is not applicable.

RESULT

A keyword search of two electronic databases, PubMed and ScienceDirect, resulted in 497 articles. The first screening based on title and abstract resulted in 52 relevant articles. Then, 52 papers were further reviewed and assessed for eligibility. Finally, this paper reviewed five RCT papers that compared Dupilumab with placebo in patients with severe uncontrolled asthma (Fig.3) (Wenzel *et al.*, 2013, 2016; Castro *et al.*, 2018; Rabe *et al.*, 2018; Bacharier *et al.*, 2021). Table 1 summarizes the details of the five included studies.

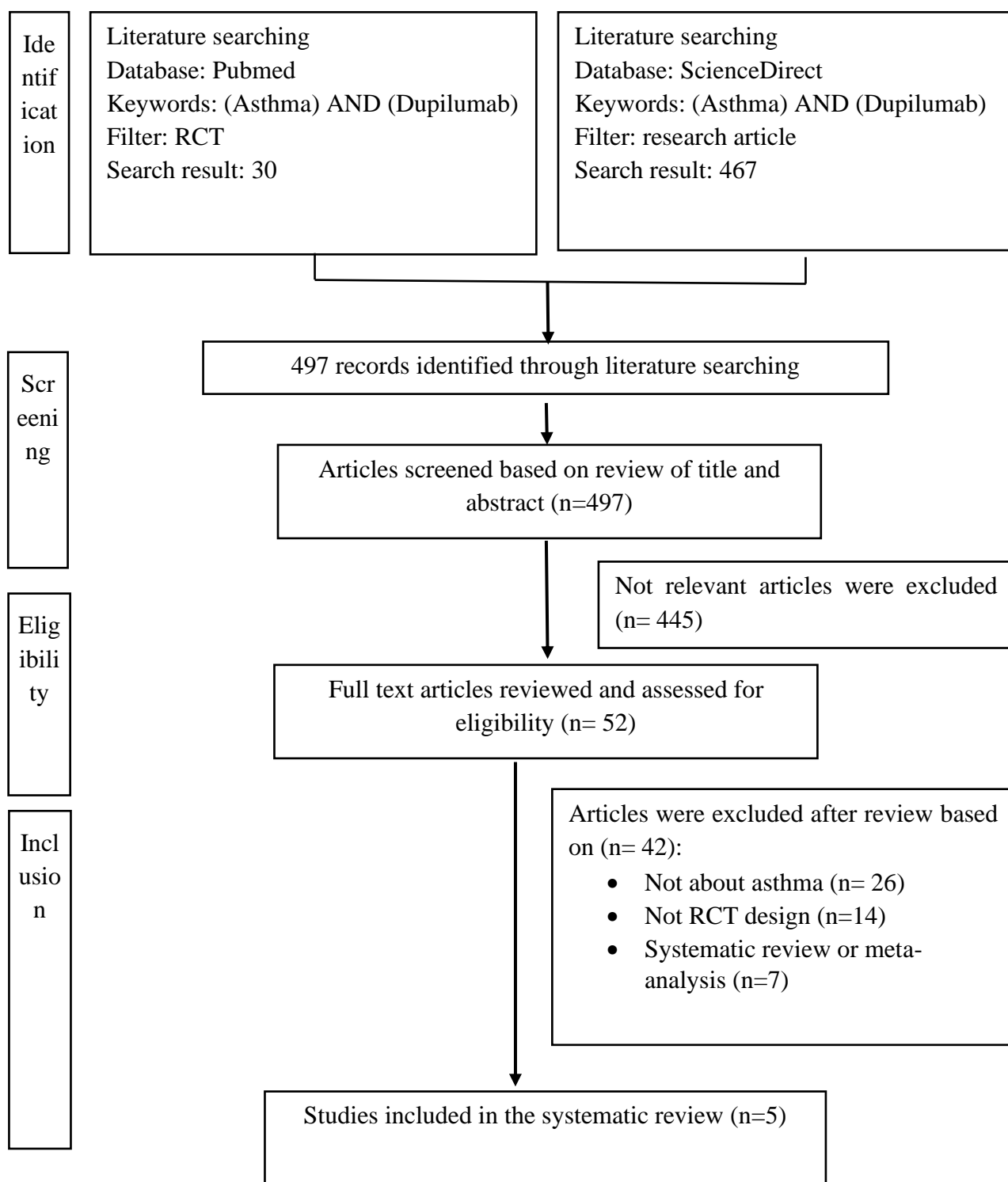


Figure 3. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Flow Diagram of Literature Search and Studies Selection (Page *et al.*, 2021)

Quality of Articles

Assessment of articles with the CASP checklist showed that all five RCTs (Wenzel *et al.*, 2013, 2016; Castro *et al.*, 2018; Rabe *et al.*, 2018; Bacharier *et al.*, 2021) in included studies had good quality (5; 100%) (Fig.4). All studies were randomized, double-blind, and analyzed based on the

intention-to-treat principle. All outcomes were mentioned and measured statistically with *p* and confidence intervals (CI).

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Wenzel, <i>et al</i> 2013	+	+	+	+	+
Wenzel, <i>et al</i> 2016	+	+	+	+	+
Castro, <i>et al</i> 2018	+	+	+	+	+
Rabe, <i>et al</i> 2018	+	+	+	+	+
Bacharier, <i>et al</i> 2021	+	+	+	+	+
Low risk of bias: + ; uncertain risk of bias: ? ; high risk of bias: -					

Figure 4. Risk of bias summary of included studies

All five RCTs included in this review were randomized and double-blinded with different Dupilumab doses, with the most frequently used dose of Dupilumab 200-300 mg every two weeks. Other dosages included 300 mg every week and 200-300 mg every four weeks. Thus, all baseline characteristics in these five included studies were similar. The meta-analysis of the primary outcome (the annualized rate of severe asthma exacerbation) was carried out using data from four studies only because the authors could not obtain the raw data from Rabe's study (2018). This statistical analysis found that Dupilumab as an add-on therapy significantly showed a consistent effect in lower the annualized rate of severe asthma exacerbation (RR= 0.46; 95% CI 0.36- 0.58; *p*=0.007) (Figure 5).

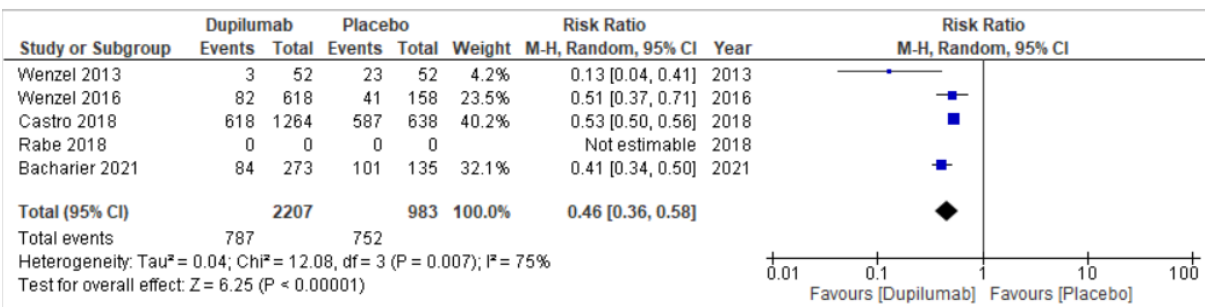


Figure 5. Forest plot of an annualized rate of severe asthma exacerbation

Table 1. The Characteristics of Included Studies

Author (year)	Method	Patient or population	Intervention	Control	Outcomes		
					The annualized rate of severe asthma exacerbation	Change in FEV1 from baseline	Adverse events
Wenzel, S. <i>et al</i> (2013)	RCT (randomized, double-blind, placebo-controlled, parallel-group, phase 2A study)	Adults (18-65 years old), persistent, moderate-to-severe asthma, elevated blood eosinophil count (≥ 300 cells per microliter), or an elevated sputum eosinophil level ($\geq 3\%$). In addition, inhaled glucocorticoids (medium to high dose) and LABAs could not control the symptoms. LABAs in the study were fluticasone ≥ 250 μg and salmeterol 50 μg twice daily or equivalent. (intervention=52; control=52)	Subcutaneous injections of Dupilumab (300 mg) once weekly for 12 weeks	Placebo	Dupilumab vs placebo: odds ratio 0.08; 95% confidence interval [CI], 0.02 to 0.28; $p < 0.001$	Dupilumab vs. placebo, difference 0.27 (0.11 to 0.42) $p < 0.001$	Injection-site reactions, nasopharyngitis, nausea, and headache occurred more frequently in Dupilumab than with a placebo
Wenzel, S. <i>et al</i> (2016)	RCT (randomized, double-blind, placebo-controlled, parallel-group, pivotal phase 2b clinical trial)	Adults (aged ≥ 18 years) with an asthma diagnosis for ≥ 12 months treated with medium-to-high-dose inhaled corticosteroids (twice daily) plus a long-acting β_2 agonist (LABA) for at least one month before the screening. The LABA in the study was fluticasone propionate ≥ 250 μg or equivalent.	Subcutaneous Dupilumab 200 mg every two weeks (n=150)	Placebo (n=158)	≥ 1 severe exacerbation event during the 24-week treatment period: Risk reduction of 0.269 (0.157-0.461; $p=0.0002$)	In overall population: FEV1 increased significantly at week 12 ($p < 0.0001$) In ≥ 300 eosinophils/ μL subgroup: FEV1 increased significantly at week 12 ($p=0.0008$) In < 300 eosinophils/ μL subgroup: FEV1 increased significantly ($p=0.0034$)	Upper respiratory tract infection (14% in Dupilumab group vs. 18% in placebo), injection-site erythema (13% in Dupilumab group vs. 8% in placebo), and headache (10% in Dupilumab group vs. 13% in placebo)
			Subcutaneous Dupilumab 300 mg every two weeks (n=157)	Placebo (n=158)	≥ 1 severe exacerbation event during the 24-week treatment period: Risk reduction of 0.265 (0.157-0.445; $p=0.0001$)	In overall population: FEV1 increased significantly at week 12 ($p=0.0002$) In ≥ 300 eosinophils/ μL subgroup: FEV1 increased significantly at week 12 ($p=0.0063$) In < 300 eosinophils/ μL subgroup: FEV1 increased significantly ($p=0.0086$)	
			Subcutaneous	Placebo	≥ 1 severe	In overall	

			Dupilumab 200 mg every four weeks (n=154)	(n=158)	exacerbation event during the 24-week treatment period: Risk reduction of 0.415 (0.260-0.664; $p=0.0093$)	population: FEV1 increased significantly at week 12 ($p=0.0304$) In ≥ 300 eosinophils/ μL subgroup: FEV1 increased not significantly at week 12 ($p=0.2774$) In < 300 eosinophils/ μL subgroup: FEV1 increased not significantly ($p=0.0795$)	
			Subcutaneous Dupilumab 300 mg every four weeks (n=157)	Placebo (n=158)	≥ 1 severe exacerbation event during the 24-week treatment period: Risk reduction of 0.599 (0.396-0.907; $p=0.1380$)	In overall population: FEV1 increased significantly at week 12 ($p=0.0048$) In ≥ 300 eosinophils/ μL subgroup: FEV1 increased significantly at week 12 ($p=0.0212$) In < 300 eosinophils/ μL subgroup: FEV1 increased not significantly ($p=0.1231$)	
Castro <i>et al.</i> (2018)	RCT (phase 3, randomized, double-blind, placebo-controlled, parallel-group trial)	Patients ≥ 12 years old and had physician-diagnosed asthma ≥ 1 year. In addition, respondents were treated with medium-to-high-dose inhaled glucocorticoid plus up to two additional controllers (e.g., a long-acting β_2 -agonist or leukotriene-receptor antagonist). The inhaled glucocorticoid was fluticasone propionate at a total daily dose of ≥ 500 μg or equipotent equivalent.	Subcutaneous Dupilumab 200 mg (loading dose of 400 mg) or 300 mg (loading dose of 600 mg) every two weeks for 52 weeks	Placebo (1.14 ml or 2 ml)	Dupilumab 200 mg vs placebo: 47.7% lower rate of exacerbations with Dupilumab than with placebo ($p<0.001$) Dupilumab 300 mg vs placebo: 46.0% lower rate of exacerbations with Dupilumab than with placebo ($p<0.001$)	Dupilumab 200 mg vs placebo (at week 12): Dupilumab 0.32 L vs. placebo 0.18 L (difference, 0.14 L; $p<0.001$) Dupilumab 300 mg vs placebo (at week 12): Dupilumab 0.34 L vs. placebo 0.21 L (difference, 0.13 L; $p<0.001$)	There were injection-site reactions (15.2% in the 200 mg Dupilumab subgroup vs. 5.4% in the placebo group, and 18.4% in the 300 mg Dupilumab subgroup vs. 10.3% in the placebo group), eosinophilia (4.1% in Dupilumab group vs. 0.6% in the placebo group). In addition, severe adverse events (8.2% in the Dupilumab group and 8.4% in the placebo group) include pneumonia (0.3% in the Dupilumab group and 0.3% in

							the placebo group).
Rabe <i>et al.</i> (2018)	RCT (international, randomized, double-blind, placebo-controlled, phase 3 trial)	Patients ≥ 12 years old, had physician-diagnosed asthma ≥ 1 year, receiving regular systemic glucocorticoids in the previous six months. During the four weeks before the screening, treated with high-dose inhaled glucocorticoid (fluticasone propionate at a total daily dose of >500 μg or equipotent equivalent) in combination with up to two controllers (i.e., a long-acting β_2 -agonist or leukotriene-receptor antagonist) for at least three months	Subcutaneous Dupilumab (at a dose of 300 mg, after receiving a 600-mg loading dose on day 1) every two weeks for 24 weeks	Placebo	There was a reduction rate of severe asthma exacerbations by 59% (95% CI, 37 to 74) in the Dupilumab group vs. placebo.	Higher FEV1 in the Dupilumab group than in the placebo group at week 24 by a least-squares mean value of 0.22 liters (95% CI, 0.09 to 0.34)	Viral upper respiratory tract infection (9% in the Dupilumab group vs. 19% in the placebo group), injection-site reaction (9% in the Dupilumab group vs. 1% in the placebo group)
Bacharier, <i>et al.</i> (2021)	RCT (multinational, randomized, placebo-controlled, phase 3 trial, Liberty Asthma VOYAGE (Evaluation of Dupilumab in Children with Uncontrolled Asthma)	The samples were children from 6 to 11 years old and physician-diagnosed with moderate-to-severe asthma (using GINA guidelines). Respondents had at least a 3-month history of receiving either a medium-dose inhaled glucocorticoid combination with a second controller. Or Respondents received high-dose inhaled glucocorticoid alone or in combination with a second controller at a dose that had been stable for at least one month.	Subcutaneous Dupilumab (273 patients) (dose of 100 mg for those weighing ≤ 30 kg and 200 mg for >30 kg) every two weeks for 52 weeks.	Volume-matched placebo (135 patients) every two weeks for 52 weeks.	Dupilumab 0.31 (95% CI, 0.22-0.42) vs. placebo 0.75 (95% CI, 0.54- 1.03). Significant relative risk reduction: 59.3%; 95% CI, 39.5 to 72.6; $p<0.001$)	Predicted prebronchodilator forced expiratory volume in 1 second (ppFEV1) at week 12: significant mean difference (mean difference, 5.2 percentage points; 95% CI, 2.1 to 8.3; $p<0.001$) between Dupilumab (10.5 \pm 1.01 percentage point) and placebo group (5.3 \pm 1.4 percentage points)	Viral infection of the upper respiratory tract (12.2% with Dupilumab and 9.7% with placebo), eosinophilia (5.9% on Dupilumab vs. 0.7% on placebo), parasitic infections (2.6% in the Dupilumab group)

DISCUSSION

Efficacy of Dupilumab as add-on therapy in uncontrolled asthma patients

The first RCT by Wenzel *et al.* (2013) showed that a subcutaneous injection of Dupilumab 300 mg once a week lowered annualized rate of severe asthma exacerbation compared to placebo in adult patients with persistent, moderate, and severe asthma (odds ratio 0.08; 95% confidence interval [CI], 0.02 to 0.28; $p<0.001$) (Wenzel *et al.*, 2013). Furthermore, Wenzel *et al.* (2016) investigated various subcutaneous Dupilumab regimens (200 mg every two weeks, 300 mg every two weeks, 200 mg every four weeks, and 300 mg every four weeks) for 24 weeks compared to placebo in adults. The results revealed a significant reduction in exacerbation events in three regimens (200 mg every two weeks, 300 mg every two weeks, and 200 mg every four weeks) but not 300 mg every four weeks. The results align with the RCT by Castro

et al. (2018), which assessed the efficacy of subcutaneous Dupilumab 200 mg and 300 mg every two weeks but in a more extended follow-up period (52 weeks). That study showed a significant reduction of annualized exacerbation by 47.7% and 46.0%, respectively (Castro *et al.*, 2018). Another RCT in 2018 also assessed the efficacy of Dupilumab 300 mg with a loading dose of 600 mg on day one. The study also showed a reduction in severe asthma exacerbations by 59% (95% CI, 37 to 74) (Rabe *et al.*, 2018). Moreover, the newest RCT by Bacharier et al. (2021) also focused on evaluating the efficacy of Dupilumab in children (6-11 years old), with dosage varied based on the child's weight. A child with ≤ 30 kg body weight received 100 mg of Dupilumab every two weeks, while samples >30 kg received 200 mg every two weeks for 52 weeks. This systematic review and meta-analysis found that the annualized rate of severe asthma exacerbations in the Dupilumab group was lower than in the placebo group (RR 0.46; 95% CI 0.36- 0.58; $p=0.007$). Previous systematic review and meta-analysis in 2018 also showed a similar result to this paper, despite not including the children population (aged 6-11 years old) (Zayed *et al.*, 2019).

Dupilumab has a complex mechanism and is associated with eosinophil count in reducing severe asthma exacerbation, as mentioned by Zayed et al. (2018). Dupilumab can potentially suppress asthma exacerbation by blocking both IL-4 and IL-13, reducing eosinophil production (IL-4 mediated), mucous production, and preventing airway remodeling (IL-3 mediated, unrelated to the eosinophilia-associated Th-2 response) (Zayed *et al.*, 2019). This notion is supported by findings of a significant reduction of severe asthma exacerbations annual rate and an improvement in FEV₁ in asthma patients receiving Dupilumab compared to placebo, regardless of their eosinophil count.

The effect of Dupilumab may be dose-dependent, as demonstrated by Castro *et al.* (2018), one of the RCTs included in this systematic review. Higher and more frequent Dupilumab doses, either 200 mg every two weeks or 300 mg every two weeks, are required to prevent the annualized rate of severe asthma exacerbations (Castro *et al.*, 2018). However, there is still too little RCT conducted to assess the dosing effect on the Dupilumab efficacy. Therefore, we conducted a meta-analysis in this current study that includes all doses given in the RCT studies.

The secondary outcome of this meta-analysis was the change in FEV₁. Dupilumab 300 mg once a week, 200 mg every two weeks, and 300 mg every two weeks significantly showed the consistent result in the increase of FEV₁ (Wenzel *et al.*, 2013, 2016; Castro *et al.*, 2018; Rabe *et al.*, 2018; Bacharier *et al.*, 2021) (5;100%). However, Dupilumab 200 mg or 300 mg every four weeks showed no significant increase in FEV₁ (Wenzel *et al.*, 2016). It might be due to the low frequency of doses.

Safety of Dupilumab

The most common adverse events of Dupilumab subcutaneous reported were injection site reactions (Wenzel *et al.*, 2013, 2016; Castro *et al.*, 2018; Rabe *et al.*, 2018), upper respiratory tract infections

(Wenzel *et al.*, 2016; Castro *et al.*, 2018; Rabe *et al.*, 2018; Bacharier *et al.*, 2021), and eosinophilia (Castro *et al.*, 2018; Bacharier *et al.*, 2021). All five studies in this meta-analysis (5;100%) showed no significant differences in any adverse events between Dupilumab and the control group.

CONCLUSION

Dupilumab as add-on therapy in patients with uncontrolled asthma significantly lowered the annualized rate of severe asthma exacerbations and increased FEV1 in all five included studies. The most common adverse effects of using Dupilumab were injection site reaction, upper respiratory tract infections, and eosinophilia. Thus, this review concludes that using Dupilumab in uncontrolled asthma patients is beneficial and well-tolerated.

Although all studies included in this systematic review have a low risk of bias, it still can't point out the best dose of Dupilumab for add-on therapy in moderate-to-severe uncontrolled asthma patients. Moreover, RCT studies assessing Dupilumab efficacy and safety in the Indonesian population are still lacking. Thus, there should be more RCT studies (with more samples for achieving generality), especially in Indonesia, to determine the optimal dose.

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The Peripheral Vascular Status in Individuals with Type 2 Diabetes Mellitus

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A B S T R A C T

Poor vascularization in individuals with diabetes will worsen blood circulation due to high glucose in the blood. One of the risk factors leading to diabetic foot ulcers (DFU) is peripheral vascular disease. This study aims to identify the peripheral vascular status in individuals with type 2 diabetes mellitus (T2DM) at Kebonsari Public Health Centre, Surabaya. The research design in this study used a quantitative descriptive approach. There were 40 respondents with an accidental sampling. The data collection was carried out for four weeks, from May to June 2020. The research instrument was an observation sheet to record the Dorsalis Pedis artery pulse and ankle-brachial index (ABI). In addition, a digital sphygmomanometer was used to measure the Dorsalis Pedis artery pulse. Most respondents had the normal Dorsalis Pedis artery pulse in the right legs (80%), 20% had bradycardia, and none had tachycardia (0%). In addition, they had the normal Dorsalis Pedis artery pulse in the left legs (70%), 20% had bradycardia, and none had tachycardia (0%). Furthermore, they had the normal ABI values in the right legs (55%), 45% had borderline ABI values, and none had ischemic and critical ischemic (0%). In addition, they had the normal ABI values in the right legs (52%), 47% had borderline ABI values, and none had ischemic and critical ischemic (0%). Most individuals with T2DM at the Kebonsari Public Health Center, Surabaya, had normal peripheral vascular status. However, few respondents had bradycardia in the Dorsalis Pedis artery pulses, and almost half had borderline ABI values.

INTRODUCTION

Degenerative non-communicable diseases (NCDs) are a global and local public health problem. The World Health Organization (WHO) in 2010 reported that Diabetes Mellitus (DM) is one of the non-communicable diseases with an increasing number of sufferers. It has attracted a lot of attention because of the expanding number of sufferers and the growing complications of diabetes, such as vascular disorders or angiopathy in the diabetic foot (Bistara *et al.*, 2020).

Poor vascularization in individuals with diabetes will worsen blood circulation due to high glucose in the blood. It results in narrowing, blockage, and poor blood circulation (Bistara *et al.*, 2022). This condition, coupled with advanced age and comorbidities (cardiovascular), can worsen blood circulation. Further, poor management of diabetic foot angiopathy can become diabetic foot ulcers (DFU). In conclusion, one of the risk factors leading to diabetic foot ulcers is peripheral vascular disease (Embuai, 2019). Thus, examining peripheral vascular status is essential to prevent DFU.

Research conducted by Norman, Davis, and Bruce in America (2016) explained the incidence of Peripheral Artery Disease (PAD) was 13.6% of the 1,294 samples. In addition, the PAD incidence in individuals with diabetes was 3.7% per year. Furthermore, a study revealed that patients with diabetes were four times more likely to lead peripheral arterial insufficiency caused by atherosclerosis (Bill and

Letter, 2019). World Health Organization (WHO) estimates there will be 21.3 million individuals with DM in Indonesia in 2030. In addition, 15% of them will experience complications of diabetic ulcers, especially DFU. Furthermore, the Surabaya District Department of Health Office in 2018 reported that 199,104 individuals with DM registered with health providers in the southern city of Surabaya (Huda and Widayanti, 2019). The preliminary study at the Kebonsari Public Health Center in Surabaya found that 5 of 7 individuals with type 2 diabetes mellitus (T2DM) had foot ischemia.

Disorders of blood vessels in type 2 diabetes can occur in macrovascular (macroangiopathy) & microvascular (microangiopathy). Macroangiopathic disorders are associated with atherosclerosis causing the narrowing of large and medium arteries in the lower legs and feet (Ainiyah *et al.*, 2022). In addition, hypertriglyceridemia and hypercholesterolemia play a role in atherogenesis. Individuals with diabetes mellitus are the potential to have narrowing of the tibial and personal arteries between the knee and ankle. Then, the decreased supply of oxygen and nutrients causes an ischemic foot. Ischemic foot is characterized by rest pain; reduced pulse rate in the Dorsalis Pedis, tibial and popliteal arteries; and cold feet and thickened nails. Furthermore, tissue necrosis and ulcers usually begin from the tip of the foot or leg (Hikmat Permana, 2018).

In addition, microangiopathy leads to capillary thrombosis, so blood vessels become stiff (reduced relaxation). Then, the condition makes it difficult for erythrocytes to pass due to the thickening of the basement membrane. As a result, there is capillary obstruction so that the tissue becomes ischemic. Eventually, the tissue becomes necrotic and causes diabetic ulcers (Chaidir, Wahyuni, and Furkhani, 2017).

The ankle-brachial index (ABI) measurement can determine peripheral vascular disorders (Husin, Hudaja, and Kristianto, 2016). It is a non-invasive examination often used in individuals with DM and PAD to determine peripheral vascular status. Furthermore, it can assess the prognosis of the diabetic foot and follow up with appropriate wound management. An investigation conducted in China by Xu *et al.* showed a high specificity (83.3-99.0%) and high accuracy (72.1-89.2%) on the ABI (Ante Brachial Index) ≤ 0.90 in detecting vessels stenosis $\geq 50\%$ (Pebrianti, Nugraha and Platini, 2018). In addition, research reported that the sensitivity rate of ABI measurement was 95%, and its specificity was almost 100% (Hijriana and Sahara, 2020). The ABI measurement method is a simple and non-invasive procedure that makes patients feel comfortable. In addition, it only takes less than 15 minutes. Moreover, the cost is affordable. This study aims to identify the peripheral vascular status in individuals with type 2 diabetes mellitus (T2DM) at Kebonsari Public Health Centre, Surabaya.

METHOD

The research design in this study used a quantitative descriptive approach. There were 40 respondents with an accidental sampling. Inclusion criteria were individuals with T2DM treated at Kebonsari Health Center Surabaya and taking diabetic medication. The exclusion criteria were individuals with foot ulcers. The data collection was carried out for four weeks, from May to June 2020. The research instrument was an observation sheet to record the Dorsalis Pedis artery pulse and ankle-brachial index. In addition, a digital sphygmomanometer was used to measure the Dorsalis Pedis artery pulse. The classification of Dorsalis Pedis artery pulse is tachycardia (pulse rate >100x/minute), bradycardia (pulse rate <60x/minute), and normal (pulse rate 60-100x/minute). The ankle-brachial index (ABI) test was measured by counting the right and left Dorsal Pedis arteries' systolic divided by the right and left brachial arteries' systolic. The interpretation of ABI is critical ischemia (score <0.4), severe ischemia (score <0.5), borderline (score 0.6 –0.8), and normal (score ≥0.9 – 1.3). The ethical clearance of this research was carried out at Sekolah Tinggi Ilmu Kesehatan Hang Tuah Surabaya with certificate number PE/30/VI/2020/KEPK/SHT.

RESULT

Most respondents were female (55%), 49-55 years old (47.5%), and housewives (40%). In addition, they graduated from Senior High School (50%). Furthermore, they did regular checkups with healthcare providers (77.5%) and performed foot care and diabetic foot exercise (75%) (Table 1).

Table 1 Characteristics of Respondents in Individuals with Type 2 DM at the Kebonsari Public Health Surabaya from May to June 2020 (n=40)

Characteristics of Respondent		Total	Percentage
Sex	Male	18	45 %
	Female	22	55 %
Age	49 – 55 years	10	47.5 %
	56 – 61 years	23	40 %
	62 – 67 years	12	12.5 %
Education	Elementary School	11	13 %
	Junior High School	7	30 %
	Senior High School	21	50 %
	University	2	5 %
Occupation	Labor	7	17.5%
	Housewife	16	40%
	Government Employees	3	7.5%
	Retired	1	2.5%
	Private Employees	13	32.5%
Regular checkups with healthcare providers	Yes	31	77.5 %
	No	9	22.5%
Foot care and diabetic foot exercises	Yes	30	75 %
	No	10	25 %

Table 2 shows that of 40 respondents, most have the normal Dorsalis Pedis artery pulse in the right legs (80%), 20% have bradycardia, and none have tachycardia (0%). In addition, most respondents have the normal Dorsalis Pedis artery pulse in the left leg (70%), 20% have bradycardia, and none have tachycardia (0%).

Table 2 Dorsalis Pedis artery pulse in Individuals with Type 2 DM at the Kebonsari Public Health Surabaya from May to June 2020 (n=40)

Pulse Rate	Right Leg		Left Leg	
	Frequency	Percentage	Frequency	Percentage
Normal (60-100)	32	80%	28	70%
bradycardia (<60)	8	20%	12	30%
Tachycardia (>100)	0	0%	0	0%
Total	40	100%	40	100%

Table 3 indicates that of 40 respondents, most have the normal ankle-brachial index in the right legs (55%), 45% have borderline ABI values, and none have ischemic and critical ischemic (0%). In addition, most respondents have the normal ankle-brachial index in the right legs (52%), 47% have borderline ABI values, and none have ischemic and critical ischemic (0%).

Table 3. Ankle Brachial Index in Individuals with Type 2 DM at the Kebonsari Public Health Surabaya from May to June 2020 (n=40)

Ankle Brachial Index	Right Leg		Left Leg	
	Total	Percentage	Total	Percentage
Normal	22	55%	21	52%
Borderline	18	45%	19	47%
Ischemic	0	0%	0	0%
Critical Ischemic	0	0%	0	0%
Total	40	100%	40	100%

DISCUSSION

This study found that most respondents had normal Dorsalis Pedis artery pulses in the right and left legs (Table 2). It may be because most of them did regular checkups with healthcare providers and performed foot care and diabetic foot exercises (Table 1). Foot care and diabetic foot exercises can help increase sensitivity and improve glycemic control by increasing pressure in the arteries. It can cause the widening of the arterial walls and pressure of peripheral blood vessels in the vascular channels of the feet (Santosa and Widi Rusmono, 2016). In addition, it reduces the plaques in the blood vessels due to atherosclerosis or others. So that blood circulation becomes smoother and the Dorsalis Pedis pulse becomes stronger (Arif, 2018). A previous study showed that foot exercise could increase the Dorsalis Pedis pulse in individuals with type 2 diabetes. The study indicated that the mean pulse rate before the intervention was 72,058 times/minute and 79,647 times/minute after the intervention (Arif, 2018). Furthermore, regular checkups help control the pulse frequency within the normal range. It includes pulse frequency, blood

pressure, blood sugar examinations, and other tests for individuals with diabetes. Furthermore, it can early detect diabetes complications (Bistara, Zahroh and Wardani, 2019).

However, few respondents had bradycardia in the Dorsalis Pedis artery pulses in the right and left legs (Table 2). It may be because a few did not do foot care and diabetic foot exercises (Table 1). Individuals with diabetes who do not perform foot care and diabetic foot exercise potentially decrease blood flow to the legs due to continuous hyperglycemia. As a result, hyperglycemia can damage blood vessels and nerves. In addition, it can thicken the blood flows in blood vessels, resulting in decreased blood flow to the feet' skin and nerves (D. d. A. Y. Handaya, 2016). Bradycardia in uncontrolled diabetes can lead to diabetic retinopathy, heart disease, and nerve damage. It also can cause diabetic foot ulcers. Furthermore, 15% of diabetes incidences develop into diabetic foot ulcers within five years (Huda, 2017).

Almost half respondents in this paper were 49-55 years (Table.1). According to the Ministry of Health Republic of Indonesia, the age is classified as early elderly. As age increases, the recurrence rate of diabetic foot ulcers increases by 70%. It is because insulin resistance increases with advancing age. Insulin resistance contributes to decreased muscle mass (sarcopenia), overweight, reduced physical activity, and decreased pancreas function (Sujana, 2019).

According to Eva Decroli (2019), the duration of diabetes mellitus predisposes blood circulation disorders (angiopathy). It occurs because individuals who have had diabetes for years' experience narrowing or blockage of blood vessels, especially in the lower extremities, because of blood viscosity due to high blood glucose levels. Hyperglycemia affects the flexibility of red blood cells to release oxygen so that there is decreased oxygen supply. As a result, peripheral hypoxia causes ineffective peripheral tissue perfusion. Inadequate peripheral tissue perfusion can be characterized by weak pulse, changes in motor function, differences in skin characteristics, CRT filling time > 3 seconds, the presence of extremity edema, pain, tingling, and changes in skin color to pale or cyanosis (Huda, 2017; Huda and Widayanti, 2019).

Our findings also showed that half of the respondents had a normal ankle-brachial index in the right and left legs (Table 3). It may be because most of them did regular checkups with healthcare providers and performed foot care and diabetic foot exercises (Table 1). The Kebonsari Public Health Centre has programs to prevent diabetic foot in individuals with diabetes. Normal ankle-brachial index means that blood is circulating well without any significant obstruction to the peripheral blood vessels. Thus, blood circulation adequately meets nutritional and oxygen supplies in the lower extremities. ABI evaluates foot vascularization in individuals to detect chronic complications of diabetes, one of which is diabetic foot ulcers (DFU). Furthermore, neurological abnormalities, vascular disorders, or peripheral artery disease (PAD) can cause DFU. Vascular disorders in the form of blockages in peripheral arteries can cause foot ulcers. Thus, diabetic foot ulcers are often associated with the ankle-brachial index (Dahlia *et al.*, 2019).

Diabetic foot exercise can improve circulation, especially in the foot area (Guirguis-Blake *et al.*, 2018). Foot movements performed during diabetic foot exercises are like a foot massage. The movements apply pressure and can increase endorphin secretion. The hormone reduces pain and blood vessel vasodilatation, resulting in a decrease in blood pressure, especially brachial systolic pressure, which is directly related to the ankle-brachial index (Bozkurt *et al.*, 2011). A prior investigation revealed that most respondents (71.4%) who performed diabetic foot exercises had normal ABI values (0.9 - 1) (Megawati, Utami and Jundiah, 2020). Guyton & Hall explain that foot exercise contains movements in the legs, so they can tense up the leg muscles and compress the veins around the leg muscles. The foot exercise pushes blood toward the heart and decreases venous pressure, a mechanism known as a venous pump. The mechanism will improve blood circulation in the legs (Wahyuni, 2013).

However, almost half of the individuals with T2DM in this study had a borderline value of ABI (0.6 to 0.8) (Table 3). It means perfusion changes in blood vessel walls that affect the transport of oxygen and nutrients to tissues. The intima layer thickens due to cellular proliferation and fibrosis. In addition, the fibers in the media layer are calcified, thin, and cut. So, the collagen accumulates in the intima and media layers. These changes cause blood vessel stiffness, resulting in increased peripheral vascular pressure and impaired blood flow (Aulia *et al.*, 2019).

Patients with diabetes often experience changes in the elasticity of the capillaries of blood vessels, thickening of blood vessel walls, and the formation of plaques or thrombi that cause impaired peripheral vascularization. Thus, the Ankle-Brachial Index in individuals with diabetes tends to have lower ABI values than normal (Y. Handaya, 2016). Peripheral blood flow disorders, especially in the legs, are marked by a decrease in the ABI value. It is due to atherosclerosis and lack of physical exercise (Wahyuni, 2013).

CONCLUSION

Most individuals with type 2 diabetes mellitus (T2DM) at the Kebonsari Public Health Center, Surabaya, had normal peripheral vascular status. However, few respondents had bradycardia in the Dorsalis Pedis artery pulses, and almost half had borderline ABI values. Thus, preventing peripheral blood flow disorders in the lower extremities in individuals with T2DM is crucial to prevent diabetic foot ulcers.

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Patient Satisfaction with Healthcare Services Among Inpatients in The Covid-19 Isolation Room

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A B S T R A C T

Patient care in the isolation room differs from other rooms, including strict hygiene, proper personal protective equipment, and minimal patient contact. Furthermore, this study aims to portray patient satisfaction with healthcare services among inpatients in the COVID-19 isolation room. It was a descriptive study using a retrospective descriptive methodology. The population was inpatients in the COVID-19 isolation room at Surabaya Islamic hospital for January-May 2021. In addition, the sample was 128 respondents with a total sampling method. The authors used a questionnaire portraying patient satisfaction with health care services based on reliability, assurance, tangible, empathy, and responsiveness dimensions. The data was processed descriptively in a frequency distribution table. The results showed that respondents were satisfied with the reliability dimension (the ability of doctors and nurses to explain, listen, and speed up handling complaints). In addition, they were satisfied with tangible (room facilities, cleanliness of rooms, cleanliness of beds and bathrooms); empathy (attention of doctors, the ability of nurses to motivate and communicate well); assurance (friendly and polite healthcare services, safe healthcare services, and good healthcare service), and responsiveness (fast and accurate healthcare treatments, diagnostics, and easy healthcare procedures). Thus, inpatients in the COVID-19 Isolation Room at Surabaya Islamic hospital for January-May 2021 were satisfied with healthcare services based on reliability, assurance, tangible, empathy, and responsiveness dimensions. However, the empathy dimension had the lowest score among the five dimensions. So, emotional intelligence training is essential to improve health workers' empathy for patients.

INTRODUCTION

Patient care in the isolation room differs from other rooms, including strict hygiene, proper personal protective equipment (Jaya and Syarufuddin, 2015), minimal patient contact, and food intake in isolation rooms to assist efforts for the healing and recovery of patients. Furthermore, in a study interviewing nine patients in the isolation room, six said that nurses tended to be less cooperative and less interactive (Lely and Suryati, 2018). Thus, this condition can influence the hospital's Bed Occupancy Rate (BOR). Specifically, the BOR at Surabaya Islamic hospital in 2013 was 78%, which is still far from the ideal hospital target of 85% (Izza, Setianto, and Dhamanti, 2021).

A survey in 2019 among patients in inpatient care showed their level of patient satisfaction with the soft skill aspect of nurses was 80.03%. The elements included the speed of nurses in assisting patients, giving information, the appearance of the nurse, and hospital food services (Mardijanto, Astutik, and Budiman, 2020). Other aspects that were still lacking included the attitude of the medical staff, patient food delivery errors, meal frequency and timing (Kusuma, Suryoko, and Budiatmo, 2018), ward atmosphere, and food

taste. Thus, nurses' ability in various aspects of patient services still needs improvement (Nahriyah, 2016).

Customer service is one indicator of service quality to attract customers (Widya Astari, Noviantani, and Simanjuntak, 2021). Low satisfaction will cause companies, in this term hospitals, to decline. Patients feel satisfied when health workers can fulfill their needs, desires, or expectations. A study regarding patient satisfaction among 2000 inpatients in hospitals in East Java found that 17% were satisfied with hospital service quality, while 83% were not. The study also provided information that the complaints of the patient were the lack of communication (80%), attention (66.7%), and friendliness (33.3%) in nurses (Agustina and Sakawati, 2020).

Every citizen has the right to obtain Minimum Service Standards (MSS). MSS's provisions regarding the type and quality of services are regulated by the government (Ariska and Handayani, 2019). Based on Government Regulation Number 2 of 2018 concerning Minimum Service Standards, the standard of customer satisfaction is 90%. However, the average customer satisfaction in the isolation room was still relatively below the minimum service standard (Pangerapan D, 2018). The quality of health services should be efficient and effective. It focuses on the needs and expectations of patients, a code of ethics, health service standards, and scientific developments. Thus, it can achieve optimal health degrees (Irawan *et al.*, 2022).

The COVID-19 pandemic affects the health service sector. Healthcare systems and facilities must adapt to the COVID-19 health protocol in healthcare services to prevent transmission to patients, health workers, and individuals in the hospital environment. Thus, hospitals must perform the protocols, especially during the CARE (Community Activity Restriction Enforcement) period (Chriswardani *et al.*, 2016). During the COVID-19 pandemic, health workers actively participate in health services. They have higher workloads and longer work time (Naldi *et al.*, 2021), are too often in contact with patients, and have changes in working hours (White *et al.*, 2020). Thus, It results in higher levels of stress and burnout experienced by health workers (Irawan *et al.*, 2022). There is concern that it could reduce the quality of health services to patients, impacting the quality of hospital services. Thus, this study aims to portray patient satisfaction with healthcare services among inpatients in the COVID-19 Isolation Room.

METHOD

This paper was a descriptive study, objectively describing the quality of the situation using a retrospective descriptive methodology. The population was inpatients in the COVID-19 isolation room at Surabaya Islamic hospital for January-May 2021. In addition, the sample was 128 respondents with a total sampling method. The inclusion criteria were conscious, not paralyzed, and good eyesight patients; the patient was first treated in the COVID-19 isolation room. The authors used a questionnaire portraying patient

satisfaction with health care services based on reliability, assurance, tangible, empathy, and responsiveness dimensions. The categorization of patient satisfaction was based on Government Regulation Num. 2 of 2018 concerning Minimum Service Standards; the standard of customer satisfaction is 90%. Data was collected using Google Forms and stored in Excel. The data was processed descriptively in a frequency distribution table. This study obtained ethical feasibility from the Health Research Ethics Committee Faculty of Public Health Universitas Airlangga, with certificate number 133/EA/KEPK/2022.

RESULT

Most respondents in this paper were male (61.7%). In addition, they were 46 - 55 years old (26.6%) (Table 1).

Table 1. Characteristics of Respondents

Characteristics of Respondents	Frequency	Percentage
Gender		
Male	79	61.7%
Female	49	38.3%
Age		
< 25 Years	15	11.7%
25 - 35 Years	27	21.1%
36 - 45 Years	31	24.2%
46 - 55 Years	34	26.6%
> 55 Years	21	16.4%

Respondents were satisfied with the reliability dimension. Furthermore, they had good patient satisfaction with the communication and speed of healthcare service by doctors and nurses. However, doctors' communication got the lowest mean score of these four components, so it needs to be improved (Table 2).

Table 2. Patient Satisfaction with Health Care Services based on Reliability Dimension

Reliability Dimension	Mean Score	Percentage
The doctors provide an informative explanation regarding the action	4.5	90.2%
The nurses listened to the patient's complaints well	4.8	95.3%
The speed of nurses in providing nursing care to patients	4.6	92.3%
The speed of doctors in handling complaints	4.6	91.1%
Overall	4.6	92.2%

Respondents were satisfied with the assurance dimension. Furthermore, they had good patient satisfaction with doctors' and nurses' friendly and polite manner while providing health care services. Thus, they felt safe and comfortable (Table 3).

Table 3 Patient Satisfaction with Health Care Services based on Assurance Dimension

Assurance Dimension	Mean Score	Percentage
Doctors provide health care services in a friendly and polite manner	4.6	91.6%
Nurses provide health care services in a friendly and Polite manner	4.8	96.4%
Patients feel safe with the health care services given by doctors and nurses	4.7	93.6%
Nurses provide good nursing care so that patients feel comfortable	4.8	95.2%
Overall	4.7	94.2%

Respondents were satisfied with the tangible dimension. Furthermore, they had good patient satisfaction with room facilities, room cleanliness and tidiness, bed cleanliness, clean water, and bathroom. However, the availability of clean water and the bathroom condition got the lowest mean score of these four components (Table 4).

Table 4. Patient Satisfaction with Health Care Services based on Tangible Dimension

Tangible Dimension	Mean Score	Percentage
Room Facilities	4.7	93.3%
Room cleanliness and tidiness	4.7	93.9%
Bed cleanliness	4.6	91.3%
Clean water and bathroom	4.5	90.0%
Overall	4.6	92.1%

Respondents were satisfied with the empathy dimension. Furthermore, they had good patient satisfaction when the doctors reduced patient anxiety about the disease, nurses comforted and motivated patients, also nurses communicated well with the patients. However, respondents were unsatisfied with the doctors' attention to each patient (Table 5).

Table 5. Patient Satisfaction with Health Care Services based on Empathy Dimension

Empathy Dimension	Mean Score	Percentage
Doctors pay attention to each patient	4.4	88.8%
Doctors reduce patient anxiety about the disease	4.5	90.0%
Nurses comfort and motivate the patients	4.7	94.2%
Nurses communicate well with patients	4.5	90.0%
Overall	4.5	90.7%

Respondents were satisfied with the responsiveness dimension. Furthermore, they had good patient satisfaction when nurses fulfilled their needs. In addition, they were pleased with fast and accurate healthcare treatments and diagnostics, also easy healthcare procedures (Table 6).

Table 6. Patient Satisfaction with Health Care Services based on Responsiveness Dimension

Responsiveness Dimension	Mean Score	Percentage
Nurses fulfilling patients' needs	4.6	92.8%
Fast and accurate healthcare diagnostics	4.6	92.7%
Fast and accurate healthcare treatments	4.6	92.7%
Easy and uncomplicated healthcare procedures	4.6	92.5%
Overall	4.6	92.7%

DISCUSSION

Customer satisfaction, exceptionally patient satisfaction, is one of the metrics used to assess a company's or hospital's viability. The more satisfied customers or patients are with the products or healthcare services, the better the business development will be. Therefore, it is not surprising that customer or patient satisfaction always gets special attention when formulating a business strategy. Service quality is composed of several elements, so customer satisfaction has dimensions. Many theories relate to service quality and customer satisfaction. Parasuraman spawned the idea of the SERVQUAL dimension. The SERVQUAL dimension is a dimension to measure service quality (Mustika and Sari, 2019). It can assess

the gap between customer expectations and customer satisfaction with the service they receive (Karmila *et al.*, 2021).

Our findings found that respondents were satisfied with the tangible dimension (Table 4). Tangible is the ability of hospitals in concrete things to provide the best service for customers (Muhammad Risya Rizki, 2018). It can be seen and felt directly by the patients. Several facilities related to tangibles are (1) sufficient room facilities, (2) clean and tidy rooms, (3) clean beds, and (4) clean water and bathroom (Mardijanto, Astutik, and Budiman, 2020). This study revealed that inpatients in the COVID-19 isolation room had good patient satisfaction with room facilities, room cleanliness and tidiness, bed cleanliness, clean water, and bathroom. However, the availability of clean water and the bathroom condition got the lowest mean score of these four components (Table 4).

In addition, this research showed respondents were satisfied with the reliable dimension (Table 2). Reliability means that in providing services, every employee must have the ability in knowledge, expertise, independence, mastery, and high professionalism. So it results in satisfactory service without complaints (Sagala and Marbun, 2022). Reliability is the company's ability to provide services for customers. If tangibles are about concrete things, reliability is arguably more abstract because reliability is directly related to consumer expectations. Reliability in health care services includes (1) The doctor providing an informative explanation regarding the action, (2) The nurse listening to the patient's complaints well, (3) The speed of nurses in providing nursing care to patients, (4) The speed of doctors in handling complaints (Izza, Setianto and Dhamanti, 2021). This study revealed that inpatients in the COVID-19 isolation room had good patient satisfaction with the communication and speed of healthcare service by doctors and nurses. However, doctors' communication got the lowest mean score of these four components (Table.2)

Furthermore, this paper indicated that respondents were satisfied with the responsiveness dimension (Table 6). Responsiveness is how the company provides services responsive to all customers' desires and demands (Meliala, 2018). Its reflection is when employees explain unknown services so the community can understand them. Thus, a wise, detailed explanation of organizational procedures and work mechanisms is crucial so that the services can get a positive response from customers. In general, responsiveness contains a coherent delivery but is still easy to understand. Responsiveness in healthcare services includes (1) Nurses fulfilling patients' needs, (2) Fast and accurate healthcare diagnostics, (3) Fast and accurate healthcare treatments, and (4) Easy and uncomplicated healthcare procedures. This study revealed that inpatients in the COVID-19 isolation room had good patient satisfaction when nurses fulfilled their needs. In addition, they were pleased with fast and accurate healthcare treatments, diagnostics, and easy healthcare procedures (Table 6).

Every service requires certainty. It is obtained when employees can provide guaranteed services so that the community can receive satisfactory services (Muhammad Risya Rizki, 2018). Assurance is related to the certainty that customers get from the behavior of business actors. Respondents in this investigation were satisfied with the assurance dimension (Table 3). Assurance reflects good communication and a polite attitude toward customers. It increases customer trust in services. Assurance in healthcare services includes (1) Doctors providing health care services in a friendly and polite manner, (2) Nurses providing health care services in a friendly and polite manner, (3) Patients feeling safe with the health care services given by doctors and nurses, and (4) Nurses provide good nursing care so that patients feel comfortable. This study revealed that inpatients in the COVID-19 isolation room had good patient satisfaction with doctors' and nurses' friendly and polite manner while providing health care services. Thus, they felt safe and comfortable (Table 3).

Service will run smoothly and be qualified when the service provider has a sense of empathy and commitment to service (Widya Astari, Noviantani, and Simanjuntak, 2021; Irawan *et al.*, 2022). Empathy is related to customer satisfaction. Respondents in this paper were satisfied with the empathy dimension (Table 5). Empathy is closely associated with sincerity and attention to each customer. Specifically, it will help health workers know patients' needs and want. Empathy in health care services includes (1) Doctors paying attention to each patient, (2) Doctors reducing patient anxiety about the disease, (3) Nurses comforting and motivating the patients, and (4) Nurses communicating well with patients (Agustina and Sakawati, 2020). This study revealed that inpatients in the COVID-19 isolation room had good patient satisfaction when the doctors reduced patient anxiety about the disease, nurses comforted and motivated patients, also nurses communicated well with the patients. However, respondents were unsatisfied with the doctors' attention to each patient (Table 5).

Health workers can identify patients' demands and desires by assessing the five dimensions of customer satisfaction. Thus, it can improve the quality of healthcare services. Health workers should not hesitate to ask for patients' feedback regarding their satisfaction with their healthcare services as an evaluation. In addition, it can make patients feel closer to health workers (Pangerapan D, 2018).

CONCLUSION

Inpatients in the COVID-19 Isolation Room at Surabaya Islamic hospital for January-May 2021 were satisfied with healthcare services based on reliability, assurance, tangible, empathy, and responsiveness dimensions. Therefore, health workers must maintain the quality of healthcare services. However, the empathy dimension had the lowest score among the five dimensions. Thus, emotional intelligence training is essential to improve health workers' empathy for patients. In addition, enhancing the ability and quality

of nursing services, applying a code of ethics and professional service standards, and respecting patients' rights are crucial.

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The Relationship of Education Level and Economic Status with The Use of Scraping on The Elderly Based on Transcultural Nursing

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A B S T R A C T

Complementary nursing and alternative medicine have been widely used by the community, one of which is scrapings. Scrapings are believed to be effective in curing symptoms of unwell in the elderly because the method is easy. It also does not require a lot of money. However, the impact of using scrapings that are carried out continuously will cause an addiction effect. Efforts to improve the health status of the elderly can be influenced by various factors, including cultural and social culture. This study aims to determine the relationship between education level and economic status with the use of scrapings on the elderly. This study employed a correlation design with a retrospective approach and observational analysis with quantitative methods. The population in this study were all the elderly in the village of Prambon Tergayang, Soko District, Tuban Regency, as many as 68 people. The sample in this study was 42 elderly who were willing to become respondents. The result showed a relationship between educational factors and the use of scrapings by the elderly. The Spearman Rho statistical test showed the p-value = 0.007. There was no relationship between economic factors and the use of scrapings by the elderly (p-value = 0.071). Research examining the effect of scrapings on the health of the elderly can be focused on as a topic for future research.

INTRODUCTION

Complementary nursing and alternative medicine have been widely used by the community, one of which is scrapings. According to the National Center of Complementary and Alternative Medicine, complementary and alternative therapies are treatments that consist of various medical practices and products that are not part of conventional medicine (Indriani, 2019). The World Health Organization (WHO) states that 75-80% of the world's population has undergone non-conventional treatment. Non-conventional treatment is a treatment that can use traditional methods such as scrapings. The minister of health of republic Indonesia explained that traditional medicine is one of the efforts to treat other ways outside of medicine and or nursing, which are widely used by the community in overcoming health problems (RI, 2003). In Asia, the use of conventional medicine is also in great demand. Several countries such as Vietnam, China, Cambodia, and Indonesia have almost the same conventional treatment, one of which is scraping, as it is called in Indonesia. In Vietnam, they call scraps Cao Gio, Cambodia calls them Goh Kyol, and in China, they call scraps Gua Sha but the Chinese use jade as a scraping tool (Triratnawati, 2010).

According to Efendi and Makhfudli (2009) scraping is a traditional method of pressing and sliding a blunt object such as a coin or spoon repeatedly on the skin's surface until a red patch appears. The survey results on research by Didik (2004), 390 respondents in the city of Solo, showed that 87% had done

scrapings, and 64% believed scrapings were very useful for colds and muscle pain. According to research conducted by Suryani and Sianturi (2013), scrapings are believed to be effective in curing symptoms of unwell in the elderly who experience physical changes as an effort to handle when they are not feeling well because the method is easy, effective, and does not require much money. However, using scrapings that are carried out continuously will cause an addiction effect so that existing health services are not used effectively by the elderly. Only now, scraping is a treatment method that has yet to have a specific policy regarding its use, although studies show that scrapings do not have a severe impact. However, using scrapings on the elderly will pose a risk to health due to physiological changes (Supadmi, 2013).

According to the World Health Organization (WHO), in 2020, the world's population aged 60 years and over will reach 900 million people. In Southeast Asia, the elderly population is 8% or around 142 million people. The number of older people in Indonesia in 2017 reached 269.9 million people, equivalent to 10.6% of the entire population of Indonesia, with the first largest number of older adults in DI Yogyakarta Province, which was 13.69%, the second Central Java Province was 12.05%, and the three East Java Provinces amounted to 11.80%. Data on the number of older adults in Surabaya in 2019 was 219,164 people (Kementerian Kesehatan Republik Indonesia, 2018). According to the East Java Population Profile (2020), the percentage of older adults in East Java has reached 5,183,447 people, or 13.06% of the total population of East Java. This figure tends to increase compared to the previous year, which was 12.64%. This shows that East Java is an area with a population structure towards an aging population. It was also stated that the highest elderly population in East Java province based on the highest order was in the Regencies of Magetan, Pacitan, Ponorogo, and Lamongan, followed by Tuban.

Efforts to improve the health status of the elderly can be influenced by various factors, including cultural and social culture. This is in accordance with the transcultural nursing theory by Leininger and R McFarland (2002), which examines nursing care based on cultural similarities and differences. The dimensions of the cultural and social structure in theory proposed by Leininger include economic and educational factors. An ethnographic study by Suryani and Sianturi (2013) showed that economic and cultural factors influenced the selection of scrapings to treat colds in a farming community in Sleman Yogyakarta. In a study conducted by Permasatasari, L. I., Lukman, M., (2014), there are several differences in the determinant factors that influence the search for traditional medicine by the Cengkareng community, including predisposing factors (age, gender, number of family members, economic status, ethnicity, religion, value of health and illness and level of education), supporting factors (health service rates), and the needs of the Cengkareng community.

In a preliminary study conducted by researchers in the elderly village of Prambon Tergayang, Soko District, Tuban Regency, on May 22, 2020, there were 9 out of 10 older adults who used scrapings as the main treatment for unwell conditions such as fever, muscle aches, aches, chills, nausea, dizziness, and

flatulence. In this case, factors related to using scrapings on the elderly still need to be investigated. Based on this, the researcher is interested in conducting a study entitled "The Relationship between Education Level and Economic Status with the Utilization of Scrapings in the Elderly Based on Transcultural Nursing in Prambon Soko Village, Kab. Tuban".

METHOD

This study employed a correlation design with a retrospective approach and observational analysis with quantitative methods. This study uses a quantitative type of research using a Cross-Sectional approach (Relationships and Associations) that emphasizes the time of measurement or observation of independent and dependent variable data only once a time. The population in this study were all the elderly in the village of Prambon Tergayang, Soko District, Tuban Regency, as many as 68 people. The sample in this study was 42 older adults in the village of Prambon Tergayang, Soko District, Tuban Regency, who were willing to be respondents. The sampling method used in this study is a non-probability sampling type, namely purposive sampling. This research was conducted in the village of Prambon Tergayang, Soko District, Tuban Regency. The collecting and processing of data used an instrument, namely the education and economics questionnaire. Data management is done using a scoring technique. Then the scoring data was analyzed to see the relationship between the problems discussed using the Pearson correlation test.

RESULT

This study's demographic characteristics described respondents' characteristics, including gender, age, occupation, religion, and ethnicity.

Table 1 The Characteristics of respondent in Prambon Tergayang Village, Soko Tuban District (N=42).

Characteristic	Total (Σ)	Percentage (%)
Gender		
Male	19	45
Female	23	55
Age		
60 -70 years old	14	33
71-80 years old	28	67
>80 years old	0	0
Occupation		
Pensionary	5	12
Private employees	6	14
Merchant	6	14
Unemployment	25	60
Religion		
Islam	42	100
Ethnic		
Javanese	42	100

Table 1 shows that of the 42 respondents, more than half were female, with 23 respondents (55%). More than half of the respondents were 71-80 years old (67%, n=28). The respondents' occupation was mainly

unemployment (60%, n=25). Based on table 5.1, all respondents were Islam (100%), and all were Javanese (100%).

The education level of the elderly

Table 2 Distribution of Respondents' Characteristics based on the education level of the elderly in Prambon Tergayang Village, Soko Tuban District.

Education Level	Frequency	Percentage (%)
High	6	14
Medium	11	26
Low	25	60
Total	42	100

Table 2 shows, the most of respondents had low educational level (60%, n=25).

The economic status of the elderly

Table 3 Distribution of Respondents' Characteristics based on the economic status of the elderly in Prambon Tergayang Village, Soko Tuban District.

Economic Status	Frequency	Percentage (%)
Low	25	59,5
High	17	40,5
Total	42	100

Table 3 shows that from 42 respondents, more than some respondents have a low economic status (59.5%, n=59.5).

The use of scraping on elderly

Table 4 Distribution of Characteristics of Respondents based on the use of scrapings by the elderly in Prambon Tergayang Village, Soko Tuban District.

No	Use of scraps	Frequency	Percentage
1	High frequencies	26	62
2	Medium frequencies	7	16
3	Low frequencies	9	22
	Total	42	100

Based on the table 4, it shows that from 42 respondents, more than half respondents used scrapings (62%, n=26).

The Relationship between Education Level and The Use of Scraping

Table 5 Cross Distribution of Relationship between Education Level and The Use of Scraping in the Elderly in Prambon Tergayang Village, Soko Tuban District.

Education Level	Use of scraps						Total	
	Low		Medium		High		n	%
	n	%	n	%	n	%		
High	2	5	2	5	3	7	6	14
Medium	1	2,3	2	5	9	22	11	26
Low	6	14,7	3	6	14	33	25	60
Total	9	22	7	16	26	62	42	100

Spearman *Rho Test* $\rho = 0,007$ $r = 0,472$

Based on table 5, six respondents (14.7%) indicated a low level of education and low-frequency use of scrapings. Three respondents (6%) have a low level of education while using scrapings shows a moderate

frequency. Fourteen respondents (33%) had a low level of education, while the use of scrapings showed a high frequency.

There was a respondent (2.3%) who had a medium and low level of education in using scrapings, two respondents (5%) having a moderate level of education and a moderate frequency of using scrapings, and most respondents (22%, n=9) have an education level. and followed by a high frequency of scrapings.

Then, two respondents (5%) have a high level of education, but the frequency of scraping is low. Two other respondents (5%) have a high level of education and a moderate frequency of scraping, and six respondents (14%) have a high level of education and frequency of scraping. Analysis using Spearman Rho statistical test $p=0.007$ ($p=$ value <0.05). These results indicate that Hypothesis 1 is accepted. There is a relationship between the level of education and the use of scrapings on the elderly. The value of $r = 0.472$. It can be interpreted as a strong and positive relationship between the level of education and scrapings on the elderly.

The Relationship between Economic Level and Utilization of Scraps

Table 6 Cross Distribution of Relationship between Economic Status and The Use of Scraping in the Elderly in Prambon Tergayang Village, Soko Tuban District

Economic Status	Use of scrapings						Total	
	Low		Medium		High		n	%
	n	%	n	%	n	%		
Low	4	9,9	6	14	15	36	25	59,5
High	5	12,1	1	2	11	26	17	40,5
Total	9	22	7	16	26	62	42	100

Spearman *Rho Test* $\rho = 0,071$ $r = -0,09$

Based on table 6, four respondents (9.9%) had low economic status and scraping frequency. Six other respondents (14%) had low economic status, but the frequency of scrapings is in the moderate category. A total of 15 respondents (36%) had low economic status, but the frequency of scrapings is in the high category.

Then, five respondents (12.1%) had high economic status but low use of scrapings. One respondent (2%) had a high economic status but was low in the use of scrapings, and the remaining respondents (26%, n=11) had high economic status and were followed by a high frequency of scrapings.

Analysis using Spearman Rho statistical test obtained $p = 0.071$ ($p=$ value <0.05). These results show that H1 is rejected, meaning there is no relationship between economic factors and the use of scrapings on the elderly. The value of $r = -0.09$ can be interpreted as having no significant relationship between economic factors and the use of scrapings on the elderly.

DISCUSSION

The Relationship of Education Level with Scraping Utilization in the Elderly

The results showed a relationship between educational factors and the use of scrapings on the elderly. This is in line with Sari and Prastianty research (2017), which states that the educational factor is significant for the Jambi Malay tribe with education or knowledge of various experiences in overcoming a health problem.

Leininger and R McFarland (2002), suggests that health behavior is shaped by various factors that work together. The higher an individual's education, the individual's belief can be supported by scientific evidence that is rational and can adapt to a culture that is in accordance with his health condition. According to Nugroho (2000), the higher the individual's education is expected to be able to carry out something important for himself and their community.

The category of 'moderate education level' in this research was the respondents who graduated from junior high school or equivalent also respondents who graduated from high school or equivalent. The results show that 31 respondents graduated from junior high school or the equivalent, and 16 graduated from high school or the equivalent. Respondent code no.1 has a high education level: he graduated from college but still uses scrapings to help relieve unwell feelings. According to Mubarak and Chayatin, (2009), the level of education can affect awareness of the importance of health for oneself and the environment, which can encourage the need for health services. The elderly with higher formal education will have higher knowledge than the elderly with lower education levels. Supardi, Jamal and Loupatty (2012), stated that the number of educated people who did not finish high school/equivalent was 1.17 times higher than the population who graduated from high school/equivalent.

Education is one of the supporting factors in the use of scrapings. Education is not only knowledge and learning outcomes but also experiences gained from the surrounding culture and habits. People choose the treatment method of using scrapings because it is obtained from previous people's experiences and the community's habits, so using scrapings becomes a suggestion for the elderly to get rid of feeling unwell. Factors in the theory of transcultural nursing that are more strongly related to using scrapings in the elderly are technological factors, beliefs and philosophy factors, social factors and family attachments, cultural values and lifestyle factors, and prevailing policy factors.

The Relationship between Economic Level and Scraping Utilization in the Elderly

This study's results indicate no relationship between economic factors and the use of scrapings on the elderly. This study's results align with Didik (2004) which explains that a person's education level does not significantly influence treatment behavior, whether treatment uses traditional or modern, or conventional methods. Research conducted by Supardi, Jamal and Loupatty (2012), also explains that the economic level of the Indonesian population does not have a significant relationship with the use of traditional medicine or traditional medicine.

The study's results showed no relationship between the education factor and the use of scraping on the elderly. Family income can determine the health status of the family. Good family income can affect maintaining cleanliness and subsequent handling based on family income. Meanwhile, low-income families can only meet their needs in health facilities according to their abilities (Kemenkes, 2017). However, this does not apply to families with good incomes but have many family members whose living expenses are covered. According to Leininger and R McFarland (2002), people will take advantage of the material resources they have to pay for their illness to recover quickly.

The results showed that 25 respondents had low economic status and 17 had high economic status, even though they both had high scores on using scrapings. It can be said that economic factors are not related to the use of scrapings on the elderly. No matter the high or low economic status of the elderly, they still use scrapings to relieve the mild symptoms of their disease. Economic factors do not guarantee that the elderly choose a medication treatment. It is evident that even respondents with high economic status also use scrapings as a treatment method.

CONCLUSION

It can be concluded that the education factor is related to the use of scrapings by the elderly (p-value = 0.007), while the economic factor is not related (p-value = 0.071). Further research needs to be done to examine the effects of scrapings on the health of the elderly.

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Relationship Of Gestational Age With Hyper Bilirubin Incidence In 3 Days Neonates At Dustira Cimahi Hospital

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A B S T R A C T

One of the most typical clinical manifestations of the infant is hyperbilirubinemia. Jaundice sends more than 85% of term newborns back to the hospital within the first week of life. 60% of term newborns and 80% of preterm (less term) infants have hyperbilirubinemia. If hyper bilirubin is not appropriately treated, it can damage brain cells, cause seizures, and progress to kernicterus, even causing death. Even if the newborn gets kernicterus and recovers and can be passed, the baby can grow but not develop optimally and can even cause long-term effects such as mental impairment. This type of research is analytical research. This study was an observational study that related two variables: namely, the relationship between gestational age and the incidence of hyperbilirubinemia in neonates aged three days. The type of approach in this research is cross-sectional. Sampling was done using a purposive sampling technique with as many as 286 samples. The median gestational age for neonates with hyperbilirubinemia at Dustira Cimahi Hospital in 2021 was 36 weeks, still considered preterm, with a minimum gestational age of 30 weeks and a maximum of 43 weeks. The median bilirubin level in neonates with hyperbilirubinemia at Dustira Cimahi Hospital in 2021 was 10 mg/dL which was still classified as physiological hyper bilirubin, with a minimum level of 5.52 mg/dL and a maximum level of 16.03 mg/dL. There was a significant relationship between gestational age and the incidence of hyperbilirubinemia in neonates aged 3 days at Dustira Cimahi Hospital in 2021 with moderate strength and negative correlation direction.

INTRODUCTION

Hyperbilirubinemia is one of the most common clinical phenomena found in newborns. More than 85% of term infants return to the hospital for jaundice within the first week of life. Hyperbilirubinemia occurs in 80% of preterm (less term) infants and 60% of term (term) infants. This situation will cause the dominance of unconjugated bilirubin in the blood. In some infants, unconjugated bilirubin is a normal transition state, but in some infants, an excessive increase in bilirubin can potentially be toxic and cause death. Therefore, baby who experiences jaundice must be distinguished, whether physiologically or pathologically. The activity benefit for appropriate treatment can be given (Kosim *et al.*, 2014). Hyper bilirubin, if not appropriately treated, can damage brain cells, cause seizures, and develop into kernicterus, even causing death. If kernicterus can be passed, the baby can grow but not develop and can even cause long-term effects, namely mental retardation (mental retardation) (Indonesia, 2015).

In Indonesia, in 2009, there were 80,000 children with mental retardation, which increased until 2015 from 0.69% to 2.45% of the total number of children in Indonesia (Indonesia, 2017). According to the West Java Health Profile (2017), there were 5,215 children with mental retardation with various

etiologies. The biological factor is the cause of mental retardation in West Java (15%), one of which is kernicterus.

Inappropriate treatment in Hyperbilirubinemia neonates can lead to kernicterus. Kernicterus can harm the brain and cause long-term effects. The long-term effects include mental retardation (mental retardation), cerebral paralysis (abnormal muscle control, cerebral palsy), deafness and immobility of the eyes, and even death. This long-term effect can be prevented by fast and appropriate treatment so that it will not develop into kernicterus. Prevention can also be done from the antenatal period with antenatal monitoring and examination according to standards so that one of the factors causing hyperbilirubinemia, namely preterm labor, can be prevented. Dustira Cimahi Hospital is the most prominent type B referral hospital in the City and Regency of Bandung, so many referrals come both at the time of delivery and during the neonatal period. The incidence of hyperbilirubinemia in neonates at Dustira Hospital Cimahi has been relatively high for the last three years occupying the second position of the four most problems with sick babies. This study objective was to determine the relationship between gestational age and the incidence of hyperbilirubinemia in neonates aged three days at Dustira Cimahi Hospital.

METHOD

This type of research is analytical research. This observational study relates two variables: the relationship between gestational age and the incidence of hyperbilirubinemia in neonates aged three days. The type of approach in this research is cross-sectional. The independent variable in this study was gestational age. The dependent variable was the incidence of hyperbilirubinemia in neonates aged three days. Gestational age is a medical record regarding gestational age/gestational age at delivery calculated from the first day of the last menstruation (LMP). At the same time, bilirubin level is a medical record ng the results of laboratory examinations in infants aged three days with bilirubin levels >5 mg/dL.

The population in this study were all infants with hyperbilirubinemia with bilirubin levels of more than 5 mg/dL at Dustira Cimahi Hospital in 2021, with as many as 400 infants. The samples in this study were all infants aged three days with hyperbilirubinemia. Laboratory tests for bilirubin levels were carried out, with the results of bilirubin levels being more than 5 mg/dL at Dustira Cimahi Hospital in 2021, totaling 286 babies. The procedure of this study was taken from secondary data from medical records of neonates aged three days in the perinatology room of the Bandung City Hospital on November 1 to 5, 2021. The procedure was to take data from the patient's medical record, beginning with asking permission to conduct research at Dustira Cimahi Hospital and the medical record unit. Furthermore, an explanation of the aims and objectives of the stand ends with recording the measurement results on the research sheet form.

This study aims to describe the frequency distribution of gestational age and the incidence of hyperbilirubinemia in neonates aged three days at Dustira Cimahi Hospital in 2021. This study will describe numerically with a ratio scale. In this study, after the normality test, the data distribution was not normal, so the univariate analysis used was the median for the measure of concentration and the minimum maximum for the size of the spread. In this study, the statistical test used was the Spearman test because the normality test results showed that the data distribution was not normal.

RESULT

This section describes the study results at Dustira Cimahi Hospital in December 2021. This study identifies the relationship between gestational age and the incidence of hyperbilirubinemia. The sample was 286 neonates aged three days using a Cross-Sectional design and purposive sampling technique. After the data is processed and analyzed, the data can be presented as follows:

Univariate Analysis:

Table 1. Frequency Distribution of Gestational Age in Neonates with Hyperbilirubin at Dustira Cimahi Hospital in 2021

	Median (Minimum-Maximum)
Gestational Age	36 (30-42)

In the table above, it can be explained that the median gestational age of neonates with hyperbilirubinemia is 36 weeks, with a minimum age of 30 weeks and a maximum of 42 weeks.

Table 2. Frequency Distribution of Bilirubin Levels in Neonates with Hyperbilirubinemia at Dustira Cimahi Hospital in 2021

	Median (Minimum-Maximum)
Bilirubin Level	10,00 (5,52-16,03)

In the table above, it can be explained that the median bilirubin level of neonates with hyperbilirubinemia is 10 mg/dL with a minimum level of 5.52 mg/dL and a maximum level of 16.03 mg/dL. The result means that it is still classified into the physiological hyperbilirubin.

Bivariate Analysis:

Table 3. Results of the Spearman Correlation Analysis of the Relationship between Gestational Age and the Incidence of Hyper bilirubin

	Hyper bilirubin
Gestational Age	r = - 0,493 p= < 0,001 n = 286

Table 3 shows that the p-value < 0.001, which means that there is a significant correlation between gestational age and the incidence of hyperbilirubinemia. There is a relationship between gestational age with hyperbilirubinemia in neonates Then the r-value results mean the strength of the statistical correlation is 0.493. The r-value result means it has moderate strength, with a negative correlation

direction, which means that the more mature the gestational age, the lower the risk of hyperbilirubinemia. According to Dahlan (2016), if the p -value <0.05 , it has a significant correlation. Furthermore, if the value of r is at 0.4 to <0.6 , it means that it has a moderate correlation strength, and the direction of negative correlation means that the higher the variable A, the lower the variable B.

DISCUSSION

Gestation Age in Neonates with Hyper bilirubin 3 Days

This study result shows that the median gestational age in neonates with hyperbilirubinemia is 36 weeks or can be categorized as preterm, with a minimum gestational age of 30 weeks and a maximum gestational age of 42 weeks. According to Kosim *et al.* (2014), hyperbilirubinemia often occurs in 80% of preterm infants and 60% of term infants. This result follows Nelson (2012), theory that one of the factors that can cause hyperbilirubinemia is a factor that can reduce the number of enzymes, and which can increase the permeability of the brain barrier. Gestational age is one factor that affects the number of enzymes and the permeability of the brain barrier. Prematurity and immaturity can reduce the number of enzymes and increase brain barrier permeability. Hyperbilirubinemia in term infants occurs on days 2 to 4, and in premature infants occurs on days 3 to 7 (Rudolph and Hoffman, 2006).

Several previous studies corroborate this. In the research of Rai and Sharma (2018) in India, the results of babies born with gestational age <37 weeks to 38 weeks experiencing jaundice were 55.4%, while those born with gestational age 39-42 weeks were 33.1%. Anggraini research (2016) showed that out of 52 neonates with jaundice, 73.1% were born with preterm labor, and 26.9% were born with term gestational age.

In this case, the role and function of the midwife are in prevention efforts that can be carried out from the antenatal period to the neonatal period, including by carrying out good antenatal supervision, preventing preterm labor, and preventing hypoxia in the fetus and neonate.

Hyper bilirubin Incidence in Three Days Neonates.

Based on the results of data analysis, it can be explained that the median level of bilirubin in neonates with hyperbilirubinemia is 10 mg/dL with a minimum level of 5.52 mg/dL and a maximum level of 16.03 mg/dL. This result follows the theory of Fraser (2011) that hyperbilirubinemia, characterized by jaundice, will appear if the bilirubin level reaches 5-7 mg/dL, initially. According to Kosim *et al.* (2014). If not accompanied by abnormalities of bilirubin metabolism, an increase in bilirubin levels to 10-12 mg/dl is still within the physiological range. If the bilirubin level reaches > 12 mg/dl it is categorized as hyper bilirubin characterized by pathological jaundice. In addition, pathological jaundice appears for the first time in the first 24 hours and lasts 10-14 days, while physiological jaundice first appears on days 2-5.

In this case, midwife's role is to detect and differentiate between physiological and pathological jaundice based on the neonate's timing, clinical appearance, and behavior and to determine the appropriate management. With proper management, it can reduce mortality and morbidity in infants due to jaundice, as well as inform families of information about the event and its progress. In addition, the midwives' role in physiological jaundice management is to prevent infection. This prevention prevents pathological jaundice. The nurse should conduct health education regarding breastfeeding as early as possible and adequate, recommending mothers breastfeed their babies according to the baby's wishes or at least every 2 hours, recommending mothers dry the baby in the sun. Naked in the sun at 7-9 am for approximately 15-30 minutes, and recommends the mother to carry out good supervision, i.e., if the baby's jaundice does not go away in more than three days, it must immediately return to the health worker to have it checked.

Relationship of Gestation Age with Event of Hyper bilirubin in Three-Day Neonates at Dustira Cimahi Hospital In 2021

The Spearman correlation test showed that the p -value < 0.001 , which means that gestational age and the incidence of hyperbilirubinemia had a significant correlation. There was a relationship between gestational age and the incidence of hyperbilirubinemia in neonates. The r -value result is 0.493, which means it has moderate strength with a negative correlation direction. This statistical result means that the more mature the gestational age, the lower the risk of hyperbilirubinemia. According to Dahlan (2016), if the value of r is at 0.4 to <0.6 , it means that it has a moderate correlation strength, and the direction of negative correlation means that the higher the variable A, the lower the variable B. Furthermore, if the p -value <0.05 , it correlates. This result follows Nelson (2012) theory that one of the factors that can cause hyperbilirubinemia is a factor that can reduce the number of enzymes, and which can increase the permeability of the brain barrier. Gestational age is one factor that affects the number of enzymes and the permeability of the brain barrier. Prematurity and immaturity can decrease the number of enzymes and increase the brain barrier's permeability. Hyperbilirubinemia in term infants occurs on days 2 to 4, and in premature infants occurs on days 3 to 7 (Rudolph and Hoffman, 2006). It is corroborated by the theory of Kosim *et al.* (2014), which says that hyperbilirubinemia often occurs in 80% of preterm infants and 60% of term infants.

Several previous studies corroborate this. Ratuain *et al.* (2015) study regarding the relationship between gestational age and the incidence of neonatal jaundice in Wates Hospital 2013 showed that there was a relationship between gestational period and the incidence of neonatal jaundice had the relationship between gestational age and the incidence of neonatal jaundice or hyperbilirubinemia. Moreover, the study results showed that the incidence of jaundice in premature infants was 59.1%, and infants were 40.9% in a term. Rahmy (2014) regarding the relationship between infant maturity or gestational age and the incidence of hyperbilirubinemia also showed a significant relationship, and the results of this study

showed that 15.2% of preterm infants had jaundice and 24.2% of term infants. Another study that showed that gestational age was associated with jaundice was conducted by Faiqah (2018) with the results of babies experiencing jaundice with a gestational age of 37 weeks and a gestational age of < 37 weeks of 33.3%. Anggraini research (2016) showed that out of 52 neonates with jaundice, 73.1% were born with preterm labor, and 26.9% were born with term gestational age. In the research of Rai and Sharma (2018) in India, the results of babies born with gestational age <37 weeks to 38 weeks experiencing jaundice were 55.4%, while those born with gestational age 39-42 weeks were 33.1%. In addition to several studies on gestational age with jaundice, research conducted by Rohani and Wahyuni (2017), Anggraini (2016) regarding factors related to the incidence of jaundice in neonates found that 50% of the factors The most related to the incidence of jaundice is gestational age.

CONCLUSION

It can be concluded that the median bilirubin level in neonates experiencing hyperbilirubinemia at Dustira Cimahi Hospital in 2021 is 10 mg/dL, which is still classified as physiological hyper bilirubin, with a minimum level of 5.52 mg/dL and a maximum level of 16.03 mg/dL. Based on the results of the Spearman correlation test, it was found that there was a significant relationship between gestational age and the incidence of hyperbilirubinemia in neonates aged 3 days at Dustira Cimahi Hospital in 2021 with moderate strength and negative correlation direction. For further researchers, it is recommended to develop this research, by examining other factors that affect hyperbilirubinemia in neonates. In this study, the results of the correlation were moderate. This may be due to the presence of multifactorial factors that affect hyper bilirubin in addition to gestational age.

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The Effect of Early Mobilization and Body Positioning on Functional Ability in Patients with Acute Ischemic Stroke

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A B S T R A C T

There are many physical problems in post-stroke conditions which is decreased functional ability. This study aimed to determine the effect of early mobilization and body positioning on functional ability in acute stroke patients. The study design used a single blinding, randomized, and controlled trial. The sample consisted of 20 acute ischemic stroke patients selected randomly and equal distribution between the group of early mobilization and body positioning (ages 45-70, MMT 2+ and given exercises ranging from 24-48 after the attack) and the control group (age 45-70, MMT 2+ and given passive exercises 24-48 after the attack) for seven days in hospital care. All patients were evaluated with Glasgow Coma Scale, Mini-Mental State Exam, and Barthel Index. Paired t-tests and independent t-tests have been used to evaluate and differentiate between groups. The study results showed the treatment group (early mobilization and body position training) to a level of functional ability $p < 0.05$ ($p = 0.000$) and the mean -65. The control group (passive exercise) to the level of functional ability $p < 0.05$ ($p = 0.000$) and the mean -28. The difference effect between the group (early mobilization and body position training) with the control group (passive exercise) on the level of functional ability $p < 0.05$ ($p = 0.000$) with a mean difference was 36.9. Early mobilization and body position training are other approaches that can improve functional abilities in patients with acute ischemic stroke

INTRODUCTION

Stroke is a disease which affects the arteries that lead to and inside the brain. A stroke occurs when blood vessels that carry oxygen and nutrients to the brain and burst are blocked by blood clots. As a result, the brain cannot get blood and oxygen. Haemorrhagic stroke is acute focal neurological dysfunction caused by bleeding in the brain substance that occurs spontaneously due to the rupture of arteries and capillaries. In contrast, non-haemorrhagic stroke or ischemic is a disease caused by a blockage that cuts off the blood supply to the brain. This condition can cause damage to brain cells (Stroke Association, 2020).

According to data Public Health Office of Central Java (2013), stroke prevalence in Central Java, as many as 40,972 consisted of 28,430 ischemic strokes and 12,542 haemorrhagic strokes. In Surakarta, cases of stroke in the pattern of non-communicable diseases with the prevalence of ischemic stroke as many as 1,309 cases and haemorrhagic stroke of as many as 2,838 (Public Health Office of Surakarta, 2014). The effect of an increase in the stroke incidence is an increase in other health problems due to complications caused, one of which is a decrease in functional ability. Functional ability is an Activity of Daily Living (ADL) consisting of basic actions involving the care of oneself and body, including personal care, mobility, and eating. Often called physical ADLs or essential ADLs, it covers the basic skills that are usually needed to manage basic physical needs (Mlinac & Feng, 2016). Post-stroke patients with a high

degree of attack often leave residual symptoms that interfere with motor skills. Movement disorders and the inability to perform a movement properly cause a decrease in ADL's ability (Pristianto *et al.*, 2021).

Based on NICE Guidelines (2019), early body position training regularly continuous for seven days can increase the oxygen supply into the brain. The training can activate the damaged cells in the brain so that more oxygen supplies through the blood enter the brain. The brain will get nutrients to function properly, and there will be cell improvements that can affect functional activity well.

A number of training programs can be given to ischemic stroke patients to improve functional abilities, such as early mobilization and body position training. Early mobilization is an exercise that leads to the principle of regular input proprioceptive, inhibition and facilitation. It refers to improving gross motion patterns by providing sensory stimulation to facilitate voluntary movements of the synergy muscles at the onset of stroke (Becheva & Georgiev, 2017). Meanwhile, according to NICE Guidelines (2019), body positioning training help increase the oxygen supply in the blood to the brain to minimize the decrease in brain cell function.

Based on the background, the authors are interested in research to determine the effect of exercise in improving the functional ability of patients with post-acute ischemic stroke. The title is the effectiveness of early mobilization and body position training on the level of functional ability in patients with acute ischemic stroke.

METHOD

The study design was experimental with a single-blinding design. The first group (treatment group) was given passive exercise treatment, early mobilization, and body position training; and the second group (control group) was given passive exercise treatment. This study was conducted in December 2018 in the stroke ward of the Regional General Hospital dr. Soehadi Prijonegoro Sragen. The Institutional Review Board has approved this study of the Medicine Faculty, Universitas Muhammadiyah Surakarta no: 1679/B.1/KEPK-FKUMS/XI/2018.

The population of the study were ischemic stroke patients with sampling determined by inclusion and exclusion criteria, namely (a) Respondents aged 45-70 years, (b) Respondents diagnosed with ischemic stroke attacks current and recurrent acute stage on stroke wards were ascertained no worsening of neurological conditions, (c) Respondents with muscle strength of at least 2+ (antigravity position, through a partial range of motion movements), (d) Respondents with risk factors (hypertension, diabetes mellitus, cholesterol, heart disease (AMI and cardiomegaly), (e) Respondents approved informed consent and (f) were willing to follow the research. Exclusion criteria (a) the respondent was diagnosed with haemorrhagic stroke. (b) Respondents with serious complications, (c) Respondents with aphasia, (d)

Respondents with decreased consciousness, shock emboli and sepsis, (e) Respondents with severe cognitive impairment where (score MMSE is at least 19).

Respondents were divided into two groups; each group amounted to 10 people, the first group was given early mobilization and body position training, and the second group was given passive exercise treatment. The study began with an explanation by the researcher regarding the course of the research to the enumerator, whom enumerator then took over to explain to the respondent and continued to fill out the *informed consent*. Then, the respondent was given treatment randomly according to the group.

The measurement of the ability of functional activities of patients with post-acute ischemic stroke was using the Barthel Index (BI). Post-acute ischemic stroke in the group was early mobilization patients performed with 8-10 repetitions in 20-45 minutes every day for seven days, working through the application of proprioceptive modalities on sensory and proprioceptive information in improving the efficiency of movement for functional ADL. In general, giving body position training in one week is when the 24-hour acute ischemic stroke one to two sessions per day for seven days. The head may be elevated gradually after 24 hours from lying flat; this position affected the change in the saturation point of oxygen flow in the brain. The form of body position training consisted of side-lying extra positioning, side-lying sinistra positioning and supine-lying positioning on the bed.

Position of side-lying dextra with the weak side above the shoulder and left knee, place the left shoulder straight parallel to the shoulder and give a suspension, then the position of knee flexion, give cushion support. Keep the neck parallel to the spine if it is not aligned, giving a thin pillow next to the waist. Position of the side lying down left with a weak position under the body; the scapula must be shifted forward with the shoulder position until the left wrist goes straight to the ventral parallel of the shoulder. The position of left knee extension was then followed by dextra knee flexion and given a pillow as a suspension. Keep the head parallel to the spine; if it is not parallel, give a thin pillow next to the waist. A supine lying was not allowed for too long because it could cause muscle weakness, especially muscle posture. Give the pillow support from the shoulder to the wrist with the palm supination and the foot propped up using a pillow to make it straight.

In the control group, routine exercise therapy was given 15 minutes per day for seven days of physiotherapy. Passive exercise therapy was also given in the group of early mobilization and body position training. Patients and families of patients have been given information about the purpose of the exercise. The statistics used were Statistical Package for the Social Sciences (SPSS) version 23, which has been used to analyse data acquisition. Shapiro Wilk Test to find out the data was normally distributed ($p > 0.05$). Data analysis has been displayed with frequency and percentage for sample characteristics based on age. In contrast, characteristics of functional activity values were categorized as verifiable (Mean, median, standard deviation, maximum and minimum). The results of the normality test data show

that the data were typically distributed. The parametric statistical test was used, namely the Paired t-test for categorized variables (mean difference). Then the average difference test was carried out between two effective treatments using the independent t-test for categorized variables (mean difference).

RESULT

The sample consisted of 20 acute ischemic stroke patients randomly selected and equal distribution between early mobilization and body position training group (ages 45-70, MMT 2+ and given exercises ranging from 24-48 post-attack) and control group (age 45 -70, MMT 2+ and given passive exercise therapy 24-48 after the attack) for seven days in hospital care. There are differences in the effect of early mobilization and body position training with passive exercise therapy to improve functional ability in acute ischemic stroke patients.

Table 1. Characteristics of Respondents Based on Age

Age	Acute ischemic stroke	
	Frequency	%
45-50	1	5,0
51-55	2	10,0
56-60	4	20,0
61-65	4	20,0
66-70	6	30,0
71-75	3	15,0
Total	20	100

Based on Table 1, the criteria of sample respondents aged 48-73 years. The highest number of acute ischemic stroke patients aged 59, 65, 66 and 70 years (10.0%), while for other ages (5.0%).

Table 2. Effect Test Result

Group	Mean Difference	p Value	Description
Treatment (Bobath concept training and body position training)	-65	0.000	Ha accepted
Control (Conventional)	-28		

The effect test of functional activities using Paired Sample t-test obtained a value of in the treatment group is 0.000. While for the control group, the value is 0.000. Both groups of Ha were accepted because the p-value <0.05 means there is a difference in the influence of the average value of functional activities in acute ischemic stroke patients.

The effect test of functional activities using Paired Sample t-test obtained values in the treatment group is 0.000. While for the control group, the value is 0.000. Both groups of Ha were accepted because the p-value <0.05 means there is a difference in the influence of the average value of functional activities in acute ischemic stroke patients.

Table 3. Difference Effect Test Result

Group	Mean Difference	p (2-tailed)
Treatment (Bobath concept training and body position training)	36.9	0.000
Controls (Conventional)		

The table 3 uses the independent test, the results obtained $p = 0.000$ between treatment and control groups have the same results. Normal p -value <0.050 , then H_a is accepted, and H_o is rejected, which means there is a difference in the influence of the average value of the functional activity that is significant in acute ischemic stroke patients.

DISCUSSION

Our main findings show that giving early mobilization and body position training for 60 minutes can improve functional ability in patients with acute ischemic stroke. When giving early mobilization, a stimulus and conscious movement are needed; when given a stimulus and active movement, it will form a trajectory and connectivity between one nerve cell and another so that will form a signal electric after reaching the excitatory threshold of -40mV to -90mV (Ma *et al.*, 2017).

In this process, there will be Depolarization; certain ion channels will open so that ion displacement will occur down the concentration gradient; this process is called the action potential due to the exchange of K^+ ions, which are outside the membrane and Na^+ inside the membrane. As a result of the increase in the amount of sodium in the cell, while the amount of potassium remains, there is a change in the membrane's electrical potential where the intracellular electrical potential becomes more positive than extracellular (Drier *et al.*, 2018).

After Depolarization occurs, the potential resting membrane will be restored through repolarization. In this process, the Na^+ channel that were previously open will close and is followed by the opening of the K^+ channel. K^+ will move down the concentration gradient and return the membrane potential in the cell to negative (Kadir *et al.*, 2018). To generate information, it must reach the threshold (-40mV to -90mV). The chemical signal will open and then release the vesicle as a giver of information to nerve cells so that nerve cells can synapse to other nerve cells, which will improve brain function and make it easier to embed a pattern such as specific task when giving training, so that it can improve functional activity (Forrest, 2014).

In addition, giving early mobilization will control afferent input and facilitate normal postural reactions. The provision of a mobilization program in a particular region adjusts to the movement ability and ROM (Pristianto *et al.*, 2018). Afferent input is used to improve that region's quality of movement, especially on the lesion side. Facilitation of postural reactions is used to provide the experience that movements are regular (because abnormal movements originate from abnormal tones). Changes or regulation of proximal

joint position and movement affect tone (Rahayu *et al.*, 2017). Based on Purnamayanti *et al.* (2020), motion exercises given to stroke patients can improve muscle ability and plasticity stimulus. Furthermore, Amalia & Rahman (2022) stated that it is essential to maintain fitness in stroke patients by providing proper exercise.

Body positioning can improve blood circulation, provide appropriate sensory information, and improve postural stability and strength to improve functional activity in patients with acute ischemic stroke. In lying position, the patient needs a good supine position and utilizes the pillow as a support so that the pelvis does not fall backwards. It is increasing the hip extension of the hip joint, which is useful for the walking process so that the hip joint will be mobile and not rotate externally. This position stabilizes the muscles of core stability, such as m. transversus abdominis, m. multifidus, m. internal oblique, m. external oblique, m. rectus abdominis, m. sacrospinalis (longissimus thoracis and diaphragm), m. latissimus dorsi, m. gluteus maximus and m. trapezius, an increase in muscle core will cause nerve conductivity which can improve intermuscular coordination so that it can increase reaction speed and the mobility of motion function at the position change (Yu & Park, 2019).

When the pelvic floor is stable, it will maintain the projection of the body's centre of gravity when doing a movement (Bettlach *et al.*, 2016). Side-lying to the healthy side is needed in handling early stroke patients to improve the blood flow to the brain due to prolonged immobilization so that it will facilitate information that will be conveyed to the brain for improvement of tone and posture by increasing m. internal intercostalis, m. subcostal, m. transversus thoracis, m. serratus posterior inferior, m. obliquus internus, m. external abdominal obliquus and m. transversus to repair respiratory muscles due to a centralized thoracic cage in the expiratory position (Stevens *et al.*, 2018). Side-lying to the lesion side with the position of the shoulder pushed forward and not suppressed will provide a stimulus with force used by the healthy side weight to the weak side (Latimer *et al.*, 2019).

Gjelsvik *et al.* (2016) stated that body position training can improve blood circulation, provide appropriate sensory information, and improve postural stability and strength to improve functional activity in acute ischemic stroke patients. As evidenced by previous research by Chatterton *et al.* (2001), body position training can improve tone, prevent lung complications due to bed rest and maintain oxygen in the brain to improve functional activity. Clinically, our research results can help physiotherapist change their rehabilitation programs and contribute to the addition of scientific evidence from early mobilization and body position training.

CONCLUSION

Early mobilization and body position training is a different approach to improve the functional ability of acute ischemic stroke patients. In the future, a different controlled trial is needed to examine the effects of

early mobilization and body position training with the instrument Brain Derived Neurotropic Factor (BDNF) to see cell regeneration in the blood, which will determine the frequency of exercise in acute ischemic stroke patients.

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Nurses' Perceptions of Patient Safety Culture During the Pandemic in Covid-19 Referral Hospitals

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ABSTRACT

Patient safety culture is essential in creating a safe and healthy hospital environment. This study aims to portray nurses' perceptions of patient safety culture during the Pandemic in COVID-19 Referral Hospitals. This paper was a descriptive study. The population was nurses working in inpatient, Covid-19 isolation, intensive, and emergency rooms. In addition, the sample was 268 nurses with a stratified random sampling. Data collection used a questionnaire using Google Forms. It consisted of the demographic characteristics of respondents (name, gender, age, marital status, working time, education, nurse position, levels of nursing, and patient safety training) also nurses' perception of patient safety culture. The Hospital Survey on Patient Safety Culture (HSOPC) was an instrument to assess patient safety culture. Data analysis used IBM SPSS Statistics version 22.0 to describe the mean, median, minimum, and maximum values and presentation. Results showed that the mean patient safety culture among nurses in COVID-19 referral hospitals was 147.09 (62.55%). In addition, the lowest dimension of patient safety culture was feedback and communication (31.75%), while the highest was an organizational improvement (73.16%). Thus, the patient safety culture in the COVID-19 referral hospital still needed improvement. A good patient safety culture can increase patient safety and the quality of health services. Therefore, hospital management should optimize all dimensions of patient safety culture to ensure patient safety. Future research could explore predisposing factors of patient safety culture.

INTRODUCTION

Patient safety culture describes behavior, values, attitudes, perceptions, and competencies (both personally and in a group) to emphasize the organization's efforts, patterns, and capabilities in patient safety management (Ulrich and Kear, 2014). An organization with a good safety culture has mutual trust in communication, vigilance in patient safety, and confidence (Lee and Oh, 2020). Building a patient safety culture can establish and improve patient safety in the hospital. Thus, the hospital runs the program with focus and sustainability in achieving that goal (Herawati, 2015). However, building a culture is not easy. The biggest challenge is maintaining a positive culture (Syam, 2017).

A study before the COVID-19 Pandemic found that the average positive response to the nurse safety culture in Indonesia was 72.40%, with the lowest safety culture being the no-blame response and the highest culture being the expectations and actions of managers (Syam, 2017). Another research revealed that 44.55% of nurses felt good safety culture, 29.36% indicated good expectations and actions of managers, and 54.13% stated good feedback and communication in their organizations (Arini, 2018; Nurlindawati and Jannah, 2018; Fatonah and Yustiawan, 2020).

Furthermore, there were three previous studies at COVID-19 referral hospitals. The first research showed that Patient Safety Goals (PSG) indicators 1 – 6 in the Hospital Quality Indicator Report at Hospital A from January to December 2019 got an average of 90.53%, while in 2020 was 91.28%. Thus, Hospital A has not fulfilled PGS indicators by 100%. In addition, only 56.52% of nurses at Hospital B were obedient to the seven rights of medication administration. Nurses in Hospital B also faced problems in implementing effective communication with the Situation, Background, Assessment, and Recommendation (SBAR) technique, with the value of Situation was 79%, Background was 64%, Assessment was 21%, and Recommendation was 100% (Ahsan, Noviyanti and Primanoviasari, 2018). Moreover, a report on the quality of patient safety indicators at Hospital C found problems of hand hygiene compliance among nurses, with a total achievement of 83.5% in 2019 and 85.67% in 2020 (Nazri, Juhariah S and Arif S, 2015). Thus, the authors concluded that three COVID-19 referral hospitals had problems with patient safety, even though patient safety is closely related to the safety culture in the hospital.

The COVID-19 Pandemic has forced healthcare providers to adapt quickly and appropriately. It also affects nurses as frontline workers to provide safe and effective nursing care. An investigation revealed that the hospital situation during the Pandemic was like a battlefield. Thus, anxiety in nurses is inevitable (Lee, Hong, and Park, 2020). Moreover, a previous study by Taylor et al. (Taylor et al., 2020) identified 343 patient safety concerns at 71 hospitals in Pennsylvania during the Pandemic. At the same time, several studies revealed that patient safety culture significantly influenced the implementation of patient safety (Han and Jung, 2017; Moon and Lee, 2017; Im and Park, 2018; Ha and Lee, 2019; Manapragada et al., 2019; Lee and Oh, 2020). Thus, patient safety culture is essential in improving healthcare service quality (Syam and Hastuti, 2018). However, research on the patient safety culture among nurses during the COVID-19 Pandemic was limited. Therefore, this study aims to portray nurses' perceptions of patient safety culture during the Pandemic in COVID-19 Referral Hospitals.

METHOD

This paper was a descriptive study. The population was nurses working in inpatient, Covid-19 isolation, intensive, and emergency rooms. The sample was 268 nurses with a stratified random sampling. The sample size used in each hospital and room depended on the population (Swarjana, 2016). The inclusion criteria were nurses with six months minimum working time in the hospital and a minimum nursing diploma. Data collection used a questionnaire using Google Forms. It consisted of the Demographic characteristics of respondents (name, gender, age, marital status, working time, education, nurse position, levels of nursing, and patient safety training) and nurses' perceptions of patient safety culture. The instrument to assess patient safety culture was the Hospital Survey on Patient Safety Culture (HSOPC),

developed by the Agency for Healthcare Research and Quality (AHRQ) and subsequently adapted into Indonesian by Rosyada (2014) and Arini (2018). The instrument consists of 42 questions with 12 dimensions and uses a Likert scale of 1-5. The authors did validity and reliability tests resulting in a table α value and reliability of 0.879. This research obtained certificates of ethical review from the Research Ethics Committee of the Faculty of Nursing, the University of Indonesia, with Num. SK 126 / UN2. F12. D1.2.1/2021 ETHICS, the ethics review at Dr. Soetomo Hospital with Num. 0419/LOE/301.4.2/IV/2021, and Kanjuruhan Hospital with Num. 072.1/EA. KEPK-015/35.07.208/2021. Data analysis used IBM SPSS Statistics version 22.0 to describe the mean, median, minimum, and maximum values and presentation.

RESULT

Table 1 and Table 2 indicate the demographic characteristics of respondents. In addition, Table 3 shows nurses' perceptions of patient safety culture.

Table 1. The demographic characteristics of respondents by gender, education, marital status, nurse position, levels of nursing, unit, and patient safety training (n=268)

The Demographic Characteristics of Respondents	Frequency	Percentage (%)
Sex		
Male	74	27.6
Female	194	72.4
Education		
Diploma in Nursing	141	52.6
Bachelor of Nursing	21	7.8
Bachelor of Nursing and Professional Nurse Program	106	39.6
Marital status		
Unmarried	59	22
Married	209	78
Nurse position		
Nurse practitioner	205	76.5
Team leader	63	23.5
Levels of Nursing		
Pra Clinical Nurse	22	8.2
Clinical Nurse 1	74	27.6
Clinical Nurse 2	96	35.8
Clinical Nurse 3	72	26.9
Clinical Nurse 4	4	1.5
Unit		
Inpatient room	143	53.4
Covid-19 isolation room	45	16.79
Intensive room	34	12.7
Emergency room	46	17.2
Patient safety training (in the last six months)		
Yes	152	56.7
No	116	43.3

Most respondents were female nurse practitioners with a diploma in Nursing, were married, had patient safety training, and worked in inpatient rooms (Table.1). The average age of nurses was 33 years, with a

range of 23-57 years. In addition, the mean working time was eight years, with a range of 1-39 years (Table 2).

Table 2. The Demographic characteristics of respondents by age and working period (n=268)

The Demographic Characteristics of Respondents	Mean (Min-Max)	CI 95%
Age	33.00 (23-57)	33.98-36.08
Working time	8.00 (1-39)	9.82-12.00

Results showed that the mean patient safety culture among nurses in COVID-19 referral hospitals was 147.09 (62.55%). In addition, the lowest dimension of patient safety culture was feedback and communication (31.75%), while the highest was an organizational improvement (73.16%).

Table 3. Descriptive Statistics of patient safety culture among nurses (n=268)

Dimensions of Patient Safety Culture among Nurses	Mean±SD	Percentage (%)
Unit teamwork	15.41±3.35	71.31
Manager's expectations and actions in promoting patient safety	14.85±2.34	67.81
Organizational improvement	11.75±2.63	73.16
Management support	9.92±1.03	57.66
Nurses' perceptions of patient safety	14.23±2.18	63.93
Feedback and communication	5.81±2.11	23.41
Open communication	11.57±3.75	65.92
Frequency of event reporting	10.25±3.00	60.41
Teamwork between units	15.18±2.56	69.87
Staffing	12.66±1.68	54.12
Handover and patient transfer	15.02±3.02	68.87
Not blaming response	10.40±2.59	61.66
The overall patient safety culture	147.09±15.54	62.55

DISCUSSION

Our finding revealed that patient safety culture among nurses in COVID-19 referral hospitals was still below expectation (standard >75%). It still needs improvement in all dimensions of patient safety culture. Patient safety culture correlates negatively with patient safety incidents. Thus, negative patient safety culture potentially increases patient safety incidence, while a positive patient safety culture could prevent the incident (Kakemam et al., 2021; Yesilyaprak and Demir Korkmaz, 2021). Nurses with patient safety knowledge can create a patient safety culture in hospitals. Thus, they will become more confident in facing obstacles and difficulties associated with safety issues (Wang, Chou, and Lai, 2019). Therefore, the low patient safety culture in the hospitals of this study needs to be improved and become a priority so that patient safety incidents decrease and nurse compliance in patient safety increases.

Previous research on 150 nurses showed 66.33% of them had positive patient safety culture (Asadi et al., 2020). Meanwhile, before the Pandemic, AHRQ took data on 87,856 respondents in 172 hospitals, showing that 71% had positive patient safety culture (AHRQ, 2021). Thus, there was a potential decrease in patient safety culture before and after the COVID-19 Pandemic. It was potentially due to the lack of nursing resources during the Pandemic, schedule changes, and room changes. In addition, many staff

were self-isolating, so the nurse workload increased. Increased workload during the Pandemic led to changes in nurse roles in the ward, including patient safety (Denning et al., 2020). On the contrary, another study found an increased patient safety culture during the COVID-19 Pandemic. It was due to improved awareness of the importance of patient safety and risk management (Chen et al., 2021).

Patient safety culture is vital in creating a safe and healthy work environment. According to the Minister of Health of the Republic of Indonesia, Num.11 of 2017, hospitals must first build a culture of safety to ensure patient safety. Building a safety culture requires the organization's support, solid leadership, and managers' ability to listen to their staff's opinions. Thus, creating a culture of patient safety is fundamental for health workers in patient safety. It is an effort to establish and improve overall patient safety. Thus, the hospital runs the program with focus and sustainability in achieving that goal (Herawati, 2015). However, building a culture is not easy. The biggest challenge is maintaining a positive culture (Syam, 2017).

Hospitals should make policies to improve the patient safety culture. Patient safety culture surveys should continue to be carried out regularly without waiting for an accreditation schedule. There are 12 dimensions in patient safety culture, and all have an essential role in building an overall patient safety culture. In this study, the high scores were in unit teamwork, teamwork between units, and organizational improvement. Meanwhile, there should be an improvement in feedback and communication, management support, and staffing.

Unit teamwork and teamwork between units

Unit teamwork is the support between staff in the ward or the team at work. It is crucial, considering that the hospital nurses work together every shift. Thus, it takes the ability to work together and respect each other. Research before the COVID-19 Pandemic showed an average score of nurse teamwork within the unit was 72.35% (Danielsson et al., 2019; Tlili et al., 2021). It was lower than in the pre-pandemic study. It is probably due to differences in the policies or habits of the hospital. In addition, many changes have occurred in the nurse work environment during the Pandemic. One is fatigue due to increased workload inhibits the nurses from carrying out their roles.

In addition, teamwork between units is essential. Nurses should coordinate with other departments when providing nursing care, such as the radiology unit, to perform diagnostic examinations. However, teamwork between units in this paper still needs further improvement, with a score of 69.87%. Previous studies also found the mean score was 51.07% (Danielsson et al., 2019; Tlili et al., 2021). The roles of head nurses are crucial to enhance the teamwork between nursing staff. One is allowing members to express their opinions to build a patient safety culture within the unit. Inadequate structure within the team, low manager leadership, low awareness to help each other and performance, and ineffective communication cause a lack of teamwork among nurses (Hwang and Ahn, 2015). Distrust and disrespect

for fellow staff, failure of the manager to lead, loss of coordination, lack of knowledge and understanding of staff regarding the patient's condition, and lack of communication cause teamwork issues (O'Connor et al., 2016). Efforts to overcome those issues are increasing the role of the managers or head nurses in creating open communication and enhancing their leadership. In addition, training on improving teamwork, workshops on improving service quality, and implementing quality improvement can positively enhance cooperation (Paguio and Yu, 2020). Thus, the head nurses have an essential role as a manager within the scope of the unit. They need to create innovations and be willing to hear opinions from staff to improve unit teamwork.

Managers' expectations and actions in promoting patient safety

The expectations and actions of managers in promoting patient safety are the ability of the head nurses to improve the patient safety culture within their unit. Research conducted before the COVID-19 Pandemic in different places obtained an average score of 59.58% (Danielsson et al., 2019; Tlili et al., 2021). This paper scored higher than the previous one during the COVID-19 Pandemic. It indicates that head nurses were more often promoting safety to protect staff and patients during the Pandemic. During the Pandemic, nursing managers tend to be more caring and responsible for guiding their teams (Lee, Hong, and Park, 2020).

Nursing staff expects head nurses to praise their accomplished work, hear and consider their suggestions, and pay attention to nurse workload. In addition, head nurses should be able to anticipate patient safety incidents within the unit. During the Covid-19 Pandemic, head nurses have a higher workload. In addition, the higher dependence of nursing staff on them makes them work hard to meet staff expectations. During the Pandemic, nursing managers must ensure nurses' psychological and physical needs (White, 2021). However, lack of time, leadership, education, training, management support, and increased workload cause poor leadership in nurse managers (Hughes, 2018).

Organizational improvement

Organizational improvement is how the organization realizes the mistakes that have occurred and learn continuously to avoid errors and make positive changes. Research before the COVID-19 Pandemic showed an average score of organizational improvement was 54.28% (Danielsson et al., 2019; Tlili et al., 2021). Meanwhile, this paper showed an 18.88% higher score than the previous one during the Pandemic. The hospital has passed the new normal period from the COVID-19 Pandemic (Lum et al., 2020). Thus, the hospitals have adapted during the COVID-19 Pandemic to improve patient safety culture and prevent patient safety incidents.

Ineffective planning implementation, unrealistic plans and achievement times, organizational failures to create staff awareness, lack of staff trust in management, weak leadership, and ineffective communication can inhibit organizational improvement (Longenecker and Longenecker, 2014). The implementations of

good organizational behavior are encouraging staff towards behavior improvement, designing and implementing change programs, improving the quality of service to patients, and helping staff overcome conflicts (Robbins and Judge, 2017). During the Pandemic, the hospital became a constantly changing environment, and there is an adaptation for organizational improvement. Internal and external factors influence organizational improvement (Alonazi, 2021). Therefore, it requires a commitment from the organization to make changes, learn from mistakes, improve communication, improve the role and leadership of managers, and carry out management functions well.

Management Support

Management support for patient safety is a hospital policy and program to improve patient safety. Research before the COVID-19 Pandemic showed an average score of management support was 47.73% (Danielsson et al., 2019; Tlili et al., 2021). Meanwhile, this paper found a 9.92% higher score than the previous one during the Pandemic. During the Pandemic, management support is crucial to help staff get through the pandemic crisis. Factors contributing to the successful handling of the Pandemic in hospitals are the cooperation and support of management, the leadership of managers, and the improvement of staff trust in managers (Abdulmohsen et al., 2019). The implementation of management support during the Pandemic is adequate preparation, strengthening cooperation between professions, updated workflows according to the latest conditions, and good personal protective equipment supply (Hou et al., 2020). In addition, psychological and physical support, gathering staff opinions, and arranging nursing resources and nurse shifts are essential (Kackin et al., 2020).

Hospital management during the COVID-19 Pandemic activated crisis management. The Indonesian Commission on Accreditation of Hospitals establishes the accreditation standards for Facilities and Safety Management. In addition, hospitals develop and maintain disaster management programs to respond to natural and other disasters that can occur in the community, including endemic or pandemics. Crisis management starts with prevention, planning, reaction to the crisis, and the recovery process. Hospitals should emphasize providing adequate information, supporting team performance, and improving manager competence in crisis management (Jankelová et al., 2021).

Feedback and Communication

The score of feedback and communication in this paper indicated the lowest dimension of patient safety culture. It means that hospital management could not provide feedback and communication to nurses, especially in patient safety incidents. However, research before the COVID-19 Pandemic found an average score of 68.75% (Danielsson et al., 2019; Lee and Oh, 2020).

Lack of advice regarding improving behavior, staff respect for managers, fear of disappointing others and damaging professional relationships, physical barriers, and lack of self-confidence cause ineffective feedback and communication. Efforts to overcome the issues are performing careful planning before

giving feedback and specific goals, discussions, and feedback, self-reflection, paying attention to non-verbal instructions, and self-evaluation after giving feedback (Hardavella et al., 2017). The head nurse can provide constructive feedback to improve the hospital ward's quality (Altmiller, 2012). Constructive feedback can begin with showing empathy, caring for staff, and reflecting on feedback skills. The head nurse must make incident reports as organizational improvement, and therefore feedback should be a positive response to staff.

Open Communication

The open communication dimension in this investigation needed continuous improvement. Research before the COVID-19 Pandemic obtained an average open communication score of 55.54% (Danielsson et al., 2019; Y. mi Lee & Oh, 2020; Tlili et al., 2020). Lack of nurse readiness, unsupportive work and management environment, and suboptimal leadership of the head of the room inhibit open communication (Pattabi et al., 2018). Managers can practice nine steps in communicating with staff during a pandemic. The steps consist of increasing the frequency of communication, staying focused on the information provided, improving leadership values, being calm, maintaining a chain of command, settling down authority, engaging, caring for staff, and forming two-way communication with constructive feedback (Clark, 2020). Some recommendations to improve open communication during the COVID-19 Pandemic are by implementing crisis management, taking communication during the Pandemic, providing up-to-date information on COVID-19, preparing psychological support for staff, providing communication training and managers exemplifying behaviors that are following the culture of open communication (Saudi Patient Safety Center, 2020).

Non-Blaming Culture

The non-blaming culture for staff when making mistakes is crucial to improve patient safety. Research before the COVID-19 Pandemic found an average non-blaming culture was 55.10% (Danielsson et al., 2019; Y. mi Lee & Oh, 2020; Tlili et al., 2020). This study found that the score was 6.5% higher than the previous studies. Nurses with non-blaming responses will have high non-blaming culture (Saudi Patient Safety Center, 2020). Managers have an essential role in creating open communication, maintaining teamwork and commitment within the organization, and learning from mistakes to create non-blaming culture. Management, especially hospital management, should develop a culture of justice, openness, and learning using various media. One is the just culture algorithm, which has proven effective in making decisions and creating open, fair, and reliable communication so that staff can report without fear of being blamed (Brindley et al., 2014).

Frequency of Event Reporting

Research before the COVID-19 Pandemic found the average frequency of event reporting was 64.35% (Danielsson et al., 2019; Y. mi Lee & Oh, 2020; Tlili et al., 2020). This study found that the score was

4.25% lower than the previous studies. During the COVID-19 Pandemic, event reporting decreased (Denning et al., 2020). Staff tends to be afraid to report patient safety incident because they think it will be a boomerang for themselves in the future (Chegini et al., 2020). Management, especially hospital management, should support staff in event reporting to identify errors and communication failures (Umberfield et al., 2019). Organizational support, training, instruments for patient safety incident analysis, and the role of head nurses in leading and strengthening the staff could increase the frequency of event reporting (Anderson and Kodate, 2015).

Staffing

Research before the COVID-19 Pandemic found average staffing score was 47.24% (Danielsson et al., 2019; Y. mi Lee & Oh, 2020; Tlili et al., 2020). This study found that the score was 6.88% higher than the previous studies. Some recommendations for regulating human resources during the Pandemic include planning and implementing adequate training either online or offline. Furthermore, other suggestions were determining the ratio of nurses to patients with suspected or positive Covid-19 patients (e.g., 1:1 or 2:1 in ICU). Moreover, hospital management should increase teamwork, organize care units (covid and non-covid patients), and ensure staff safety in providing care (Saudi Patient Safety Center, 2020).

Nurses' perceptions of patient safety

Research before the COVID-19 Pandemic found the average score of nurses' perceptions of patient safety was 59.61% (Danielsson et al., 2019; Y. mi Lee & Oh, 2020; Tlili et al., 2020). This study found that the score was 4.31% higher than the previous studies. However, nurses' perception of patient safety was relatively low. It can be due to the high workload among nurses. Nurses' perceptions of patient safety in this study highlighted nurses' view of patient safety as a priority, meaning that despite the increased workload, nurses still concern with patient safety. Therefore, the role of hospital management and the head nurses in improving nurses' perception is crucial. Thus, nurses can ensure patient safety (Lotfi et al., 2018).

Handover and patient transfer

Research before the COVID-19 Pandemic found average handover and patient transfer was 61.95% (Danielsson et al., 2019; Lee and Oh, 2020). This study found that the score was 6.92% higher than the previous studies. Thus, hospital management should support the handover and patient transfer process.

The standard operating procedure of Hospital access and service continuity (here and after called ARK) 2.2 establishes processes for managing patient flows throughout the hospital, one of which is the patient transfer process (KARS, 2019). In addition, ARK 3.3 contains hospital information about patients in the transfer process. There should be transfer records between wards in the transfer regulations in the handover process to ensure the transfer of essential information. There is a handover process between the sending and receiving health workers in the patient transfer process. Therefore, SKP 2.2 regulates the

communication process in the patient handover (KARS, 2019). Patient handover is the transfer of professional and accountable responsibilities from all aspects of patient care or patient pools to other care providers (Robertson et al., 2014). Therefore, communication is crucial for patient safety, particularly in patient handover (Methangkool et al., 2019). Patient handover is essential to continuous care for patients in the transitional phase of care. In addition, patient handover between wards in the hospital is an integral dimension of patient safety. Thus, nurses should pay the same attention as other nurse duties, such as preparing medicines or wound care (Ballantyne, 2017).

CONCLUSION

The patient safety culture in the COVID-19 referral hospital still needed improvement. A good patient safety culture can increase patient safety and the quality of health services. In addition, feedback and communication had the lowest score in the dimension of patient safety culture. Meanwhile, the best score was an organizational improvement. Hospital management should optimize all dimensions of patient safety culture to ensure patient safety. Future research could explore predisposing factors of patient safety culture.

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Mental Health Stigma Among Generation Z Students in Salafi Islamic Boarding Schools

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A B S T R A C T

Salafi Islamic boarding schools adhering to traditional religious learning can potentially create mental health issues. The mental health problems often experienced by Generation Z students in Islamic boarding schools potentially led to the emergence of stigma. This study aims to describe mental health stigma among Generation Z students in Salafi Islamic boarding schools. It used a quantitative design and a survey approach. The population was Generation Z students in Salafi Islamic boarding schools. Furthermore, there were 155 samples by stratified random sampling. This study was carried out in 3 boarding schools in Bantur District, Malang Regency, from January to February 2022. The variable was mental health stigma. The data were collected by distributing a questionnaire to Generation Z students at Salafi Islamic boarding schools in the Bantur District. The questionnaire used the Peer Mental Health Stigmatization Scale (PMHSS). The PMHSS consisted of 2 indicators: Stigma agreement (self-stigma) and stigma awareness (social stigma). Data analysis used median and percentile values because the data was not normally distributed. Normality test used Kolmogorov-Smirnov using SPSS Statistics 25. The results showed that social stigma had a median value of 40, self-stigma had 40, and overall mental health stigma had 80. In conclusion, Generation Z students in the Salafi Islamic boarding schools had a high mental health stigma. Therefore, efforts to reduce and prevent the Stigma in Salafi Islamic boarding schools through a technology-centered approach and cross-sectorial collaboration with Public Health Center or health workers are crucial.

INTRODUCTION

Mental health can impact health status individually, socially, and in the environment. Depression, anxiety, stress, substance abuse, and psychotic disorders are the manifestations of mental health problems (Stuart, 2013). Thus, mental health issues are essential. The World Health Organization (WHO) stated that 450 million people lived with mental disorders in 2013. Furthermore, In Indonesia, the number was 1.7 million in 2013. Unfortunately, the incidence in 2018 increased to 7% from 2013. In addition, mental health issues in 2018 also increased, with 6.1% of individuals over 15 years old experiencing depression. Furthermore, emotional, and mental health problems also increased to 9.8% from 6% in 2013, with individuals aged 15 years and above being predominant (Kementerian Kesehatan Republik Indonesia, 2018).

Lack of public knowledge about mental health care correlated with increasing mental health problems in society (Yin et al., 2020). Further, it can create a stigma toward people with mental health problems. In addition, the results of an Indonesian study of 1,269 people noted that stigma was influenced by several factors, one of which was age (Hartini et al., 2018). Furthermore, external factors are also essential in the individuals' ability to receive knowledge. Knowledge will change a person's perception of an object,

either a negative or positive perception. One of the external factors was the media or technology (Baki, Birgoren, and Aktepe, 2018).

Currently, the Indonesian population is dominated by Generation Z, 15–25 years old. Generation Z is an intelligent generation that constantly uses the Internet for information and learning media (Verma, BHARDWAJ and SACHAN, 2019). However, Generation Z is at risk of experiencing mental health problems, especially the risk of early psychosis. It is because the generation is often more concerned about technology than their social environment (Enos, 2020). Therefore, Generation Z potentially experiences a stigma of mental illness (Stangl et al., 2019).

Indonesia is the country with the largest Muslim population in the world. Thus, boarding schools in Indonesia are overgrowing (Muazza et al., 2018). Nowadays, many Generation Z parents choose to send their children to Islamic boarding schools. However, schooling in Islamic boarding schools potentially affects the children's mental health. They feel sad, lonely, and excluded, face difficulties adapting, and come into fights or violent engagements between friends (Khamida et al., 2020). The mental health problems often experienced by Generation Z students in Islamic boarding schools led to the emergence of stigma. The stigma is influenced by gender and level of piety (Abuhammad and Al-Natour, 2021).

Islamic boarding schools, especially Salafi ones, are known to be traditional institutions administering informal learning. Thus, generation Z probably lacks health information because Salafi Islamic Boarding Schools only focus on religious education. Their students think and lead their lives under the guidance of religion (Nor, 2021). A preliminary study on three students of Generation Z in Salafi Islamic boarding schools found that their perception of individuals with mental illness was due to evil spirit possession, empty heart disease, and a lack of worship or intimacy with God. They believed that ruqyah by Kyai could overcome mental health issues. In addition, two students stated that female students in the Islamic boarding school often get possessed by evil spirits and lose their minds. That preliminary study illustrated the problems faced by Generation Z students within the Salafi Islamic boarding school, especially concerning mental health stigma. This study aims to describe mental health stigma among Generation Z students in Salafi Islamic boarding schools.

METHOD

This research used a quantitative design and a survey approach. The population was Generation Z students in Salafi Islamic boarding schools. Furthermore, there were 155 samples by stratified random sampling. This study was carried out in 3 boarding schools in Bantur District, Malang Regency, from January to February 2022. The variable was mental health stigma. The data were collected by distributing a questionnaire to students at Salafi Islamic boarding schools in the Bantur District.

The questionnaire used the Peer Mental Health Stigmatization Scale (PMHSS) (Mckeague et al., 2015). The PMHSS consisted of 2 indicators: stigma agreement (self-stigma) and stigma awareness (social stigma). Furthermore, stigma agreement refers to young people's beliefs about stereotypes, prejudices, and discriminatory behavior. Meanwhile, stigma awareness refers to their perception of stigmatized attitudes espoused by most members of society (Nearchou et al., 2021). There were 24 question items in the PMHSS, consisting of eight questions on self-stigma, eight on social stigma, and eight on positive questions that were not of both scales (4 on social stigma and four on personal stigma). The scoring of the instrument was based on the Likert scale, consisting of Strongly disagree (score=1), Disagree (score=2), neither agree nor disagree (score=3), agree (score=4), and strongly agree (score=5). The questionnaire interpretation was the higher the value, the greater the social stigma, self-stigma, and overall mental health stigma. Data analysis used mean and standard deviation for data with normal distribution. However, when the data distribution was not normal, it used median and percentile values. Normality test used Kolmogorov-Smirnov using SPSS Statistics 25. This research has received ethical approval from the Ethics Committee of STIKES Kepanjen Malang.

RESULT

Most respondents were female (75.5%) and in early adolescence (61.2%). In addition, almost half of them confessed to enrolling in Islamic Boarding Schools due to their parent's advice. Nearly all the respondents disagreed that traumatic experience was the cause of mental health problems (90.3%). Most believed that mental health problems were God's punishment (96.1%) and were caused by possession or similar phenomenon (90.3%). Some students also perceived that physical violence causes mental health problems (60.6%) (Table 1).

Table 1 Characteristics of Generation Z respondents in Salafi Islamic boarding schools (n = 155)

Characteristics of respondents	Frequency	Percentage (%)
Sex		
Male	66	42.5
Female	89	75.5
Age		
Early adolescent (12–16 years old)	95	61.2
Late adolescent (17–25 years old)	60	38.8
Reason to enroll in Islamic Boarding School		
Peer invitation	34	21.9
Voluntary decision	43	27.8
Parent's advice	64	41.2
A desire to escape	14	9.0
Have you ever seen or met a friend who has strange behavior?		
Yes	148	86.5
No	7	4.5
The cause of mental health problems is traumatic experiences.		
Agree	15	9.7
Disagree	140	90.3

Mental health problems are God's punishment.		
Agree	149	96.1
Disagree	6	3.9
Mental health problems result from possession or similar phenomenon.		
Agree	140	90.3
Disagree	15	9.7
The cause of mental health problems is physical violence.		
Agree	94	60.6
Disagree	61	39.4

Figure 1 indicates the Q-Q plot of mental health stigma among Generation Z in the Salafi Islamic boarding schools mostly went along a line, but some strayed far from the line. Therefore, the data were assumed not to be normally distributed. In addition, the result of the Kolmogorov-Smirnov normality test was 0.000 ($\alpha < 0.05$). In conclusion, the data were not normally distributed. Thus, the concentration and dissemination of data were measured using median and percentile values.

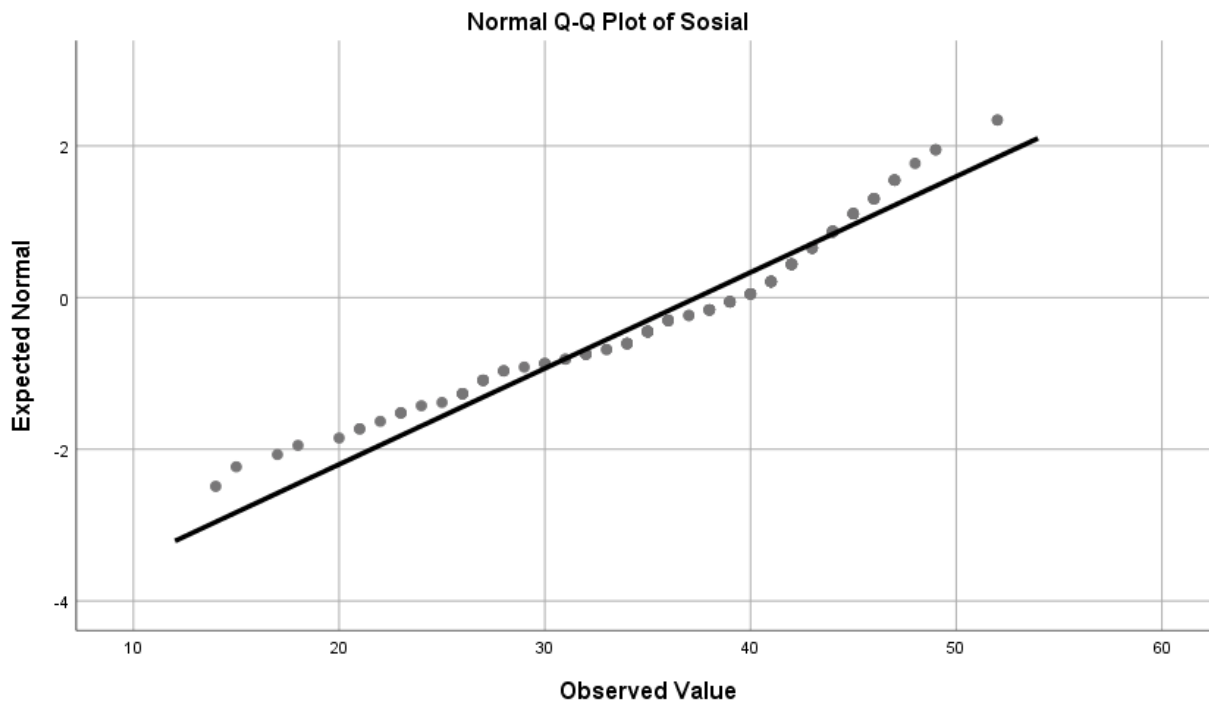


Figure 1. Q-Q plot of mental health stigma among Generation Z in the Salafi Islamic boarding schools

Mental health stigma has two types: social stigma and self-stigma. The social stigma had a median value of 40. In addition, self-stigma had a median value of 40 (Table 2). Thus, respondents demonstrated a high level of social stigma and self-stigma. Furthermore, overall mental health stigma among Generation Z in the Salafi Islamic boarding schools had a median value of 80 (Table 3). Therefore, overall mental health stigma was high among Generation Z in the Salafi Islamic boarding schools.

Table 2. Mental health stigma among Generation Z in the Salafi Islamic boarding schools per indicator (n = 155)

Mental health stigma	Minimum	Maximum	Median
Social Stigma	14	52	40
Self-stigma	12	56	40
Overall mental health stigma	26	102	80

DISCUSSION

Mental health stigma consists of two types, self-stigma, and social stigma. Our findings found that the self-stigma among Generation Z in this study was high. Self-stigma is a feeling of having mental health problems, and the person experiencing it can recognize and approve of the stigma of their condition. It can result in the person behaving negatively toward themselves (Schwarzbold *et al.*, 2021). The factors affecting self-stigma include sociodemographics, consisting of gender, age, status, and education. In this study, all respondents were Generation Z (12–25 years old). The generation is of the productive age range and is incredibly well-versed in using technology (Jaciow and Wolny, 2021).

In addition, this study revealed that the social stigma among Generation Z in the Salafi Islamic boarding schools was high. Social Stigma refers to negative characteristics attached to a person due to environmental influence (Jung, von Sternberg, and Davis, 2017). The high social stigma was probably due to a lack of knowledge of mental health problems among Islamic Boarding Schools students. Inadequate knowledge about mental health issues can raise prejudices, stereotypes, discrimination, and exclusion (Stangl *et al.*, 2019). Salafi Islamic boarding schools still adhere to traditional education systems. The learning methods are still centered on studying *kitab kuning*. Therefore, the novelty literature available is minimal (Musaddad, 2021). As a result, the literacy levels of Generation Z in the Salafi Islamic Boarding Schools related to mental health problems, especially self-stigma, and social stigma, are inadequate.

Furthermore, this paper revealed that the overall mental health stigma among Generation Z in the Salafi Islamic boarding schools was high. One factor affecting mental health stigma is the education system applied in Islamic boarding schools, including using technology as a source of literacy to improve students' knowledge (Kholili, 2021). In addition, the phenomena of Islamic boarding schools or *Kyai* not involving health workers in health problem prevention are ubiquitous. Moreover, many students have more trust in the opinions of *Kyai* than in health education from health workers (Bajari, Wahyudin, and Erlandia, 2019).

Cross-sectorial collaboration can prevent mental health stigma among Generation Z in Islamic Boarding Schools. One is establishing a Poskestren to avoid health problems in Islamic Boarding Schools. In addition, using media and technology concerning health knowledge is essential because Generation Z heavily relies on technology in learning (Seibert, 2021). Another preventive effort is using a

psychotherapeutic approach, such as psychoeducation. Furthermore, a psychological approach is crucial to prevent mental health problems in the community (Alfianto *et al.*, 2019). Playing Sufi music also can be one way in Islamic boarding schools (Gurbuz-Dogan *et al.*, 2021). Students also believe in the spiritual approach used by *Kyai*. Therefore, the mental health stigma among Generation Z in Islamic boarding schools can be overcome by the collaboration between *Kyai* and health workers.

Ruqyah (n): Islamic ritual used to expel demons or jinn that disturb the body of Muslims, like Exorcism in Catholicism

Kyai (n): an expert in Islam, usually used among the ethnic Javanese people.

Kitab kuning (n): the traditional set of Islamic texts used by the educational curriculum of the Islamic seminary in Indonesia

Poskestren (n): it stands for Islamic Boarding School Health Post. It is part of one form of Community-Based Health Efforts (UKBM) in Islamic boarding schools.

CONCLUSION

In conclusion, Generation Z students in the Salafi Islamic boarding schools had a high mental health stigma. Therefore, efforts to reduce and prevent the Stigma in Salafi Islamic boarding schools through a technology-centered approach and cross-sectorial collaboration with Public Health Center or health workers are crucial.

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The Determinant Factors in Managing Dengue Hemorrhagic Fever During the Covid-19 Pandemic: A Literature Review

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A B S T R A C T

During the COVID-19 Pandemic, differentiating tropical infectious diseases and COVID-19 can be challenging due to overlapping clinical presentations. Fever and nonspecific symptoms in early COVID-19 may be challenging to distinguish from dengue hemorrhagic fever (DHF) and malaria because respiratory signs may be absent or manifest later in the disease course. This literature review analyzes the determinant factors in managing DHF during the COVID-19 Pandemic. This paper was a systematic literature review of national and international journals in the Google Scholar and PubMed databases from 2019 to 2022. We used the PICOS framework to find articles. The Indonesian and English keywords were the speed of health service, dengue hemorrhagic fever, and COVID-19. There were two included studies in this systematic review. The results showed that during the Covid-19 Pandemic and the dengue epidemic, a triage strategy was crucial to detect Covid-19 that could potentially be misdiagnosed as DHF. In addition, the first delay in seeking care treatment for dengue infection was due to financial constraints and previous dengue infection. Moreover, the second delay was because of the availability of transportation, traffic density, and residency location. Furthermore, the third delay was because of the hospital's capacity. Thus, the determinant factors of managing Dengue Hemorrhagic Fever during the COVID-19 Pandemic were the similarity of the signs and symptoms of dengue fever with Covid-19, financial aspects, transportation factors, the hospital distance, and hospital capacity.

INTRODUCTION

Dengue fever and coronavirus disease 2019 (COVID-19) has begun to overlap, especially in tropical and subtropical regions. It is due to the high prevalence of dengue fever in these regions during the COVID-19 Pandemic (Agudelo Rojas, Tello-Cajiao, and Rosso, 2021). Dengue Hemorrhagic Fever (DHF) is an acute epidemic disease caused by a virus transmitted by *Aedes aegypti* and *Aedes albopictus*. The symptoms from mild to high fever, headaches, pain in the eyes, muscles, and joints, and spontaneous bleeding. Dengue fever can appear throughout the year and can affect all age groups. In addition, the course of DHF is speedy. Adequate DHF management can reduce the complications, namely Dengue Shock Syndrome and mortality (Heris Santy and Arminah, 2015)

World Health Organization (2011) estimates around 50-100 million annually. DHF is the leading cause of mortality and morbidity in Southeast Asia, with 57% occurring in Indonesia. Furthermore, its incidence in Indonesia until July 2020 reached 71,633. However, its number was lower compared to 2019, with 112,954 cases (Indonesian Ministry of Health, 2020). During the Covid-19 Pandemic in early 2020, the Ministry of Health Republic of Indonesia recorded more than 65,000 cases of dengue fever throughout

Indonesia. There were 100 to 500 cases of dengue fever per day in 2020. Moreover, the death rate for dengue fever was almost 400 people. It is a challenge in the Covid-19 Pandemic, especially for individuals in malaria-endemic areas (KPC PEN, 2020).

People avoid medical care during the COVID-19 Pandemic. The anxiety about COVID-19 transmission in health facilities makes individuals with chronic diseases unable to control their illnesses. They also delay complaints, so the risk of complications increases. The speed of health services during the Pandemic may experience an extended time due to screening for COVID-19, whether a rapid test or a CT scan (Kompas, 2020b). Confirmed cases of COVID-19 in the West Kalimantan region amounted to 1,675 people, 1,335 cured (79.70%), and 21 dead (Kumparan, 2020). These conditions can impact the speed of managing DHF.

The rapid spread of COVID-19 and DHF in the Pandemic poses a severe threat to human health and severely impacts public health. Therefore, adequate management is crucial to increase patient recovery. Thus, the researchers conducted a literature review on determinant factors in handling DHF cases during the COVID-19 Pandemic.

METHOD

This paper was a systematic literature review of national and international journals in the Google Scholar and PubMed databases. Authors searched literature sources by entering keywords and selected journals based on the inclusion and exclusion criteria. The population was all journals with the determinants of the speed of service for DHF. Furthermore, the sample was journals about the determinants of managing DHF during the COVID-19 Pandemic. We used the PICOS framework to find articles. The framework consists of the population/problem to be analyzed in scientific work, intervention or action taken on the problem, comparison from other management, outcomes or results obtained in previous studies that follow the themes of the literature review, and study design used to review.

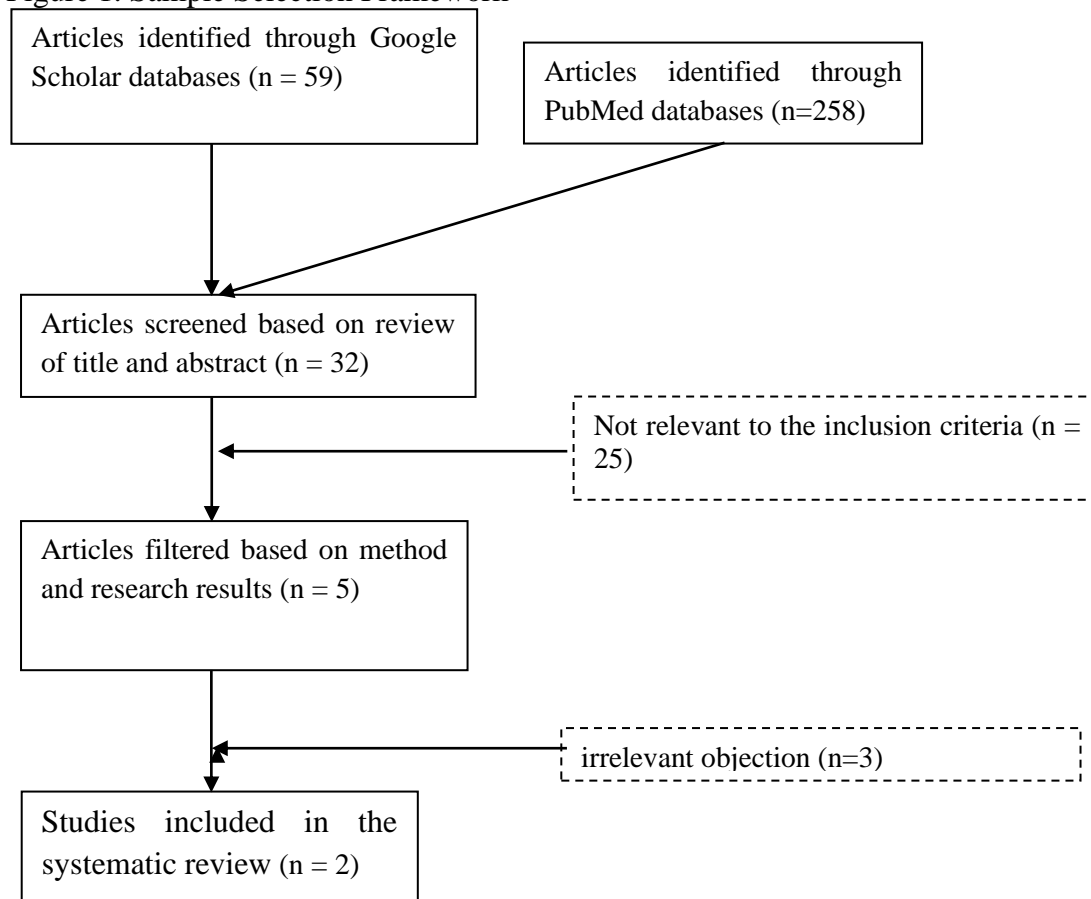
Table 1. Inclusion and exclusion criteria with format PICOS

Criteria	Inclusion	Exclusion
Population/problem	Individuals with DHF in the COVID-19 Pandemic	
Intervention	No intervention	
Comparison	No comparison	
Outcome	Managing DHF in the COVID-19 pandemic	
Study design	Descriptive study and Mixed Method Study	
Publication years	<i>Post-2019</i>	
Language	English, Indonesian	Another language English and Indonesian

We initially searched articles using Google Scholar and PubMed from 2019 to 2022. We used keywords and Boolean operators (AND, OR NOT or AND NOT) to expand or specify the search, making it easier

to determine the used articles. The Indonesian and English keywords were the speed of health service, dengue hemorrhagic fever, and COVID-19. There were 317 articles in national and international journals with the keywords. Furthermore, diagram 1 shows the sample selection framework in this literature review.

Figure 1. Sample Selection Framework



RESULT

The reviewed articles were two studies with different journals, titles, number of samples, places of study, and duration. Still, both had an overview of the determinant factors of managing DHF during the COVID-19 Pandemic. The types of research from the two journals were qualitative and mixed method. Table 1 summarizes the details of both.

Table 1. The Characteristics of the articles reviewed

Author / Years	Title	DOI	Objective	Method	Results
(Wee <i>et al.</i> , 2020)	Experience of a Tertiary Hospital in Singapore with Management of a Dual Outbreak of COVID-19 and Dengue	https://doi.org/10.4269%2Fajtmh.20-0703	To describe how the triage strategy to eliminate DHF patients from Covid-19 patients	Observational research in Tertiary Hospital in Singapore from January 2020 to May 2020 in the Emergency Department (ED)	A triage strategy that receives febrile patients with viral prodromal and no epidemiology COVID-19 risk to designated wards for COVID-19 testing over two months successfully reduced the risk of healthcare-related transmission from undetected cases during the dual outbreaks of COVID-19 and dengue fever.
(Ligsay <i>et al.</i> , 2021)	“We Tried to Borrow Money, but No One Helped.” Assessing the Three-Delay Model Factors Affecting the Healthcare Service Delivery among Dengue Patients during COVID-19 Surge in a Public Tertiary Hospital: A Convergent Parallel Mixed Methods Study	https://doi.org/10.3390/ijerph182211851	To describe the delay in care among parents of the patients seeking treatment for dengue and examine the factors affecting the severity of dengue (dengue with warning signs; severe dengue)	The study used a convergent parallel design mixed-method approach using Key Informant Interviews (KII) and a survey guided by the Three-Delay Model among 24 respondents at the National Children’s Hospital (NCH).	Results showed that the first delay in seeking care treatment for dengue infection was due to financial constraints and previous dengue infection. In addition, the second delay was because of the availability of transportation, traffic density, and residency location. Furthermore, the third delay was because of the hospital's capacity. Moreover, the bivariable analysis showed that travel time from home to NCH, health care service from previous health facilities, and parents’ educational background played a role in the severity of dengue infection.

DISCUSSION

Tropical areas have a high prevalence of the arboviral disease. During the COVID-19 Pandemic, differentiating tropical infectious diseases and COVID-19 can be challenging due to overlapping clinical presentations. Fever and nonspecific symptoms in early COVID-19 may be challenging to distinguish from dengue fever and malaria because respiratory signs may be absent or manifest later in the disease course (Wee *et al.*, 2020). A study by Wee *et al.* (2020) examined the cases of dengue fever during a pandemic. The study explained that during the Covid-19 Pandemic and the dengue epidemic, a triage strategy was crucial to detect Covid-19 that could potentially be misdiagnosed as DHF. The study suggested that adherence to strict triage algorithms to differentiate disease is essential for infection prevention and control. In addition, the likelihood of coinfection, although low, needs to be eliminated. Similar clinical manifestations shared by Covid-19 and dengue fever have raised concerns, especially in dengue-endemic countries with limited resources and diagnostic challenges.

In addition, the cross-reactivity of the immune response in this infection is an emerging concern, as pre-existing DENV antibodies can potentially influence Covid-19 via antibody-dependent enhancement (ADE). An Italian study found that Covid-19 patients presented with erythematous skin, rash, urticaria, and vesicles. Those skin manifestations were also reported in Madrid. Thus, skin manifestations, including rash or petechiae, increase the challenge of differentiating dengue and Covid-19 in dengue-endemic areas. In Indonesia, there are no reports of misdiagnoses between Covid-19 and DHF in the literature. However, there has been an increase in cases of dengue fever in the country. There have been 68,000 cases since 21 June 2020 (Li *et al.*, 2020). Furthermore, the Ministry of Health Republic of Indonesia in early 2021 noted that cases of dengue fever reached 100 to 500 incidences per day.

Wee *et al.* (2020) found that tertiary hospitals in dengue-endemic countries competed with Covid-19 during the dengue epidemic. Dengue fever became the primary differential diagnosis in a small proportion of Covid-19 patients, likely because of the early availability of chest imaging and basic diagnostic testing at the triage. Therefore, in most cases, clinicians could differentiate between dengue hemorrhagic fever and Covid-19. However, there was potential for dengue misdiagnosis in the minority of unexpected Covid-19 cases without epidemiological risk factors and dengue-compatible clinical syndromes (fever, thrombocytopenia, and absence of pulmonary infiltrate). It is due to the false-positive dengue IgM serology by Rapid Diagnostic Tests (RDT). A triage strategy in admitting febrile patients with viral prodromal and no epidemiological risk for COVID-19 to designated wards for COVID-19 testing over two months reduced the risk of healthcare-associated transmission.

In addition, Ligsay *et al.* (2021) conducted a study at the National Children's Hospital (NCH) located in Quezon City, a special tertiary and training hospital under the Department of Health (DOH) in the Philippines that provides care to children. Data collection was from February to March 2021 during the

COVID-19 community quarantine restrictions in Metro Manila. The study described the delay to care among parents of patients seeking treatment for dengue infection in Quezon City, the Philippines, using the Three-Delay Model. In addition, it determined and estimated the effect of the time-delay factors on the patients' dengue infection severity. The study was carried out on 24 dengue patients. The parents in the study had an average age (\pm SD) of 33.8 (\pm 8.3) years old, did not go to college (63%), and were primarily residents of Quezon City (63%). In addition, most patients were 0-12 years old (67%) and females (63%). Furthermore, they were of low socioeconomic class or had an average household income of PHP 0–10,000.00 (68%). Figure 1 presents the factors affecting the delay to care among parents of the patient's seeking treatment for dengue infection (Ligsay *et al.*, 2021).

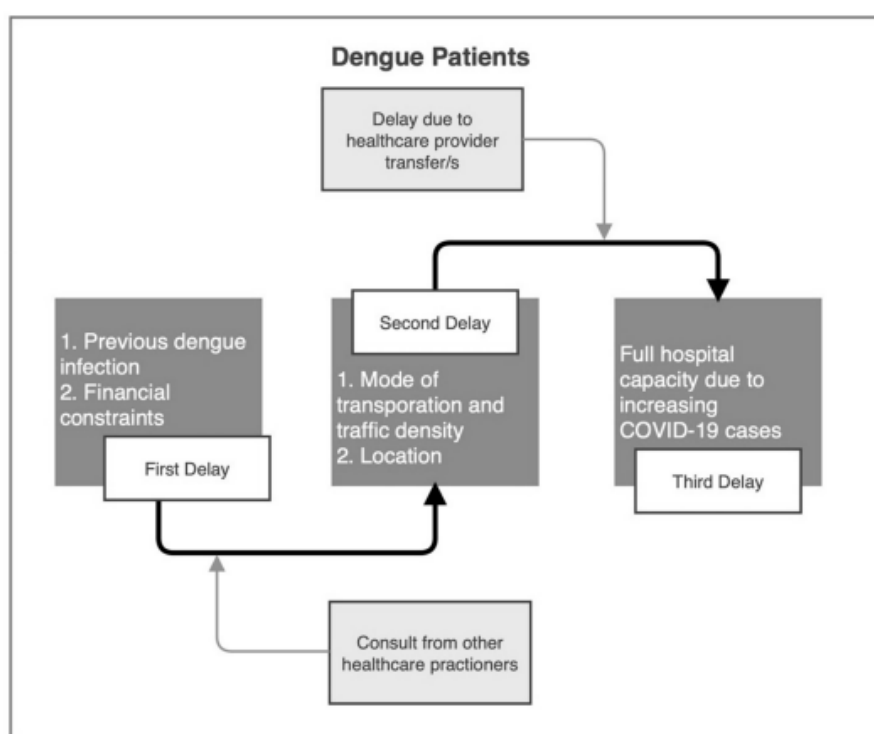


Figure 1. Three-Delay model for the qualitative assessment of delay to care among parents of the patient's seeking treatment for dengue infection (Ligsay *et al.*, 2021).

The study results found that the first delay among most parents of patients seeking treatment for dengue infection was due to the inability to cover the costs of hospitalization or medical treatment. Thus, it led to their hesitancy to bring their child to the hospital for treatment. However, most parents immediately brought their child to the nearest health facility when the patient's symptoms worsened. In addition, another first delay was due to a previous dengue infection. Parents with previous dengue infection hastened the decision-making during their child's illness.

Furthermore, the availability of transportation, traffic density, and residency location was second delay factors affecting the healthcare service delivery among Dengue Patients during COVID-19. Moreover, the

third delay was full hospital capacity due to increasing COVID-19 cases. NCH was not their first-choice health facility because it is not near their residence. Most parents opted for NCH because of many hospital refusals due to increasing COVID-19 cases, leading to some hospitals operating at and above total capacity. The parents were also aware that NCH might not immediately administer proper treatment to their child because of COVID-19 cases, but they still waited for their child to get treated even though it took them many hours (Ligsay *et al.*, 2021).

Delays or errors in diagnosis can lead to inadequate treatment that harms patients and health workers without appropriate personal protective equipment (PPE). A diagnostic test with high specificity is crucial for diagnosing dengue infection quickly and accurately calculated from when the patient arrives until treatment. A good response time for patients is 5 minutes. The factors affecting response time were the number of personnel and other supporting components such as laboratory, radiology, pharmacy, and administrative services. On-time response in the hospital is when the time required does not exceed the standard time (Fadhilah, Harahap, and Lestari, 2015). Delays in identifying the early symptoms, be it from dengue fever, coronavirus, or other causes, will affect the speed of treatment and the rate of recovery.

CONCLUSION

The determinant factors of managing Dengue Hemorrhagic Fever during the COVID-19 Pandemic were the similarity of the signs and symptoms of dengue fever with Covid-19, financial aspects, transportation factors, the hospital distance, and hospital capacity.

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Type and Duration of Mask Use Related To Acne Vulgaris During The Pandemic Period

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A B S T R A C T

The masks' use has been a suggested strategy to counter COVID-19 transmission throughout this disease outbreak; however, wearing masks tightly closed for an extended period can cause acne vulgaris. The mask's form and duration of use are two factors that may affect the occurrence of acne vulgaris. Therefore, more research is needed to determine the impact of using masks on the prevalence of acne vulgaris. This study aimed to analyze the relationship between the type and duration of mask use and the prevalence of acne vulgaris in the citizens of Kawistowindu Village during the pandemic. This study used an analytical-observational study with a cross-sectional approach, with a sample of 63 people who met the inclusion and exclusion criteria throughout the neighborhood of RT.02 RW.01 Kawistowindu Village. The sample was chosen using a simple random sampling technique. Questionnaire forms, history-taking instruments, and physical examination techniques were used to collect data—the analysis used the Chi-Square test. The results showed that during the pandemic era, there was a significant correlation between the type of mask and the duration of mask use with the occurrence of acne vulgaris ($p=0.000$; $p=0.004$). In conclusion, in the pandemic era, the mask form and duration of mask use could be linked to acne vulgaris

INTRODUCTION

COVID-19 has emerged as a global health problem since 2020. The World Health Organization then designated the COVID-19 pandemic on March 11, 2020 (Kemenkes RI, 2020a). The cause of COVID-19 is Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) (Kemenkes RI, 2020b), whose virus allows it to be spread through aerosols or droplets directly or indirectly (Wang & Du, 2020; WHO, 2020d).

WHO recommends using masks to prevent and limit the spread and transmission of COVID-19 (Susilo et al., 2020). A mask is a self-protection device used to prevent and limit the spread of COVID-19 (WHO, 2020a). In general, masks are divided into three groups: medical masks, non-medical masks, and N95 masks. The Centers for Disease Control and Prevention (CDC) recommends wearing a cloth mask because some individuals with COVID-19 without symptoms can still transmit the SARS-CoV-2 virus (CDC & Centers for Disease Control and Prevention, 2020).

Medical masks are mandatory for all health workers and those entering hospitals or other health facilities. In addition, N95 masks are recommended for health workers who treat COVID-19 patients (WHO, 2020b). A Study had shown that prolonged use of tight masks may lead various skin problems such as

dermatitis, acne, pigmentation, and redness of the face. The most frequently reported problem is the acne incidence (Hidajat, 2020).

Acne is a chronic inflammatory skin disease and obstruction of the pilosebaceous gland that has diverse clinical images such as papules, comedones, pustules, scar tissue, and nodules (Han et al., 2020). There is a distinctive clinical picture of acne caused using masks, namely the acne on the face area covered by the mask, such as cheeks, nose, chin, and surrounding areas of the mouth. Acne caused by masks is estimated to be linked to various factors such as the material or type of mask, duration of use, acne history, and cosmetics use (Hidajat, 2020).

Acne caused by wearing a mask is estimated to be caused by a combination of stress, friction, and stretching caused by prolonged use of the mask. Prolonged use of a tight mask can lead to humid and heated conditions and may endanger local pressure on the skin to obstruct the pilosebaceous glands (Hidajat, 2020). High temperatures may as well affect acne because they negatively affect the sebum excretion rate (Sebum excretion rate/SER). SER will increase by 10% for every 1°C increase in temperature (Han et al., 2020). Changes in surface sebum composition and skin hydration can increase acne flares if masks are used for a long time during the COVID-19 pandemic (Hidajat, 2020).

The incidence of acne caused by masks has been reported in various research publications. In 2004, Tan reported two cases of acne in health workers with a history of about three months of continuous use of N95 masks. They all reported having the same distribution of acne exacerbations, namely in the cheek, chin, and perioral areas. Another study, conducted by Wasfa, involved 150 health professionals with mask-induced acne, which was reported at 56%. A previous study found that 24 people (28%) and while 61 people (72%) developed new acne lesions after starting to wear masks for extended periods (Wasfa et al., 2020).

Based on the above, mask use is strongly recommended to prevent the spread of COVID-19 during the pandemic. However, more attention is needed on the impact of mask use on the incidence of acne vulgaris so that researchers can identify the correlation between the type and duration of mask use.

METHOD

This study used an analytic observational method with a cross-sectional approach. This study was conducted in January 2022 in RT.02 RW.01 Kawistowindu Village, Duduksampeyan District, Gresik, East Java. The sample of 63 people was calculated using the Slovin formula and chosen with a simple random sampling technique. The inclusion criteria are being registered as a member of the Kawistowindu Village community of RT. 02 RW. 01 and use masks for daily activities outside the room, aged between 14 and 40. The exclusion criteria are suffering from facial skin diseases such as perioral dermatitis and rosacea, current menstruation, family history of severe acne, and daily use of cosmetics. The signing of

the informed consent was carried out before data collection. Data were collected using a questionnaire that was distributed to the subjects and by taking anamnesis, as well as a physical examination accompanied by a general practitioner to assess the type of skin and UKK (Ujud of Skin Disorders) experienced by the sample. Data were analyzed using the Chi-Square test. This study has been approved by the Faculty of Medicine Ethics Committee, University of Muhammadiyah Semarang No.149/EC/FK/2021.

RESULT

Table 1. The Characteristics of the sample community RT.02 RW.01 Kawistowindu Village.

Variable	Frequency (%)
Age	
14-27	28 (44,4)
28-40	35 (55,6)
Gender	
Male	32 (50,8)
Female	31 (49,2)
Occupation	
Unemployed	15 (23,8)
Entrepreneur	12 (19,0)
Farmer	22 (34,9)
Trader	11 (17,5)
Farm Worker	3 (4,8)
Skin Type	
Dry	2 (3,2)
Normal	21 (33,3)
Oily	14 (22,2)
Combination	26 (41,3)
Mask Type	
Medical Mask	25 (39,7)
Non-Medical Masks	38 (60,3)
Duration of Mask Usage	
≥ 6 hours	30 (47,6)
< 6 hours	33 (52,4)
The Incidence of Acne Vulgaris	
With Acne	23 (36,5)
Without Acne	40 (63,5)
Area of Acne Vulgaris	
No acne	40 (63,5)
Cheek	11 (17,5)
Nose	2 (3,2)
Chin	9 (14,3)
Around the Lips	1 (1,6)

In Table 1, the most significant sample was aged 28–40, with equal to 35 people (55.6%). By gender, the sample ratio is 1:1. Most samples are farmers, of which 22 people (34.9%). There are 26 samples (41.3%) of the complex skin types, 38 people (60.3%) used non-medical mask types, 33 samples (52.7%) used the masks less than 6 hours a day, 40 people (63.5%) did not develop acne vulgaris, and 11 samples (17.5%) of the most common area of acne were cheeks.

Table 2. The correlation between mask types and duration of use and the incidence of acne vulgaris.

Variable	incidence of Acne Vulgaris		p	RP (CI 95%)
	Yes n (%)	No n (%)		
Mask Type				
Medical Mask	17 (68)	8 (32)	0,000	4,307 (1,970-9,413)
Non-Medical Mask	6 (15,8)	32 (84,2)		
Duration of Mask Usage				
≥ 6 hours/day	17 (56,7)	13 (43,3)	0,004	3,117 (1,417 –6,857)
< 6 hours/day	6 (18,2)	27 (81,8)		

Based on table 2, the results show that the sample using medical masks who experienced acne vulgaris was 17 people (68%), while the sample using non-medical masks who did not experience acne vulgaris was 32 people (84.2%). The analysis showed a significant correlation between the type of mask used and the incidence of acne vulgaris ($p=0.000$). According to the table, the value of $RP=4.307$ (CI 95% 1,970-9,413). This finding indicates that people who use a medical mask are four times more likely to experience acne than those who use a non-medical mask.

In addition, based on Table 2, the samples using masks with more than six hours per day were 17 people (56.7%), while the samples using masks with less than six hours per day were 27 people (81.8%). This result shows that people who use masks for more than six hours a day have a higher incidence of acne than those who use masks for less than six hours. This analysis found that the duration of mask use was significantly related to the incidence of acne vulgaris ($p=0.004$). Based on this table, the value is $RP=3.117$ (CI 95% 1.417-6.857). It shows that those who use masks for more than six hours per day are three times more likely to develop acne vulgaris than those who use masks for less than six hours.

DISCUSSION

This study has shown that the types of masks are related to the incidence of acne vulgaris. Samples using medical masks are more likely to develop acne than non-medical masks. This result is consistent with a *cross-sectional* study conducted by Alkubaisi that showed a significant correlation between mask types and skin diseases. This study found that the sample that experienced the most acne vulgaris was the sample that used the type of medical mask (Alkubaisi, 2020). Research conducted by Leelawade also revealed that wearing a medical mask showed a two times higher risk of adverse skin reactions than wearing a non-medical mask. Based on this, it is hoped that the public can use this non-medical mask to avoid skin disorders, especially the acne vulgaris. (Techasatian et al., 2020). Chanxu Han revealed that most of his research samples who had a previous history of acne experienced exacerbations or recurrences after using medical masks (Han et al., 2020).

The World Health Organization (WHO) regulates that masks are divided into two types: medical masks and non-medical masks. Medical masks are composed of respirators and surgical masks (WHO, 2020b).

The surgical mask is a disposable mask with three to four layers in the middle as a filter layer. The respirator mask is a medical mask with high filtration power, and it prevents virus exposure because there are no gaps or leaks. Respirator masks are classified according to standards such as KN95 (Chinese standard), N95 (American NIOSH standard), KF95 (Korean standard), and FFP2 (European standard). These medical masks are made of synthetic fiber polypropylene, and non-medical masks are made of other materials such as cotton (WHO, 2020c). The combination of fabrics used in masks determines filterability and breathing convenience (Dwirusman, 2020). Fabrics made from natural fibers such as cotton, linen, silk, and lyocell are more breathable to the skin than synthetic fibers that tend to remove moisture from the skin (Chua et al., 2020).

Tan's research suggests that acne is the most frequently reported adverse reaction to medical masks, which has two plausible explanations (Foo et al., 2006; Tan, 2004). First, a heated and humid microclimate is formed on the part of the face covered with a tight mask that is prone to acne. Second, occlusion of the pilosebaceous duct due to local skin pressure from the masks can lead to acne (Dréno et al., 2018; Foo et al., 2006).

This study found a significant relationship between the duration of mask use and the incidence of acne vulgaris. The longer duration of mask use, the higher the acne vulgaris incidence. Leelawade's *cross-sectional* study, there is a significant correlation between acne and long-term mask use (Techasatian et al., 2020). Wasfa Hayat's study also showed a significant increase in acne incidence among subjects who wore masks for more than six hours a day (Wasfa et al., 2020).

Long-term use of masks can cause exacerbation not only of existing acne but also increases the incidence of mechanical acne, such as lesions caused by long-term contact with the ingredients used in the mask. The increased warmth and moisture of the facial skin due to exhaust air and sweat can worsen this matter (Han et al., 2020; Wasfa et al., 2020).

According to Changxu Han's research, areas of the face that often have acne vulgaris are the cheek and nose. The incidence of acne was significantly higher in samples using masks for more than six hours per day than in samples using masks for less than six hours per day (Han et al., 2020). Another study of health workers conducted by Lan and others also found that samples using masks for more than 6 hours had twice the risk of developing skin disease compared to samples using masks for less than 6 hours (Lan et al., 2020).

Hua evaluated that changes in the skin after long-term use of the mask can lead to changes in the skin microenvironment, such as dehydration, increased sebum, and increased pH. Trans-epidermal water loss and sebum dysregulation are pro-comedogenic factors that cause the development of *Cutibacterium acnes* bacteria so innate immune responses can lead to inflammatory lesions (Hua et al., 2020). Sebum excretion also increased two hours after using the mask and continued to increase four hours after use.

These findings may encourage individuals to take 15-minute break every four hours (Howard et al., 2020; Hua et al., 2020).

Acne caused by wearing a mask is called a Maskne. Maskne is caused by friction, repeated stress, sweat, and skin stress (Pervun & Babenko, 2021). Long-term use of a tight mask can lead to wet and hot conditions and may put local pressure on the skin to block the pilosebaceous gland (Hidajat, 2020). High temperatures are also closely correlated with acne, negatively affecting the sebum secretion rate (Sebum Excretion Rate/SER). When sebum excretion rate changes directly with local temperature changes, the sebum excretion increases by 10% for every 1°C increase, and squalene significantly affects surface lipids as temperature increases (Rudd & Walsh, 2021; Searle et al., 2021). High skin humidity can also cause acne due to clogged pores and irritation at the top of the pilosebaceous duct. Changes in sebum composition and moisture on the skin surface and destruction of the skin's protective layer can lead to the imbalance of bacterial microflora on the skin and cause acne (Gomolin et al., 2020; Teo, 2021). This finding is consistent with studies showing that most of the samples using masks in this study had the combination and oily skin types.

CONCLUSION

The type and duration of mask use were significantly related to the incidence of acne vulgaris during the pandemic period in the community of RT.02 RW.01 Kawistowindu, Duduksampeyan District, Gresik, East Java.

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Improving the Children' Nutritional Status and Food Technology Skills in Processing Main Food and Healthy Snacks Among Mothers with Preschool Children

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A B S T R A C T

Indonesia's child nutrition problem was becoming a national health problem. Food technology was expected to be the solution. Five-year-old nutritional status data was malnutrition and severe malnutrition in 2013 (12.1%) and 2018 (10.2%). A preliminary study results in Al Hidayah Kindergarten showed that four of five mothers (80%) do not know how to process, serve the main food and make healthy snacks for their children. This research aimed to analyze the improvement of the children's nutritional status and food technology skills in processing main food and healthy snacks among mothers with preschool children through intervention. Methods were pre-experimental research design with one group pre-posttest design. The populations were all 42 mothers and children in Sumbersecang Kindergarten, and the samples were 16 people chosen by simple random sampling. The instruments were questionnaires, checklists, counselling sheets, and weight scales. The data were analyzed using paired t-tests with SPSS v.16. This study found that 50% of mothers have a good level of knowledge. 31.3% of mother skills increase after the intervention, 31.3% of children are obese, their weight gain after intervention decreases by 25% and does not experience weight loss as much as 6.3%. Statistical test (p -value = 0.000 $<$ α 0.05). The technology of processing main foods and healthy snacks can improve the mother's skills and later improve the nutritional status of pre-school children

INTRODUCTION

The preschool period is the most important phase that can affect the growth and development of children in adulthood including reproductive health because the diet behavior chosen by children and children begin to learn the likes and dislikes and tastes, and the smell of food and selective in choosing food (Putri & Lasri, 2016). Preschool children are one of the groups prone to nutrition because children are often sick (Nekitsing *et al.*, 2018).

Children's nutrition problems at preschool and school age are still a problem in Indonesia and various countries worldwide, both in developed and developing countries. Children's nutrition problems in developed countries such as Canada and the United States are obesity problems and children's eating menu choices in the form of fruits, vegetables, and sweet foods that contain (Lehto *et al.*, 2016). In comparison, the problem of child nutrition in developing countries such as Indonesia is the problem of malnutrition, obesity, and children's eating choices, either by children or parents (Putri & Lasri, 2016).

The nutritional status of five-year-olds (toddlers) data in Indonesia in 2019 showed that the prevalence of stunting has decreased. The number decreased from 37.2% (in 2013) to 29% (in 2015) and 27.5% (in 2016) and rose again to 29.6% (in 2017) and then 30.8% (in 2018). In contrast, the prevalence of skinny

(wasting) from 12.1% (in 2013) dropped to 10.2% (in 2018) (Ministry of Health, 2018). Nutrition problems occur in rural areas, with a stunting percentage of 42.1% and in urban areas, with a percentage of 32.5% (Aridiyah *et al.*, 2015).

Nutritional Status data with weight per age index in East Java in 2016 were: severe malnutrition (3.36%), malnutrition (13.94%), good nutrition (80.68%), obesity (2.02%), and data in 2017 began to experience improved nutrition with very malnutrition rates dropping to (2.9%), malnutrition (12.2%), good nutrition increased to (83.2%) and obesity (2.2%) (Ministry of Health RI, 2019).

Probolinggo District Health Office data in 2016 from the weighing of 79,202 toddlers reported by the Public Health Center in 2016 was known that there were 1,311 toddlers Under the Red Line (BGM) (1.65%). While the data of Nutritional Status Monitoring (PSG) on the Prevalence of Malnutrition (BB/ U) in 2016 (1.65%), an increase compared to 2015 (1.59%). While the prevalence of malnutrition in 2016 was 9.44%, an increase compared to 2015 (8.65%). Some of the data on the nutritional status of toddlers is the nutritional status of children aged five years only who are preschool-age children (Dinkes Kab. Probolinggo, 2017).

A preliminary study found that four (80%) of 5 preschool children's mothers at Al Hidayah Kindergarten (TK) Sumbersecang, Probolinggo said they did not know how to process and serve main foods and healthy snacks that have nutritional value for their children. Of the four mothers who did not know how to process and serve food, two mothers (40%) had a malnutrition status child, one person (20%) had obesity, and one other person (20%) had normal nutrition according to age. In comparison, for one mother who knows how to process and serve main meals and snacks, the nutritional status of her child was normal (20%).

The results of the study (Pavilianingtyas, 2017) concluded that factors that cause the nutritional status of obese children, i.e. agent factors, host, and environmental. The agent factors include infectious diseases suffered. The host factors include gender, child health conditions, and food intake. While the environmental factors include the socioeconomic status of parents, education level, parental knowledge level, occupation, and parenting styles, including skills in making children's food, peers, tribes and environments (such as the growing number of convenience stores selling fast food and foods with preservatives. At the same time, other causes that cause malnutrition or obesity, according to research (Osera *et al.*, 2012), were the level of maternal education selection of meals by mothers, including family and child diet.

Healthy, good, and correct eating behavior is a balanced, nutritional behavior consisting of carbohydrates, fats, proteins, vitamins, and minerals. Mother is expected to be able to make nutritious food according to the needs of the child's body and physique to maintain the child's health. So, the mother's role is very

important in determining the type of food consumed by children, especially at pre-school age. Therefore, it takes the mother's knowledge and skills to process food (Putri & Lasri, 2016).

The improper mother's skills in preparing children's food will impact the intake of food the child consumes. The food is unhealthy and lacks nutritional value according to the child's caloric needs. The condition will lead to the preschool child's nutritional status not matching his age or height. The nutritional status of pre-school children who are lacking, severely undernourished, and obese can affect their growth and development in later adulthood, affecting their reproductive system and learning achievements achieved by the child (Eliassen, 2011).

The food technology in manufacturing main foods and healthy snacks is increasing. Those innovations are expected to overcome the problem of maternal skills in processing and serving foods that are favored by children and varied and have nutritional value to improve the nutritional status of children. This study aimed to analyze the improvement of maternal skills in the technology of making main foods and healthy snacks, as well as the nutritional status of pre-school children.

METHOD

This study used an *experimental* design with a *pre-experimental type one group pretest-posttest design*.

The research population was all mothers and pre-school children in Al Hidayah Kindergarten Sumbersecang, which 42 people with the number of samples in this study as many as 16 people. The inclusion criteria for research included mothers and preschool children willing to be examined. The exclusion criteria were that the mother was not at the research site when the study took place and preschool children with a history of genetic diseases related to the digestive system and metabolism (Diabetes Mellitus, Dyspepsia).

This research sampling technique was Simple Random Sampling. This research used the simple random sampling technique. This research used questionnaires, checklist sheets, and weight scales. The data collection was conducted over a month.

On the 1st day, researchers explained the study's purpose and procedure and then distributed the informed consent sheet to the respondents. Furthermore, disseminated questionnaire including demographic data and knowledge level and explained how to fill out questionnaires and made observations using checklists about the skills of serving main meals and healthy snacks as well as measuring the nutritional status of children by weighing their weight and asking the age of the child to the mother. The researcher and the team conducted counselling and demonstration of technology for making main foods and healthy snacks. We encouraged mothers to practice it at home and provided food menus that had been made for their children. Meanwhile, on the 30th day, researchers measured the level of maternal knowledge after being

given counseling and demonstrations, as well as observing the mother's skills in serving main meals and healthy snacks, then measured nutritional status by weighing the child's weight after practice and checking the child's age.

Analysis of this research data using *paired t-test* statistics with the help of SPSS V. 16. Ethics review has been conducted by researchers before conducting research. The ethics review was conducted at STIKes Hafshawaty Pesantren Zainul Hasan with No. SK: KEPK/065/STIKes-PZH/V/2019.

RESULT

The study was conducted for one month. This study found that most of the mothers aged between 21-40 years (mean 36.8 years) (68.8%), were elementary school educated (43.8%), were housewives (81.3%), and had family income between 500,000-1,000,000 per month (56.2%). Most mothers were from Madurese and Javanese tribes (50%). They had good knowledge (50%), and (37.5%) needed more knowledge of balanced nutrition food for children. Maternal skills in making main meals and healthy snacks before intervention were less (31.3%) and good enough (68.7%). In comparison, maternal skills after intervention improved which is quite good (62.5%) and good (37.5%). The result of the child's nutritional status level did not change, but there was an increase in the child's weight during 1 month of intervention that is (56.3%) (mean 2.31) (Table 1).

Cross-tabulation results on improving maternal skills in the technology of making main foods and healthy snacks in mothers who previously had fewer skills to be good enough (31.3%) and the results of statistical tests *Paired t-test* ($p= 0.00$) (Table 2). The level of nutritional status of children was normal (62.5%) with the results of the statistical test *Paired t-test* ($p= 0.00$) (Table 3).

Table 1. Characteristics of Respondents

Characteristics (n=16)	n (%)
Age (years)	
<20	1 (6.3)
21-40	11 (68.8)
41-60	3 (18.8)
>60	1 (6.3)
Mean	36.8
Level of Education	
Elementary school	7 (43.8)
Junior high school	5 (31.3)
Senior high school	4 (25.0)
Collage	0 (0)
Employment	
Housewife	13 (81.3)
Labor	0 (0)
Farmer	1 (6.3)
Entrepreneur	1 (6.3)
Private job	1 (6.3)
Civil servants	0 (0.0)
Household Income (per month)	

IDR <500,000	5 (31.3)
IDR 500,000-1,000,000	9 (56.2)
IDR >1,000,000	2 (12.5)
Ethnic	
Madurese	8 (50.0)
Javanese	8 (50.0)
Mother's level of knowledge about nutrition for children before intervention	
Very low	0 (0.0)
Low	6 (37.5)
Middle	8 (50.0)
Good	2 (12.5)
Maternal skill before intervention	
Low competence	5 (31.3)
Middle competence	11 (68.7)
Good competence	0 (0.0)
Maternal skill after intervention	
Low competence	0 (0.0)
Middle competence	10 (62.5)
Good competence	6 (37.5)
Level Nutrition of preschool before intervention	
Very underweight	0 (0.0)
Underweight	1 (6.3)
Normal	10 (62.5)
Fat	5 (31.3)
Obesity	0 (0.0)
Level Nutrition of preschool after intervention	
Very underweight	0 (0.0)
Underweight	1 (6.3)
Normal	10 (62.5)
Fat	5 (31.3)
Obesity	0 (0.0)
Improvement of the weight of preschool after intervention	
Loss	4 (25.0)
Stagnant	3 (18.8)
Increase	9 (56.3)
Mean	2.31

Table 2. Cross Tabulation of Improving Mother's Skills in The Technology of Making Main Foods and Healthy Snacks

Skill before intervention	Skill after intervention						Total	
	Low competence		Middle competence		Good competence		n	%
	n	%	n	%	n	%		
Low competence	0	0.0	5	31.3	0	0.0	5	31.3
Middle competence	0	0.0	5	31.3	6	37.5	11	68.8
Good competence	0	0.0	0	0.0	0	0.0	0	0.0
Sum	0	0.0	10	62.6	6	37.5	16	100

p-value = 0.000 < α 0.05

Table 3. Cross Tabulation of Improving the Nutritional Status of Pre-School Children

Level Nutrition before intervention	Level Nutrition after intervention										Total	
	Very underweight		Underweight		Normal		Fat		Obesity		n	%
	n	%	n	%	n	%	n	%	n	%		
Very underweight	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Underweight	0	0.0	1	6.3	0	0.0	0	0.0	0	0.0	1	6.3
Normal	0	0.0	0	0.0	10	62.5	0	0.0	0	0.0	10	62.5
Fat	0	0.0	0	0.0	0	0.0	5	31.3	0	0.0	5	31.3
Obesity	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

Sum	0	0,0	1	6.3	10	62.5	5	31.3	0	0.0	16	100
$p\text{-value} = 0.000 < \alpha 0.05$												

DISCUSSION

This study result showed an improvement in the mother's skills in making the main food and healthy snacks and an increase in the child's weight as an indicator of the improved nutritional status.

The primary healthy food is a staple dish consisting of a complete menu eaten in the morning, day, and night. The main characteristic of healthy food according to that has a balanced nutritional value with the elements of carbohydrates, fats, proteins, vitamins, and minerals. It does not contain many flavorings and harmful dyes (Nurhayati *et al.*, 2012). In comparison, healthy snacks are snacks that contain low calories, high in protein and vitamins or minerals. Characteristics of healthy snacks do not contain any flavorings or harmful dyes (Amar, 2014).

The technology of primary food and healthy snacks processing is a strategy that is carried out by converting raw materials into more nutritional value (Center for Human Resources Education health, 2017). It extends the time and number of available foodstuffs, facilitates storage and distribution, and increases economic added value in the form of benefits and social added value, obtaining more attractive products, such as appearance, taste, and other physical properties. Simple food technology mothers can do is about how mothers can process and serve food with balanced nutrition that is interesting, varied, and preferred by the child. Food can survive for several hours or is not quickly.

Maternal skills are proficiency in manufacturing main meals and healthy snacks for children, including less-skilled, quite skilled, and skilled. Factors that affect maternal skills include age, education level, knowledge, experience, maternal attitude, motivation, skills or skills serving food, and the environment (Scaglioni *et al.*, 2018) and (Osera *et al.*, 2012). In addition, factors that affect it are the existence of tools that facilitate mothers in regulating the child's diet, for example using *the Fuzzy Sugeno Inference System* method or manual methods that are easy to practice in calculating the nutritional needs of children according to age (Wachdani *et al.*, 2012).

Based on this study's results, factors of maternal skills in food technology and the nutritional status of preschool children were indirectly influenced by factors such as maternal age, education level, occupation, income, ethnicity, and the level of maternal knowledge about nutrition.

This study (table 1) showed that the average maternal age was 36.8. This result indicated that the mother's age was in the early adult stages. In this range, mothers had enough experience cooking, serving food, or regulating the child's diet. These findings were supported by the study that significantly influences her cooking skills, attitudes, and quality of diet that will be given to their child which will further influence the selection of food by the child. Likewise, the study's results (Eliassen, 2011) showed that what mothers

eat was an example of what a child would eat. Motherhood became very important as the primary caregiver of the child. Young adult mothers tended to behave at will, including the way of feeding their children. It was also associated with maternal education and previous knowledge of providing healthy food and snacks for her pre-school children.

Furthermore, this study found that 43.8% of mothers had an elementary or low education and an income of less than 1,000,000 per month (56.2%). It will significantly affect the mother's skills in choosing a meal menu for the child, either the main meal or a healthy snack. The lower the level of maternal education, the selection of food menus for children tended to be unhealthy and had low nutritional value. This study's results are supported by Gacek (2019), which stated that mothers with a low level of education were associated with less knowledge about their child's balanced nutrition. Mothers tended to obey the child's will in choosing food according to the child's taste, without informing the nutritional value of the child, either main meals or healthy snacks. Furthermore, Scaglioni *et al.*, (2011) said the mother was the most powerful control and an example for her child compared to environmental factors and shared experiences with children about healthy food.

This research studied: the children eating behavior; the mother's level of education who did not understand the nutritional needs of children, including their growth and development needs. This study also studied the socioeconomic status of the mother or father's attention to the child and parenting patterns and family eating behaviors: the mother's ignorance about the importance of balanced nutrition for her child was presented in the main menu and snacks.

A prior study (Russell *et al.*, 2014) concluded that mothers with low socioeconomic status or who had incomes below per capita wage tend to choose food based on the price so that the nutrients present in the food were ruled out and would be the factors that affect the quality of the child's diet.

The level of mother knowledge about child nutrition in this research before intervention showed that 50% of mothers had a fairly good level of knowledge, and 37.5% had insufficient knowledge. These results showed that most mothers still needed to understand healthy nutrition for their children, its benefits, and the short-term and long-term impacts on their health and children's learning achievements. Furthermore, the mother's knowledge level would affect the mother's perception and attitude about the child's healthy food. It was stated that the mother's poor perception of healthy food would affect the child's chosen food. The child would imitate their mother's or parent's habits (Russell *et al.*, 2014).

Furthermore, the results of this study were known to mothers after being given interventions had improved skills in the manufacture of main foods and healthy snacks (31.3%) ($p=0.000$), normal child nutritional status (62.5%) and child weight increased (mean 2.31). Cooking skills interventions could positively impact knowledge of food mainly developing confidence in the cooking skills of fruit and

vegetables in groups with low socioeconomic status. The success of the skilled mother in cooking and preparing daily meals would affect the main types of foods and snacks given to her child and could affect their growth and development. The measure of growth, in this case, was the weight loss to the child's age that can form the child's nutritional status (Garcia *et al.*, 2016). So, in this study, interventions given to the mothers impact the children's nutritional status.

Children who were obese, underweight and very underweight would be able to influence their academic achievements. Obese children tended to choose foods high in calories and fat and low in fiber. According to Hermina & Prihatini S, 2016 on Individual Analysis Food Consumption Survey (SKMI) in 2014, the toddlers in Indonesia as many as 86.2% did not like to consume vegetables, and as much as 35.7% did not like fruit consumption. In comparison, the child who was underweight very underweight due to the consumption of foods low in protein and calories or fat, and the amount of intake was less.

Children had nutritional problems caused by a lack of nutrients in the consumption needed by the brain, including balanced elements of carbohydrates, proteins, fats, vitamins, and minerals. In addition, other impacts would affect the children's reproduction health in adolescence and later in adulthood. This result follows a prior study (Nekitsing *et al.*, 2018) that the child's development was influenced by the intake of nutrients consumed that will later affect the health status in adulthood, including their reproductive health. Therefore, it is important for parents, especially mothers, as the people closest to the child to pay attention to the child's healthy food needs both main meals and healthy snacks. Mothers should also prevent children from skipping their mealtime, especially preschool-age children, which can affect their nutrition status (Mary *et al.*, 2019).

CONCLUSION

Providing training or demonstration was effective in improving the mother's skills in the technology of making main foods and healthy snacks and later could improve the nutritional status of children with indicators of increasing the child's weight according to their age. However, this study has the weakness of the absence of a control group as a comparison and the need for further research by adding several respondents, the duration of the study, and methods of calculating the child's diet by non-manual methods or using applications that are easy to practice by the mother.

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