Optimization of multiplex real-time RT-PCR for respiratory syncytial viruses detection

DOI: https://doi.org/10.22435/hsji.v12i2.5529

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Received: October 22, 2021; Revised: November 26, 2021; Accepted: December 6, 2021

Abstract

Background: Multiplex real-time RT-PCR (rRT-PCR) is a fast, sensitive and specific test to detect more than one target in single PCR reaction. In this study we developed multiplex rRT-PCR for RSV-A and RSV-B since those viruses are the most common pathogen found in respiratory tract. However, in order to gain optimal reaction for RSV-A and RSV-B detection, the optimization of primers and probes specific for RSV-A and RSV B are needed.

Method: The primers and probes of multiplex rRT-PCR for RSV-A and RSV-B were selected and optimized utilizing PerlPrimer software and BLAST to analyze the secondary structures and specificity, respectively. Further testing of selected primers and probes for rRT-PCR was done using annealing temperature based on in silico analysis as mentioned above. This includes sensitivity testing with the utilization of synthesized DNA of RSV-A and RSV-B and specificity testing targeting the common viruses found in respiratory tract.

Results: The primer set and probes selected for RSV-A and RSV-B detection were specific only for RSV-A and RSV-B and showed no secondary structure. Based on primer and probe criteria for rRT-PCR such as annealing temperature, no secondary structure formed, % GC content and limit of detection, the multiplex rRT-PCR test using selected primers and probes was able to detect synthesized DNA of RSV-A and RSV-B.

Conclusion: Multiplex rRT-PCR that employing primer sets and probes targeted N gene of RSV-A and RSV-B in this study were able to be detect RSV-A and RSV-B in single PCR reaction. ***(Health Science Journal of Indonesia 2021;12(2):66-73)***

Keyword: Multiplex, real-time RT-PCR, RSV-A, RSV-B

Abstrak

Latar belakang: *Multiplex real-time RT-PCR (rRT-PCR) merupakan metode yang cepat, sensitif dan spesifik untuk mendeteksi lebih dari satu target pathogen dalam satu reaksi PCR. Penelitian ini bertujuan untuk mengembangkan multiplex rRT-PCR virus RSV-A dan RSV-B yang merupakan patogen yang paling sering ditemukan di saluran pernafasan. Optimisasi dari primer dan probe dalam multiplex rRT-PCR diperlukan untuk mendapatkan reaksi yang optimal dalam deteksi virus RSV-A dan RSV-B.*

Metode: *Primer dan probe untuk multiplex rRT-PCR RSV-A dan RSV-B dipilih dan dioptimasi menggunakan software PerlPrimer dan BLAST untuk menganalisis adanya struktur sekunder serta spesifisitas dari primer dan probe. Uji multiplex rRT-PCR dilanjutkan berdasarkan suhu annealing berdasarkan hasil analisis menggunakan PerlPrimer. Uji sensitifitas dilakukan dengan menggunakan DNA sintetis dari RSV-A dan RSV-B dan uji spesifisitas dilakukan dengan mengetes primer dan probe terhadap virus-virus lain yang umumnya ditemukan di saluran pernafasan.*

Hasil: *Primer dan probe yang dikembangkan pada penelitian ini tidak membentuk struktur sekunder dan spesifik mengamplifikasi hanya RSV-A dan RSV-B. Berdasarkan kriteria primer dan probe untuk digunakan dalam rRT-PCR yaitu suhu annealing, tidak adanya pembentukan struktur sekunder, % GC content serta detection limit, uji multiplex rRT-PCR yang dikembangkan pada penelitian ini mampu mendeteksi DNA sintetis RSV-A dan RSV-B.*

Kesimpulan: *Multiplex rRT-PCR dengan menggunakan primer dan probe untuk RSV-A dan RSV-B dapat mendeteksi RSV-A dan RSV-B dalam satu reaksi PCR.* ***(Health Science Journal of Indonesia 2021;12(2):66-73)***

Kata kunci: *multiplex, real-time RT-PCR, RSV-A, RSV-B*

The contributions of viruses as the etiology of pneumonia emphasize the importance of a routine virus detection. Polymerase chain reaction (PCR) has been used globally to detect viral pathogen since PCR is more sensitive compared to culture, direct immunofluorescence test, rapid antigen test or even serology test.[1,2] The fast development of molecular technology enables the utilization of multiplex real-time RT-PCR (rRT-PCR) to detect viral pathogens within few hours. Since then Multiplex rRT-PCR becomes a reliable routine test and its application has significantly increased within this decade.[2,3]

Acute lower respiratory infection (ALRI) or pneumonia remains one of major heath problem in low and middle-income countries that cause high mortality and morbidity in children.[4,5] The incidences of ALRI among children age less than five years old were approximated to be 120 million cases in 2010[6]. Bacteria and viruses are the common etiologies of pneumonia, however 40-60% cases were caused by viruses.[7,8] Respiratory syncytial virus (RSV) has been reported as the major viral etiology associated with severe lower respiratory tract infections in children, meanwhile, the predominant agent causing pneumonia in adult was influenza viruses.[3,9,10] RSV is classified in two main groups, RSV-A and RSV-B, with multiple genotypes within each group.[11,12]

Detection of viruses provides essential data of viral etiology that could beneficial for public health authorities such as disease investigation and epidemiology. Moreover, the detection of viruses might contribute to study the relationship between clinical manifestations of ALRI and its etiologies, in which could improving clinical management of the patients.[7,8] The identification of RSV-A and B as an etiology of ALRI could reduce the use of inappropriate antibiotics in patients and therefor preventing antimicrobial resistance.[13]

This study aimed to optimize the primer and probe set for RSV-A and B that used previously as singleplex assay into multiplex assay to detect both RSV-A and RSV-B in one assay. This method will provide efficient and fast detection method since only single reaction is needed to detect two viruses. Further, the primer and probe sets for multiplex rRT-PCR assay presented in this study could be used as reliable and fast detection method to detect RSV-A and B that commonly reported as the viral etiology of ALRI in children.

METHODS

Primer and probe sequence of RSV-A and RSV-B

This study used nucleoprotein gene of RSV-A and RSV-B as the target of primers and probe for multiplex rRT-PCR. Nucleoprotein gene was selected since this gene was conserved among the other genes in RSV-A and RSV-B genome. Sequences of nucleoprotein gene of RSV-A and RSV obtained from Gene Bank (Accession number KJ817800, U39662, AY911262, U39661, DQ780565, DQ780568, NC001781, D00736, DQ780567, AF013254) were aligned together with primer and probe sequence to detect RSV-A and RSV-B in singleplex assay based on previous study [14] using BioEdit sequence alignment software .[15]

PerlPrimer v1.1.18 [16,17] was employed to calculate the melting temperature (Tm) and GC content of each primer and probe, which then was used to define the initial annealing temperature for optimizing the rRT-PCR condition. The optimum annealing temperature of the primers sets for rRT-PCR is approximately 5°C higher than the Tm given by PerlPrimer v1.1.18 calculation. The annealing temperatures with 5°C differences were tested to obtain optimum rRT-PCR reaction using synthesized DNA that covered nucleoprotein gene fragments of RSV-A and RSV-B as positive template. PerlPrimer v1.1.18 was also used to analyze secondary structures that could be generated between primers and probes. Basic Local Alignment Search Tool (BLAST) was used to analyze the primer and probe specificity.

Singleplex rRT-PCR optimization

The optimization of the primer and probe sets were performed by running the synthesized DNA that covered nucleoprotein gene fragments of RSV-A and RSV-B. Singleplex rRT-PCR assays of RSV-A and RSV-B were performed using primers and probes shown in Table 1. Primers were used at a final concentration of 40 µM while the probe at a concentration of 10 µM. Each reaction for RSV-A and RSV-B detection was performed using SuperScript ™ III One-Step qRT-PCR System with Platinum Taq DNA Polymerase (Invitrogen, Carlsbad, CA) that consisted of 12.5 µl 2x reaction mix, 5.5 µl nuclease-free water, 0.5 µl Forward primer, 0.5 µl Reverse primer, 0.5µl probe and 0.5µl SuperScript ™ III RT and Platinum ®Taq enzyme mix. A total of 5 µL of synthesized DNA of nucleoprotein gene fragments

RSV-A and RSV-B were mixed into master mix of RSV-A and RSV-B, respectively. Synthesized DNA with concentration of 1 to 10^{-3} ng/µl was used for initial singleplex optimization, followed by 10^{-3} to 10^{-8} ng/µl in second optimization. Meanwhile, we used nuclease-free water for negative template control in all assay.

Singleplex rRT-PCR was performed on CFX96 Touch System Real-time PCR Detection System (Bio-Rad, Hercules, CA) in a total reaction volume of 25 µL. Singleplex rRT-PCR of RSV-A and singleplex for RSV-B were performed under the following conditions: reverse transcription at 55 °C for 30 min, hot start at 95 °C for 2 min and 45 cycles of PCR consisting of denaturation at 95 °C for 15 sec, primer annealing and data collection at 60 °C for 1 min. Singleplex rRT-PCR reaction was confirmed as positive if exponential amplification curve with Cycle Threshold (CT) value between 18-38 was observed.

Multiplex rRT-PCR optimization

Multiplex rRT-PCR assay was performed using primers and probes for RSV-A and RSV-B shown in Table 1 in one reaction assay. Primers were used at a final concentration of 40 µM while the probe at a concentration of 10 µM. Master-mix for multiplex rRT-PCR utilizing SuperScript ™ III One-Step qRT-PCR System with Platinum Taq DNA Polymerase (Invitrogen, Carlsbad, CA) that consisted of 12.5 µl 2x reaction mix, 0.5 µl RSV-A Forward primer, 0.5 µl RSV-A Reverse primer, 0.5µl RSV-A probe, 0.5 µl RSV-B Forward primer, 0.5 µl RSV-B Reverse primer, 0.5µl RSV-B probe, 0.5µl SuperScript ™ III RT and Platinum ®Taq enzyme mix, and 4.0 µl nuclease-free water. A total of 5 µL of mixed synthesized DNA of nucleoprotein gene fragments RSV-A and RSV-B were added into master mix of multiplex RSV-A and RSV-B. Synthesized DNA with concentration of 10^{-5} ng/µl to 10^{-8} ng/µl were used in this assay and each reaction was performed in duplicates. Multiplex rRT-PCR was performed on CFX96 Touch System Real-time PCR Detection System (Bio-Rad, Hercules, CA) in a total reaction volume of 25 µL using the same rRT-PCR protocol for singleplex mentioned above. Reaction was confirmed as positive if exponential amplification curve with Cycle Threshold (CT) value between18-38 were observed. Nuclease-free water was used for negative template control in all assay.

Sensitivity and specificity assay

Different concentration of synthesized DNA fragment were used to optimize the sensitivity of Multiplex rRT-PCR assay. In this study, concentration of 10^{-5} ng/µl to 10^{-10} ng/µl concentration was employed and each reaction was performed in duplicates. In addition, specificity assay was performed using various known viruses that could be found in respiratory tract such as Influenza A/H1pdm, Influenza A/H3, Influenza A/H5, Influenza B (Victoria), Influenza B (Yamagata), MERS-CoV, Human Parainfluenza Virus 1-4 (HPIV 1-4), Human Coronaviruses (HCOV NL63, HCOV OC43, HCOV 229E, HCOV HKU1A) and SARS.

RESULTS

Primer and probe sequence of RSV-A and RSV-B

Figure 1 and 2 shows the alignment of N gene of RSV-A and RSV-B with the primer sets and probes. The target site of the primer sets and probes were located within conserved region of N gene both in RSV-A and RSV-B. BLAST analysis shows that primer sets and probes had 100% identity with RSV-A and RSV-B (data not shown). We found no other pathogen sequences that had similarity with the primers and probes sequence, indicating the specificity of the primers and probes. The secondary structure, the Tm and GC content calculation of primer sets and probes using PerlPrimer are shown in Table 1. The primer sets and probes for RSV-A and RSV-B had GC content within the range of 30 to 56% and the Tm were between 61°C to 70°C.

Singleplex rRT-PCR optimization

Positive reaction in singleplex real-time RT-PCR was presented as sigmoid amplification curve with CT value below 38 as shown in Figure 3 and Table 2. These results confirmed that annealing temperature in 60°C for both RSV-A and RSV-B primers and probe were able to amplify RSV-A and RSV-B in singleplex set up as expected. The decreasing of synthesized DNA concentration (10^{-4} to 10^{-8}ng/µl) was coherent with the increasing of CT values. As the CT values of synthesized DNA at concentration 1 to 10^{-3} ng/µl were below 20, we did not used these concentration for further testing in multiplex assay. No amplification or CT value was observed in negative template control.

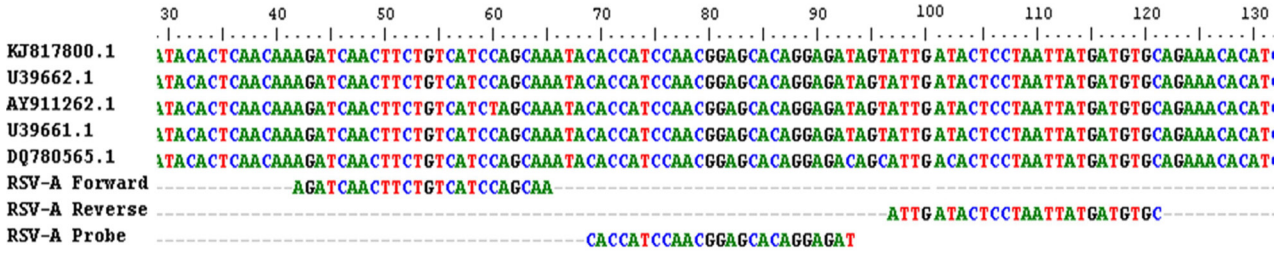

Figure 1. Alignment of N gene of RSV-A together with the primer sets and probe for singleplex rRT-PCR

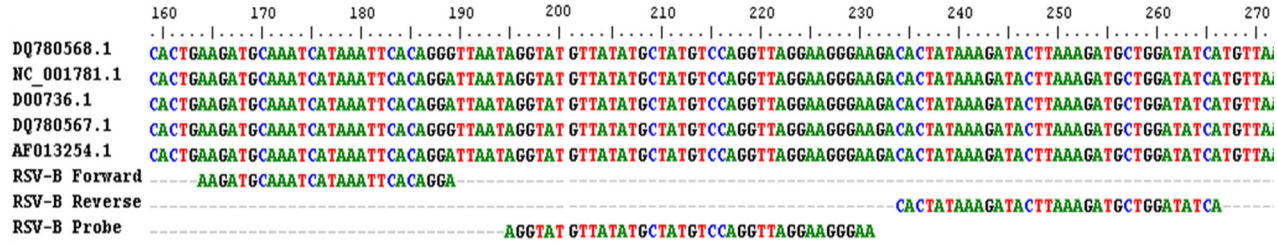

Figure 2. Alignment of N gene of RSV-B together with the primer sets and probe for singleplex rRT-PCR

Table 1. Primer and probe sequences for RSV-A and RSV-B

No	Primer/Probe	Sequence (5' to 3')	Tm (°C)	% GC Content	Secondary Structure (dimer, hairpin structure)
1	RSV-A Forward	AGATCAACTTCTGTCATCCAGCAA	64,34	41	None
2	RSV-A Reverse	GCACATCATAATTAGGAGTATCAAT	59, 96	32	None
3	RSV-A Probe	Cy5- CACCATCCAACGGAGCACAGGAGAT -Iowa Black RQ	70,54	56	None
4	RSV-B Forward	AAGATGCAAATCATAAATTCACAGGA	61,73	30	None
5	RSV-B Reverse	TGATATCCAGCATCTTTAAGTATCTTTATAGTG	62,97	30	None
6	RSV-B Probe	HEX-AGGTATGTTATATGCTATGTCCAGGTTAG GAAGGGAA -BHQ1	70,39	40	None

Multiplex rRT-PCR optimization

We performed multiplex rRT-PCR using synthesized DNA with concentration range of 10^{-4} to10^{-8} ng/µl. As shown in Table 2, the rising CT values were observed and consistent with the decreasing concentration of synthesized DNA. As expected in real-time PCR assay, the CT values had increased 3 points in each 10 fold diluted synthesized DNA. Interestingly, the same concentration of synthesized DNA in multiplex rRT-PCR gave higher CT values compared to singleplex. The negative template control of multiplex rRT-PCR, both of RSV-A and RSV-B, showed no amplification or CT values. The amplification curve of multiplex rRT-PCR was illustrated in Figure 4.

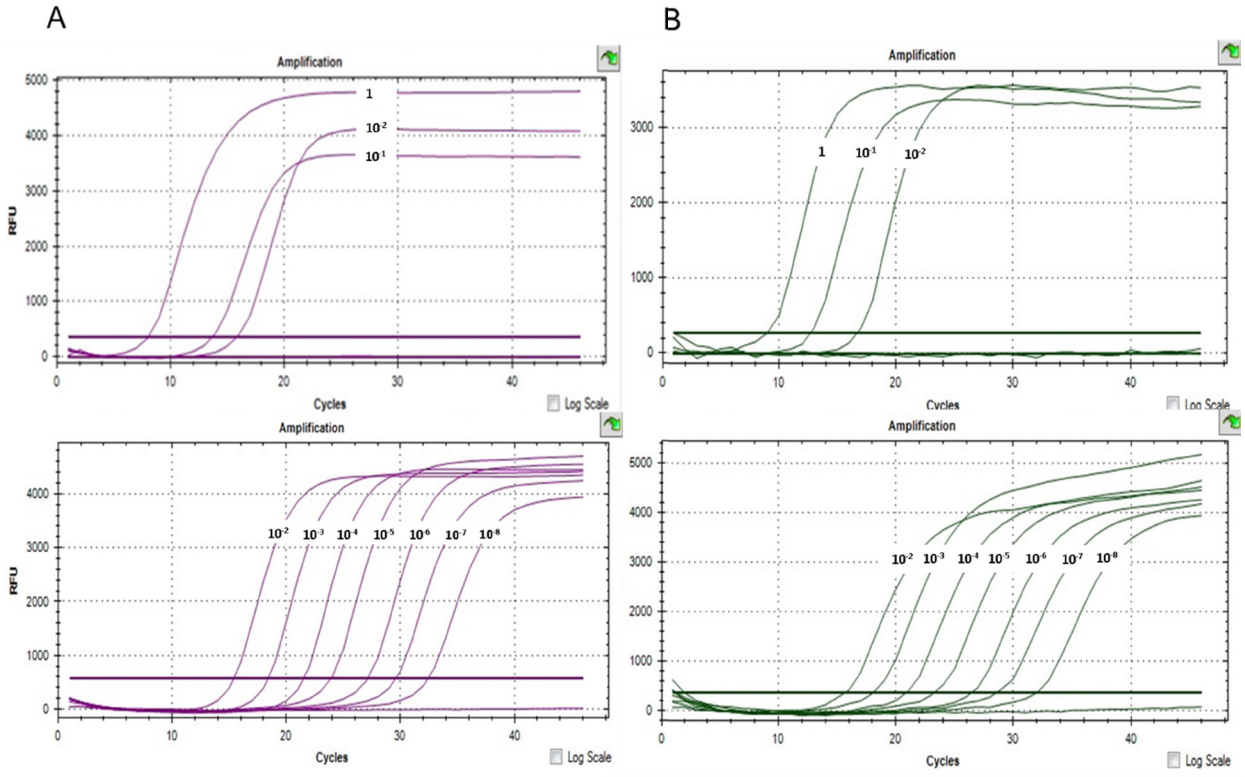

Figure 3. Amplification curve of singleplex rRT-PCR of RSV-A (Figure 3A) and RSV-B (Figure 3B) using concentration of synthesized DNA 1 to 10^{-8} ng/µl, respectively. The x axis illustrates the cycles of rRT-PCR while y axis shows the fluorescence intensity, displayed as Relative Fluorescence Unit (RFU).

Table 2. Average CT value in singleplex and multiplex rRT-PCR

Template concentration (ng/µl)	Singleplex		Multiplex	
	RSV-A	**RSV-B**	**RSV-A**	**RSV-B**
1	9,02	9,88	ND	ND
10^{-1}	13,73	13,36	ND	ND
10^{-2}	16,04	15,98	ND	ND
10^{-3}	18,37	17,86	ND	ND
10^{-4}	21,49	20,69	25, 76	27,87
10^{-5}	23,9	23,07	28,05	29,97
10^{-6}	27,11	26,24	31,34	33,97
10^{-7}	29,56	28,32	33,38	36,59
10^{-8}	32,39	31,92	38,7	39,5

ND: not done

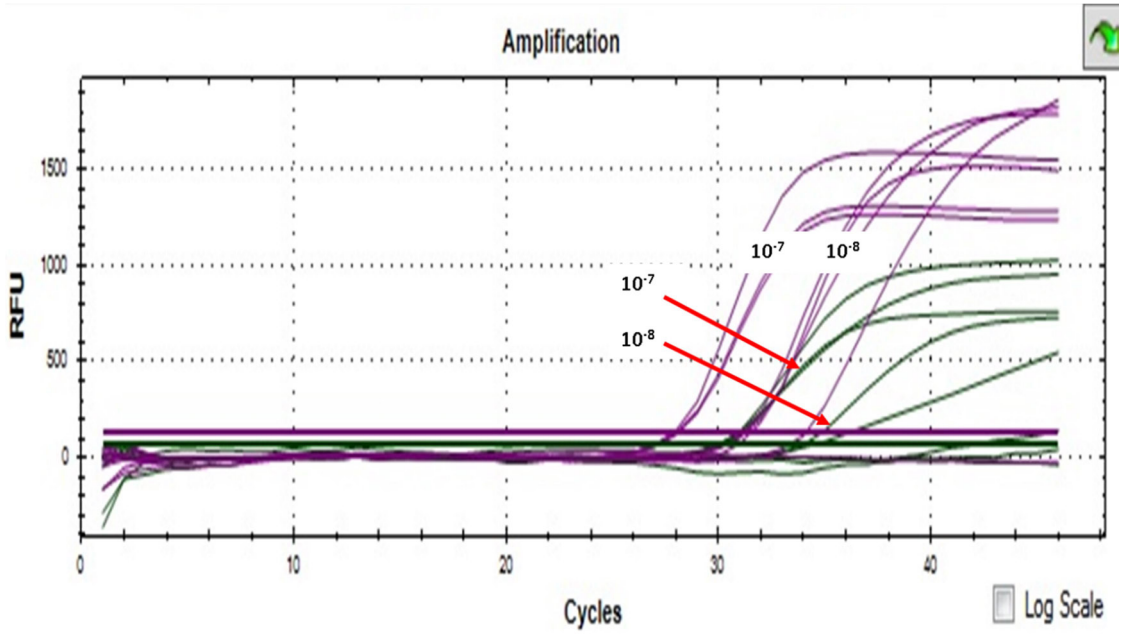

Figure 4. Amplification curve of multiplex rRT-PCR of RSV-A dan RSV-B .using synthesized DNA of 10^{-7} to 10^{-8} ng/µl. Amplification curve of RSV-A was in purple while RSV-B was in green. The x axis illustrates the cycles of rRT-PCR while y axis shows the fluorescence intensity, displayed as Relative Fluorescence Unit (RFU). Multiplex RT-PCR was done in triplicates

Sensitivity and specificity assay

Sensitivity test was carried out to understand the lowest concentration of template that could be detected using multiplex assay. In addition, the specificity testing was performed to examine other viruses in respiratory tract that could be detected using the primer set and probe for RSV-A and RSV-B. As seen in Table 3, concentration below 10^{-7} ng/µl was not able to detect both RSV-A and RSV-B. Meanwhile Table 4 shows that the multiplex assay for RSV-A and RSV-B detected no other viruses that could be found in respiratory tract such as Influenza A/H1pdm, Influenza A/H3, Influenza A/H5, Influenza B (Victoria), Influenza B (Yamagata), MERS-CoV, Human Parainfluenza Virus 1-4 (HPIV 1-4), Human Coronaviruses (HCOV NL63, HCOV OC43, HCOV 229E, HCOV HKU1A) and SARS.

Table 3. CT Value of Multiplex Sensitivity Test

Synthesized DNA concentration (ng/µl)	Average CT value	
	RSV-A	**RSV-B**
10^{-5}	29.13	29.03
10^{-6}	31.24	32.01
10^{-7}	34.13	34.63
10^{-8}	38, 08	37.97
10^{-9}	NA	41.07
10^{-10}	NA	NA

NA: Not available

Table 4. Specificity assay of Multiplex rRT-PCR for RSV-A and RSV-B

Virus	Type of template	Result
Influenza A/H1pdm	virus isolate	negative
Influenza A/H3	virus isolate	negative
Influenza A/H5	virus isolate	negative
Influenza B (Victoria)	clinical specimen	negative
Influenza B (Yamagata)	clinical specimen	negative
MERS-CoV	gene fragment	negative
HPIV 1	gene fragment	negative
HPIV 2	gene fragment	negative
HPIV 3	gene fragment	negative
HPIV 4	gene fragment	negative
HCOV NL63	gene fragment	negative
HCOV OC43	gene fragment	negative
HCOV 229E	gene fragment	negative
HCOV HKU1A	gene fragment	negative
SARS	gene fragment	negative

DISCUSSIONS

RSV groups are known to be the common cause of ALRI cases in children.[11] Conventional testing for respiratory viruses consist of various methods, including virus isolation in cell lines and serology tests. For diagnostic purposes, virus isolation requires days to perform whereas serology tests are not specific and sensitive enough.[18] The utilization of rapid detection is essential to enable implementation

of specific control measures and the limitation of virus spread.[18] The development of technique in advance molecular biology technologies have revolutionized the procedures for detection and characterization of pathogenic viruses.[19] One of the techniques that provide high throughput result and one of reliable technologies are multiplex real-time RT-PCR. In this study, we developed multiplex rRT-PCR for RSV-A and RSV-B detection in single reaction.

The initial setting for multiplex rRT-PCR is primer sets and probe. The primer and probe developed for multiplex rRT-PCR was based on basic rules of efficient primers that are 18-25 nucleotides in length, with 50-60% having G and C composition. In addition, primer set essentially are also designed to have no complementary sequence at the 3' ends between primer pairs that could form secondary structure such as primer dimer artifacts and hairpin loop.[20,21] The sequence of primer and probe in this study had been chosen to meet those criteria. Our analysis on primer probe sequences shows that no secondary structure was generated when combining two sets of primer and probes for RSV-A and RSV-B.

Detection of two or more gene target of viruses could be done with high sensitivity and specificity using multiplex rRT-PCR as this technology combines the polymerase chain reaction chemistry with the use of fluorescent reporter dye in order to observe the amplification during each PCR cycles. This study utilized the chemistry of TaqMan probe within the PCR reaction. The TaqMan probe is labeled with dual fluorescent dyes, the quencher and reporter dyes, which emit at different wavelengths.[22] As describes in Table 1, detection of two different target of viruses could be performed using this method as probes for RSV- A and RSV-B in this study were labeled with different reporter dyes, Cy5 and Hex, respectively.

The TaqMan probe sequence was specifically hybridized in the DNA target region of interest between the two PCR primers as seen in Figure 1 and 2. The probe was also designed to have higher annealing temperature compared to the PCR primers (Table 1), therefore the probes hybridized when extension (polymerization) of the primers begins. The Taq DNA polymerase with the 5'-exonuclease activity hydrolyzed the probe that have annealed previously in the target sequence. The hydrolysis of TaqMan probe caused reporter dyes no longer had close proximity to the quencher dye and consequently emitted fluorescent signal which captured by the computer system incorporated with thermal cycler.[18,22] These processes were repeated in each cycle and in the end of PCR reaction, the sigmoid amplification plot both of RSV-A and RSV-B were generated and could be analyzed.

We performed sensitivity testing in order to analyze the minimum number of copies in the sample that can be detected accurately with the optimized assay. The multiplex rRT-PCR was still able to detect synthesized DNA with concentration 10^{-7} ng/µl, suggesting that the multiplex rRT-PCR were sensitive to detect template with low concentration. The specificity testing both using in silico assay (BLAST) and rRT-PCR with real viruses or gene fragments of common viruses in respiratory tract suggested that the multiplex rRT-PCR was specific only to detect RSV-A and RSV-B. The specificity test was essential to employ in this study as this test refers to the assay that detects the appropriate target sequence instead of other or non-specific targets that present within the samples.[23]

This study did not perform the sensitivity and specificity examinations using real viruses of RSV-A and RSV-B or other respiratory viruses thus become the limitation of this study. This study utilized synthesized DNA of gene fragment that mimic the template for RSV-A and RSV B for sensitivity test or MERS-CoV, Human Parainfluenza Virus 1-4 (HPIV 1-4), Human Coronaviruses (HCOV NL63, HCOV OC43, HCOV 229E, HCOV HKU1A) and SARS for specificity test. Therefore the actual testing using clinical specimens are needed for ideal examination for further diagnostic purposes.

In conclusion, in this study we developed multiplex rRT-PCR for RSV-A and RSV-B since those viruses are the most common pathogen found in respiratory tract. Multiplex rRT-PCR is a fast, sensitive and specific test to detect more than one target in single PCR reaction. The optimization of primers and probes specific for multiplex rRT-PCR for RSV-A and RSV-B are essential therefore the optimal condition for PCR reaction to detect two targets in single PCR reaction is crucial to be accomplished. Based on in silico utilizing bioinformatics software and web analyses, the primer set and probes selected for RSV-A and RSV-B detection were specific and showed no secondary structure. Further, the optimization of the primer sets and probes was accomplished using gene fragments in a form

of synthesized DNA. Multiplex rRT-PCR that employing primer sets and probes targeted N gene of RSV-A and RSV-B in this study were able to be detect RSV-A and RSV-B in single reaction.

Acknowledgement

The author acknowledge the Virology Laboratory staffs for the technical assistance during the -process of testing the multiplex real-time RT-PCR for this study.

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Interferon gamma concentration in Diabetes Mellitus and Dyslipidemia patient

DOI: https://doi.org/10.22435/hsji.v12i2.4290

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Received: December 6, 2020; Revised: November 4, 2021 Accepted: December 3, 2021

Abstract

Introduction: Patient with diabetes mellitus (DM) and dyslipidemia occurs chronic inflamation characterized by changes in the concentration of various cytokines. This causes changes in the body's immunity so that can be easier in having an infection. One of the most important cytokines against infection is IFN-γ. This study aimed to determine IFN-γ concentration in DM and dyslipidemia patients.

Metode: An amount 234 people who received treatment at the health center in Banda Aceh in 2019 were included in this study. From each respondent, 5 ml of blood was taken to check fasting blood glucose, triglycerides, high-density lipoproteins (HDL), and inrferon-gamma (IFN-γ). Test of fasting blood glucose, triglycerides, HDL was carried out using the colorimetric enzymatic method. The IFN-γ protein concentration was examined using the sandwich enzyme-linked immunosorbent assay (ELISA) technique.

Result: IFN-γ concentration in the non-DM group was higher than in the DM group. There was a significant difference between the average IFN-γ concentration in the non-DM group compared with the DM group (p = 0.000). All DM patients had increased fasting blood glucose, most had hypertriglycerides, but HDL levels were normal. The fasting blood glucose group <126 mg / dl had a higher IFN-γ concentration than the group with fasting blood glucose levels ≥126 mg / dl. There was a significant difference in the concentration of IFN-γ between the two groups (p = 0.000). The group with triglyceride levels <150 mg / dl had lower IFN-γ levels than the group with triglyceride levels ≥ 150 mg / dl. There was a significant difference between the average IFN-γ concentration between those groups (p = 0.000). The fasting blood glucose levels ≥126 mg / dl and triglycerides levels ≥ 150 mg / dl had higher IFN-γ concentration than the group who had fasting blood glucose levels ≥126 mg / dl and triglycerides levels < 150 mg / dl.

Conclusion: There are differences in IFN-γ concentrations in people with DM, increased fasting blood glucose and dyslipidemia compared to normal people. ***(Health Science Journal of Indonesia 2021;12(2):74-80)***

Keywords: IFN-γ, diabetes mellitus, dyslipidemia

Abstrak

Pendahuluan: *Penderita diabetes mellitus (DM) dan dyslipidemia mengalami inflamasi kronik yang ditandai dengan perubahan konsentrasi berbagai sitokin. Hal ini yang menyebabkan perubahan imunitas tubuh sehingga mudah mengalami infeksi. Salah satu sitokin yang paling berperan terhadap infeksi adalah interferon gamma (IFN-γ). Penelitian ini bertujuan untuk memeriksa konsentrasi IFN-γ pada penderita DM dan dislipidemia.*

Metode: *Sebanyak 234 orang yang melakukan pengobatan di puskesmas di Kota Banda Aceh pada tahun 2019 diikutsertakan dalam penelitian ini. Dari setiap responden dilakukan pengambilan darah sebanyak 5 ml untuk dilakukan pemeriksaan kadar gula darah puasa (KGD P), trigliserida, high density lipoprotein (HDL), dan inrferon- gamma (IFN-γ). Pemeriksaan KGD P, trigliserida, HDL dilakukan dengan metode enzimatik kolorimetrik. Pemeriksaan konsentrasi protein IFN-γ menggunakan teknik sandwich Enzyme-linked immunosorbent assay (ELISA).*

Hasil: *Konsentrasi IFN-γ pada kelompok non-DM lebih tinggi dibandingkan dengan kelompok DM. Terdapat perbedaan bermakna antara rata-rata konsentrasi IFN-γ pada kelompok non-DM dibandingkan dengan kelompok DM (p=0,000). Semua penderita DM mengalami peningkatan KGD P, sebagian besar mengalami hipertrigliserida, namun kadar HDL normal. Pada kelompok KGD P <126 mg/dl memiliki konsentrasi IFN-γ yang lebih tinggi dibandingkan dengan kelompok dengan KGD P ≥126 mg/dl. Terdapat*

perbedaan bermakna perbedaan konsentrasi IFN-γ antar kedua kelompok tersebut (p=0,000). Kelompok dengan kadar trigliserida <150 mg/dl memiliki kadar IFN-γ lebih rendah dibandingkan dengan kelompok dengan kadar trigliserida ≥ 150 mg/dl. Terdapat perbedaan bermakna antara rata-rata konsentrasi konsentrasi IFN-γ antar kedua kelompok tersebut (p=0,000). Pada kelompok KGD P ≥126 mg/dl dan trigliserida ≥ 150 mg/dl memiliki kadar IFN-γ yang lebih tinggi dibandingkan dengan kelompok KGD P ≥126 mg/dl namun trigliserida <150 mg/dl. Terdapat perbedaan bermakna antara rata-rata konsentrasi konsentrasi IFN-γ antar kedua kelompok tersebut (p=0,000).

***Kesimpulan:** Terdapat perbedaan konsentrasi IFN-γ pada orang dengan DM, peningkatan KGD P dan dislipidemia dibandingkan dengan orang normal.(Health Science Journal of Indonesia 2021;12(2):74-80)*

***Kata kunci :** IFN-γ, diabetes mellitus, dislipidemia.*

Diabetes mellitus (DM) is a chronic disease that greatly affects the quality of life. Based on data from the International Diabetes Federation prevalence of DM sufferers in the world reached 9.3%. In Indonesia, the estimate of DM sufferers at the age of 20-79 years reach 10-20 million people.[1] Based on the RISKESDAS 2018 data, the prevalence of DM in Indonesia reached 1.5%. In Aceh, this rate reached 1.7%, 0.2% higher than the national rate.[2]

Blood sugar level control in DM patients is extremely concerned. Ramadhan in her research which involved 85 DM patients stated that there were 92% of patients with uncontrolled fasting blood sugar levels, and 88% of DM patients with uncontrolled blood sugar levels 2 hours post-pandrial.[3] Increased blood sugar levels are closely related to fat blood, mainly cholesterol and triglycerides.[4]

There is chronic inflammation in DM, which is marked by increased pro-inflammatory markers. [5,6] Due to chronic inflammation, there is a decrease in the immune response in DM patients.[7] Chronic hyperglycemia also causes impaired cytokine secretion.[8,9] DM patients are also frequently accompanied by dyslipidemia. Increased adipose tissue in people with dyslipidemia will increase various proinflamatory cytokines such as TNF-α, IL-1, IL-6, and TGF-β.[10]

IFN-γ is a proinflamatory cytokine that plays a major role in infection. In its functions as an immunomodulator, IFN-γ will activate macrophages, NK cells, and play a role in the migration process of various types of other leukocyte cells.[11,12] People with DM and dyslipidemia will easily be having other infectious diseases.[13,14] Patients with DM who are accompanied with tuberculosis (TB) have decreased TNF-alpha and IFN-γ concentration, which can be interpreted as a decrease in the immune response so that they are easily infected with other diseases.[15] This function disorder may occur in DM sufferers make them easier to have other infection. This condition attracted the interest of researchers to study the changes IFN-γ concentrations in patients with diabetes mellitus and nonDM, the changes in IFN-γ concentrations in dyslipidemia and normal person, and the changes in IFN-γ concentrations in hyperglycemia and hypertriglycerides, and hyperglycemia without hypertriglycerides.

METHODS

Respondents

This research was conducted for 1 year, located in Banda Aceh. The sample in this study was patients undergoing treatment at public health facility at Banda Aceh in 2019 with the criteria aged 30-60 years and not in a pregnant condition. The respondents who participated in this study were 234 people. All respondents who participated in the study had signed informed consent. From each respondent, 5 ml of blood was taken to check fasting blood sugar level, triglycerides, HDL, and IFN-γ. This research has received approval from the Health Research Ethics Commission, National Health Research and Development Department with No: LB.02.01 / 2 / KE.171 / 2019.

Fasting blood glucose, triglycerides and HDL cholesterol examination.

Measurement of fasting blood glucose, triglycerides and HDL cholesterol was carried out by the colorimetric enzymatic method.[16,17] The glucose examination was using glucose kit (cat. No. 112191), triglycerides was using triglycerides kit (cat. No.116392), HDL was using HDL kit (cat. No.108495). An amount of 1000 µl of glucose reagent or triglyceride or HDL cholesterol were filled into three test tubes, each tube will be used as

standard, sample and blank. To the two tubes were added 10 µl of sample or standard. Subsequently incubated for 10 minutes at a temperature of 25ºC. Then the fasting blood sugar/triglycerides/HDL levels are valuable with a photometer 5010 V5+ at a wavelength of 546 nm.

IFN-γ Protein examination

Measurement of IFN-γ protein concentration was using the sandwich enzyme-linked immunosorbent assay (ELISA) technique.[18] The examination was performed by usage IFN-gamma ELISA kit (cat. No. 622120). An amount of 50 µL of working strength conjugate was put into the ELISA well, then 50 µL samples of standard or serum were added and incubated for 120 minutes at 22° C. Then, wash for around 6 cycles. Then 100 µL of substrate was added and incubated for 30 minutes at 22ºC. Finally, a stop solution of 50 µL was added and it was read using Thermo Scientific Multiscan GO microplate spectrophotometer at a wavelength of 450 nm.

Statistic analysis

Respondents were divided into DM and nonDM groups. The DM group was obtained based on the doctor's diagnosis. Univariate analysis was performed on the DM and nonDM groups to obtain the average IFN-γ concentration data, the frequency distribution of DM and nonDM patients based on fasting blood glucose, triglycerides and HDL. For all respondents, bivariate analysis was carried out to obtain data on the average concentration of IFN-γ based on fasting blood glucose, triglyceride and HDL categories. Furthermore, the Mann-Whitney test was performed to obtain differences in the concentration of IFN-γ in each of these groups.

RESULTS

From the research results obtained 234 respondents consisted of 70 people diagnosed with DM by doctor and 164 people without diabetes mellitus. In Figure 1 it can be concluded that the IFN-γ concentration in the nonDM group was higher than the DM group. Based on Mann-Whitney test, there was a significant difference in the average concentration of IFN-γ between the two groups (p=0,000).

Figure 1. The average of IFN-γ concentration in the non-DM group and the DM group

From table 1 it can be concluded that in the DM group all respondents have an increase in fasting blood glucose, while in the nonDM group there were some people who have increased in fasting blood glucose. Based on the triglyceride concentration, most DM sufferers have hypertriglycerides. Based on HDL levels, most DM and nonDM sufferers have normal HDL levels.

Table 1. The frequency distribution of DM and nonDM patients based on fasting blood glucose, triglycerides and HDL.

No	Variable	DM		nonDM	
		n	%	n	%
1	Fasting Blood Glucose				
	≥ 126 mg/dl	70	89,7	8	10,3
	< 126 mg/dl	0	0	156	100
2	Triglycerides				
	≥ 150 mg/dl	40	33,3	80	66,7
	< 150 mg/dl	30	26,3	84	73,7
3	HDL				
	Low	8	22,9	27	77,1
	Normal	62	31,2	137	68.8
	Total	70	100	164	100

Based on table 2 we can conclude that group with fasting blood glucose levels <126 mg / dl had a higher IFN-γ concentration than the group with fasting blood glucose levels ≥126 mg / dl. Based on Mann-Whitney test, there was a significant difference in the average IFN-γ concentration between the two groups. The grouping of blood glucose levels in this result is <126 mg / dl or ≥126 mg / dl without regard

to the patient diagnosed DM or not.

IFN-γ concentration in the group with triglycerides ≥150 mg / dl was higher than in the group with triglycerides <150 mg / dl. Based on the Mann-Whitney test, there was a significant difference that the group with triglyceride levels <150 mg / dl had lower IFN-γ levels compared to groups with triglyceride levels ≥ 150 mg / dl (Table 2).

The group with normal HDL levels had a lower averaged IFN-γ concentration than the group with low HDL levels, but based on the Mann-Whitney test there was no significant difference in the average of IFN-γ concentration between the two groups (Table 2). People who had fasting blood glucose ≥126 mg / dl and triglycerides ≥150 mg / dl had higher IFN-γ concentration than people who had fasting blood glucose ≥126 mg / dl and triglycerides <150 mg / dl. Based on Mann-Whitney test, there was a significant difference in the average IFN-γ concentration between the two groups (Table 2).

Table 2. Differences in the average of IFN-γ concentration in various groups based on fasting blood glucose, triglycerides, and HDL (n = 234).

No	Variable	IFN		
		Mean (min-max)	SD	P value
1	Fasting Blood Glucose			
	≥ 126 mg/dl	0,0423 (0,026-0,118)	0,01489	0,000
	< 126 mg/dl	0,0496 (0,026-0,109)	0,01326	
2	Triglycerides			
	≥ 150 mg/dl	0,0499 (0,026-0,118)	0,01411	0,001
	< 150 mg/dl	0,0444 (0,026-0,109)	0,01384	
3	HDL			
	Low	0,0501` (0,026-0,118)	0,01474	0,057
	Normal	0,0467 (0,026-0,109)	0,01410	
4	Fasting Blood Glucose ≥ 126 mg/dl			
	Triglycerides ≥ 150 mg/dl	0,0442 (0,026-0,118)	0,01538	0,000
	Triglycerides < 150 mg/dl	0,0395 (0,028-0,091)	0,01389	

DISCUSSION

Interferon-gamma is a cytokine produced by CD4 + and CD8 + T lymphocytes and natural killer cells.[19] Plays a role in various infections, the production of IFN-γ is important to increase the activity of macrophages to fight infection through the mechanism of phagosome maturation blockade and nitrite oxide production (NO).[12] The study revealed that the immune system of DM patients can express different cytokine patterns, including the expression of proinflammatory cytokines IFN-γ.[20] Our discovery previously concluded that in patients with DM accompanied by TB there was a decrease in IFN-γ production.[15] This study also found similar results, a decrease in the production of IFN-γ in patient diagnosed with DM. A similar result was expressed by Price which stated that patients diagnosed DM because of increased glycation resulted in a decrease in IFN-γ production.[21]

The concentration of IFN-γ obtained by various other cytokines on the production of IFN-γ. Tan found that there was two to three-fold decrease in the levels of IFN-γ. The decreasing IFN-γ concentration in DM patients increased the chance of bacterial infection. Furthermore, the decrease in IFN-γ production is the effect of decreasing interleukin-12 (IL-12). [9] Lagman found that there was a decrease in IFN-γ concentration two-fold lower in DM compared to healthy, linking the decrease in IFN-γ with a decrease in (NO), which resulted in susceptibility to *M. tb*.[22] The decrease in NO production will affect the bacteria killing mechanism. Futhermore, the decrease is also accompanied by a decrease in GSH which results in oxidative stress. This is reinforced by the increased susceptibility to the incidence of diabetic foot in patients with long-standing DM and uncontrolled blood sugar level.[23]

However, if there is an increase in IFN-γ in DM patients, this indicates pathogenesis of hypertension in these DM patients.[20] This occurs by involving the renin-angiotensin-angiotensinogen system (RAS). The binding between angiotensin II on immune cells will increase the production of IFN-γ and the effect of adhesion that results in inflammation.[24] This continuous inflammatory process will result in hypertension.

A similar condition was also found in patients with increased fasting blood glucose levels even though they were not diagnosed with DM by health workers (Table 1). This data showed a fasting blood glucose level <126 mg / dl or ≥126 mg / dl without regard patients diagnosed diabetes or not. Many DM patients failed to control blood glucose levels. This is evidenced by Ramadhan in his research which concluded that 84% of DM patients were unable to control their blood glucose levels.[3] Chronic hyperglycemic conditions either due to inadequate treatment or ignorance of suffering from DM can result in impaired immune function.

DM patients are also often accompanied by poor triglyceride control. Research conducted by Arifin proved that there was a relationship between increased blood glucose levels and triglyceride levels increased.[4] This study found that the group with triglyceride levels ≥ 150 mg / dl had a higher IFN-γ concentration than the group with triglycerides <150 mg / dl (table 2). Mirhafez showed similar results, an increase in IFN-γ concentration in people with hypertriglycerides.[25] Research conducted by Pacifico concluded that there is an increase in IFN-γ production in obese people. Okopien explained in his study that in dyslipidemic patients occurred an increase in IFN-γ which resulted in chronic inflammation.[26] Peningkatan ini mungkin terjadi karena peningkatan $CD4^+$ dan $CD8^+$.[27] An increase in IFN-γ concentrations also occurred in people who had fasting blood glucose ≥126 mg / dl and triglycerides ≥150 mg / dl compared to people who had fasting blood glucose ≥126 mg / dl and triglycerides <150 mg / dl. Mirhafez also showed an increase in IFN-γ concentration in the group with metabolic syndrome compared to the normal. Among the various cytokines examined (IL-2, IL-4, IL-6, IL-8, IL-10, VEGF, TNF-α), IFN-γ is the most associated with the incidence of metabolic syndrome.[28] Furthermore, IFN-γ alters cell metabolism through inhibition of SIRT1. As a result of this inhibition causes metabolic disorders in skeletal muscle cells.[29] IFN-γ decreases insulin sensitivity. This also decreases glucose uptake in adipose cells.[30] Rocha proved that a decrease in IFN-γ will decrease triglycerides and glucose levels.[27]

Condition dyslipidemia is also characterized by decreased HDL levels. Low levels of HDL in the blood are used as a predictor of prognosis for patients with cardiovascular disease.[31] The results of Purwanti's study showed that 74.3% of respondents who had higher fasting blood sugar levels had low HDL levels.[32] In this study, it can be seen in table 1 that IFN-γ levels increased in the group with low HDL. This result is similar to the study conducted by Bengalem.[33] Other studies revealed a negative correlation between IFN-γ and HDL levels. IFN-γ levels in obesity with atherosclerotic can predict the potential and parameters for detection of coronary artery disease.[34]

In conclusion, there was a decrease in IFN-γ in people with increased fasting blood glucose, while in hypertriglycerides there was an increase in IFN-γ. However, in people with hyperglycemia and hypertriglyceridemia, there was an increase in IFN-γ concentration, compared to people with hyperglycemia and normal triglycerides.

Acknowledgement

Our thanks go to Dr. Fahmi Ichwansyah, S.Kp, MPH, and all health centers in Banda Aceh for their support to this study.

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The importance of hospital re-accreditation: improving the timeliness of laboratory critical value reporting

DOI: https://doi.org/10.22435/hsji.v12i2.3315

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Received: July 29, 2020; Revised: August 2, 2021; Accepted: August 30, 2021

Abstract

Background: Patient safety is the main issue in healthcare services nowadays. Delaying to inform the critical value of laboratory results is a significant source of harm for the patient. The aim of this study is to compare the timeliness of laboratory critical value reporting before and after re-accreditation as one of the service quality indicators in Hospital X.

Methods: This study was done by using observational cross-sectional in Hospital X on January - February 2020 with total sampling method of critical value reporting to the responsible clinician that originated from Intensive Care Unit (ICU), Verlos Kamer (VK), and inpatient ward (IW) 1-6 from January-December 2019. The timeliness of reporting was counted since the laboratory result was obtained until received by the responsible clinician within ≤ 30 minutes and categorized as "On time" or "Late".

Results: During 2019, there were 816 reporting which has been done before re-accreditation (511) and after re-accreditation (305) with 17 kinds of tests. The most reported test was platelet with 349 (before re-accreditation) and 101 (after re-accreditation), whilst SGOT/SGPT and albumin were the fewest one. The lowest timeliness of reporting percentage was 76,00% (February), whilst the highest was 98,48% (November). The timeliness of reporting's percentage was 84,34% (before re-accreditation) and 94,43% (after re-accreditation). The statistical analysis result revealed Pearson Chi-Square correlation was 18,535 with significance 0,000 and 3,145 odds ratio which shows that re-accreditation could significantly increase the timeliness of critical value reporting three times.

Conclusion: This result showed that re-accreditation could affect the timeliness of laboratory critical value reporting to the responsible clinicians. ***(Health Science Journal of Indonesia 2021;12(2):81-7)***

Keywords: re-accreditation, critical value, laboratory, patient safety, hospital

Abstrak

Latar belakang: *Keselamatan pasien merupakan isu utama dalam pelayanan kesehatan. Tertundanya komunikasi hasil nilai kritis laboratorium merupakan sumber bahaya yang signifikan terhadap pasien. Penelitian ini bertujuan untuk membandingkan ketepatan waktu pelaporan nilai kritis laboratorium sebelum dan setelah reakreditasi sebagai salah satu indikator mutu di RS X.*

Metode: *Penelitian dilakukan dengan cara observasional dengan metode cross sectional di RS X pada Januari - Februari 2020 dengan total sampling laporan nilai kritis kepada Dokter Penanggung Jawab Pasien (DPJP) yang berasal dari ruang Intensive Care Unit (ICU), Verlos Kamer (VK), dan ruang rawat inap 1 – 6 sejak Januari – Desember 2019. Ketepatan waktu pelaporan dihitung sejak hasil pemeriksaan didapatkan hingga diterima oleh DPJP dalam waktu ≤ 30 menit dan dinyatakan sebagai "Tepat Waktu" atau "Terlambat".*

Hasil: *Selama tahun 2019, terdapat 816 pelaporan yang dilakukan sebelum akreditasi (511) dan setelahnya (305) dengan 17 jenis pemeriksaan. Pemeriksaan trombosit menjadi yang paling banyak dilaporkan yaitu 349 (sebelum akreditasi) dan 101 (setelah akreditasi), sedangkan SGOT/SGPT dan albumin menjadi yang paling sedikit. Persentase ketepatan waktu pelaporan paling rendah adalah 76,00% (Februari) sedangkan yang paling tinggi adalah 98,48% (November). Persentase ketepatan waktu pelaporan didapatkan 84,34%*

(sebelum akreditasi) dan 94,43% (setelah akreditasi). Hasil analisis statistik didapatkan korelasi Pearson Chi-Square 18,535 dengan signifikansi 0,000 dan Odds ratio 3,145 menunjukkan re-akreditasi mampu meningkatkan kemungkinan ketepatan waktu pelaporan nilai kritis sebesar tiga kali lipat.

Kesimpulan:** Hal ini menunjukkan bahwa re-akreditasi mampu mempengaruhi ketepatan waktu pelaporan nilai laboratorium kritis kepada DPJP.* ***(Health Science Journal of Indonesia 2021;12(2):81-7)

***Kata kunci:** re-akreditasi, nilai kritis, laboratorium, keselamatan pasien, rumah sakit.*

The main issue in health services nowadays is patient safety. Every year, adverse events occur as many as 134 million cases in the hospital of middle-low income countries and are responsible for 2,6 million death because of unsafe care. It also estimated 1 of the 10 patients in a high-income countries is harmed by a various unwanted events during getting service in the hospital which half of it is preventable.[1]

The patient safety regulation in Indonesia is reflected on Ministry of Health Decree No.496/Menkes/SK/IV/2005 about Medical Audit Guideline in Hospital which has main purpose is to achieve medical service excellence, minimize medical error, and give safety to patients in the hospital. Indonesian Hospital Association (PERSI) also initiate meeting and persuade all the hospital stakeholder to be more concerned about the patient safety issue. [2]

Hospitals in Indonesia must be accredited once every 3 years in order to increase the quality of care according to Indonesia law about hospitals (Undang-Undang No. 44 Tahun 2009, Pasal 40 Ayat 1). Hospital X which was established in 1907 is a type C hospital with 194 beds inside. It has been accredited four times: once in 2011 with five primary service standards (administration, medical record, emergency, medical, and nursing service), twice in 2012 & 2016 with KARS (Komite Akreditasi Rumah Sakit) standard, and once in 2019 with SNARS 1st edition (Standar Nasional Akreditasi Rumah Sakit) criteria which got the best category (paripurna) as written on the certificate with the serial number is KARS.SERT/866/VII/2019.

Indonesia has 12 compulsory national quality indicators for hospitals which laboratory critical value reporting is one of them. *The Joint Commission* (JC) implies critical value is a test result that is significantly out of normal range and represents life threatening condition.[3] Hospital X policy declares that laboratory critical value reporting must be received by a responsible clinician within ≤ 30 minutes with the target of achievement being 100%.[4] The laboratory critical value was stated on hospital's internal regulation that was published in April 2019 which contains the critical value of hematology, clinical chemistry, electrocardiography, and radiology. This regulation was socialized together with re-education about critical value reporting for the safety of patients.

This research purpose is to compare the timeliness of laboratory critical value reporting before and after re-accreditation and in Hospital X. This study could be one of the evidence whether re-accreditation can increase the quality of hospital services.

METHODS

This study has been done by using the observational cross-sectional method from January to February 2020. The population of this study was 821 data obtained from laboratory critical value reporting documentation in Hospital X from January-December 2019. Data was originated from the Intensive Care Unit (ICU), *Verlos Kamer* (VK) or delivery room, and inpatient ward 1-6 which has well documented report. The method of sampling in this study was purposive total sampling. There were 5 data that do not meet the sample criteria, so the sample that accepted was 816 data.

The data about amount of laboratory results during 2019 was obtained from Hospital's Information System. There were 15.734 laboratory test results divided as 7.854 before and 7.880 after re-accreditation. This data describes how many laboratory test results have been delivered to 8 hospital rooms as mentioned above. The variable of this study is re-accreditation execution and the timeliness of laboratory critical value reporting before and after re-accreditation. Re-accreditation is an activity that has been held by the hospital along with KARS on July 8th - 12th, 2019. The laboratory test results performed January - July 7th, 2019 defined as "before re-accreditation", whilst July 8th - December 31th, 2019 defined as "after re-accreditation".

The timeliness of laboratory critical value reporting is reporting laboratory test results that are included in the critical criteria (according to Hospital X regulation) to responsible clinician whether verbal or written until received within ≤ 30 minutes and proven by therapy advice or SBAR (situation, background, assessment, and recommendation) documentation on medical record.[5] Regardless of the amount and type of critical laboratory result reported, it only counted as 1 report if it is the same patient and reported at the same time. The result of reporting was classified as "On Time" or "Late".

The hypothesis of this research is hospital re-accreditation could affect the timeliness of laboratory critical value reporting to the responsible clinicians. The samples were tabulated and Chi-Square was performed as a statistical analysis method on SPSS 20 application to prove the hypothesis. Ethical approval from the ethics commission of the hospital was given as ethical clearance letter No. SURKT/RST/20.09.05.001 on September 5th, 2020.

RESULTS

We found 816 documentation about laboratory critical value reporting to responsible clinicians consisting of 17 tests variation (Table 1) among it. Before re-accreditation there were 538 critical results and 344 critical results afterward. Platelet test was the most test with critical result whether before or after re-accreditation as many as 349 (64,9%) and 101 (29,4%) respectively (Table 1). On the contrary, SGPT/SGOT and albumin were the fewest tests with the critical results.

Table 1. Laboratory critical result by type of test

Test	Before Re-accreditation (%)	After Re-accreditation (%)
Platelet	349 (64,9)	101 (29,4)
Leucocyte	24 (4,5)	88 (25,6)
Hemoglobin	51 (9,5)	67 (19,5)
Hematocrit	-	2 (0,6)
APPT	3 (0,6)	-
BUN	7 (1,3)	6 (1,7)
Creatinine	39 (7,2)	25 (7,3)
Uric Acid	2 (0,4)	-
Potassium	33 (6,1)	25 (7,3)
Calcium	4 (0,7)	-
Sodium	5 (0,9)	9 (2,6)
Random blood sugar	9 (1,7)	5 (1,5)
Troponin	9 (1,7)	12 (3,5)
Total bilirubin	2 (0,4)	1 (0,3)
HBsAg	1 (0,2)	1 (0,3)
SGOT / SGPT	-	1 (0,3)
Albumin	-	1 (0,3)
Total	538 (100)	344 (100)

Tabel 2. Laboratory test results, critical laboratory test results, critical value reporting before and after re-acreditation

Room	Before Re-accreditation			After Re-accreditation		
	Laboratory Test Results	Laboratory Test Results with Critical Value	Critical Value Reporting	Laboratory Test Results	Laboratory Test Results with Critical Value	Critical Value Reporting
ICU	190	39	38	156	38	35
VK	1.018	18	18	827	15	14
IW 1	459	55	53	344	44	34
IW 2	627	77	71	634	33	32
IW 3	1.566	61	57	1.625	26	24
IW 4	1.091	86	86	1.179	70	60
IW 5	1.377	143	136	1.520	69	63
IW 6	1.526	59	52	1.595	49	43
Total (%)	**7.854 (100)**	**538 (6,9)**	**511 (95)**	**7.880 (100)**	**344 (4,4)**	**305 (88,7)**

We obtained 15.734 laboratory test results (7.854 before and 7.880 after re-accreditation) were delivered to the Intensive Care Unit (ICU), *Verlos Kamer* (VK) or delivery room, and inpatient ward (IW) 1-6 during 2019 (Table 2). Before re-accreditation, 538 (6,9%) from 7.854 laboratory test results were critical values. The laboratory critical value reporting was 511 (95%) out of 538 laboratory test results with critical values. After re-accreditation, 344 (4,4%) from 7.880 laboratory test results were critical value. The laboratory critical value reporting was 305 (88,7%) out of 344 laboratory test results with critical value. The difference about the number of reporting and the documented critical laboratory results (e.g. before re-accreditation 511 reporting from 538 critical results) happened because we only count as 1 report if it is the same patient and reported at the same time regardless of the amount and type of critical laboratory result reported. For the example, we found many test results from the same patient at the same time of reporting such as critical platelet count accompanied by critical leucocyte count or critical Blood Urea Nitrogen (BUN) result accompanied by critical of the creatinine serum.

Table 3. Timeliness critical value reporting before and after re-accreditation

Room	Before Re-accreditation		After Re-accreditation		Pearson X^2 Correlation	Sig.	OR
	On Time	Late	On Time	Late			
ICU	34	4	34	1			
VK	17	1	14	-			
IW 1	43	10	34	-			
IW 2	62	9	26	6			
IW 3	48	9	24	-			
IW 4	71	15	57	3			
IW 5	114	22	63	-			
IW 6	42	10	36	7			
Total (%)	**431 (84,34%)**	**80 (15,66%)**	**288 (94,43%)**	**17 (5,57%)**	**18,535**	**0,000**	**3,145**

The data of laboratory critical value reporting to responsible clinicians was obtained from ICU, VK, and inpatient ward (IW) 1-6 (Table 3). VK was the room with the fewest amount of reporting whether before and after re-accreditation with 18 reports (17 on time and 1 late) and 14 reports (on time) respectively. IW 5 was the room with the most reporting with 136 reports (114 on time and 22 late) before re-accreditation and 63 reports (on time) after re-accreditation. The most amount of reporting delay was coming from inpatient ward 5 before the re-accreditation. After re-accreditation, the lateness of reporting was zero on VK, inpatient wards 1, 3 and 5. The percentage of laboratory critical value reporting before re-accreditation was 84,34% on time and 15,66% late while after re-accreditation there was an improvement with 94,43% on time and 5,57% late.

The timeliness of critical value reporting's trend from January until December 2019 could be seen in picture 1. The timeliness of laboratory critical value reporting is reporting laboratory test results that are included in the critical criteria (according to Hospital X regulation) to responsible clinician whether verbal or written until received within ≤ 30 minutes and proven by therapy advice or SBAR documentation on medical record.[5] The highest enhancement of the timeliness percentage happened in May from 84,47% to 96,49%. The fewest reporting's percentage happened in February 2019 with 76,00%, whilst the most happened in November 2019 with 98,48%.

The statistical analysis of laboratory critical value reporting with Chi-Square method has met the condition with expected count values on all cells > 5, and Pearson Chi-Square Correlation result was 18,535 with significance 0,000 (Table 3). It means there is a significant differences in the timeliness of critical value reporting before and after re-accreditation group. The odds ratio of the test is 3,145. It means the chance of timeliness of critical value reporting is increased as high as three times because of re-accreditation. This analysis showed that re-accreditation could affect the timeliness of laboratory critical value reporting to the responsible clinicians.

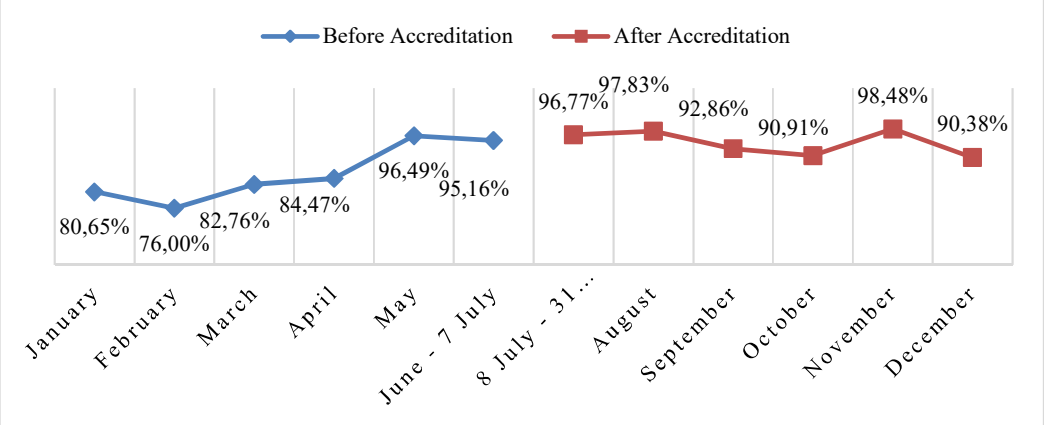

Figure 1. The percentage of laboratory critical value reporting to responsible clinician

DISCUSSIONS

We identified 17 laboratory test variations that have critical value and reported them to the responsible clinicians. The most laboratory test result with critical value was platelet followed by leucocyte and hemoglobin as mentioned in Table 1. A study in India from January 2012 to December 2013 found 5 laboratory test results with the most critical value that informed to responsible caregiver were hemoglobin 26,8%, 17,1% leucocyte, urine ketone 16,0%, platelet 10,4%, and International Normalized Ratio (INR) 10,1%.[6] Yang *et al.,* unveiled critical value of platelet, total leucocyte, and INR were 3 out of 10 laboratory tests that has strong association with the occurrence of death in patients.[7] Platelet count is one of the indicators as coagulation representative along with other indicators (respiration, liver, central nervous system (CNS), and renal) in Sequential (sepsis-related) organ failure assessment (SOFA) Score which could define septic condition which can lead multiorgan dysfunction syndrome and shock that result in death.[8,9] So, it is very important for caregivers to understand the vital role of laboratory test critical value and to report it as soon as possible to the responsible clinicians.

The critical laboratory test result percentage in our result is relatively high 4,4% (July-December 2019) and 6,9% (January-July 2019) as seen in Table 2. On the other study, the percentage is ranging from 0,4% (January - June 2017); 0,49% (January 2015 - June 2019); 0,96% (January - December 2010) and 1,02% (May - June 2015).[10,11c]The difference is we only analyze the laboratory test result from the inpatient ward which has a higher chance to contribute to critical value, whereas the previous study involved the emergency and outpatient departments.[10,6] For the example low platelet count ≤100.000/µL (thrombocytopenia) and increasing hematocrit >20% are the laboratory criteria for hospitalization on DHF cases with clinical symptoms which prone to get critical value in inpatient ward.[14]

The hospital target about laboratory critical value reporting yet achieved as they established the target is 100%. The highest achievement from the target was 98,48% that happened in November 2019 (Figure 1). In another word, there was still a lateness in critical value reporting. A study in a clinical laboratory of a university hospital in Turkey shows there was a lateness of reporting as many as 13,1% out of 2018 laboratory critical value results during May-June 2015. They found 62,8% was mild-delayed reporting (18,5 ± 4,4 minutes) and 37,2% was advanced-delayed reporting (47,1 ± 11,3 minutes). The lateness of critical value reporting ~~is~~ usually happens from 06.00 - 10.00 which is the beginning of working time and the busiest time of the day. The lateness was also observed from 12.00 - 14.00 (lunch time) and ~~at~~ from 16.00 - 18.00 which is changing time of the personnel. The reason for the lateness of reporting is morning visits preparation and the changing of the task of the personnel during those hours. The conclusion of the study is relatively increasing workload and less effective workflow planning caused the delay in critical value reporting.[13]

Lack or delay in critical value communication is one of significant sources of harm for patients. Lundberg in 1972 defined critical value concept as "pathophysiologic derangement that varies so much from normal that it is life threatening if therapy is not started immediately".[15] Those danger alarms are well understood by doctors that was proven by changes in therapy for 98% of patients in the surgical department and 91% of patients in the non-surgical department after the critical value obtained.[3] On the other study, delays in antibiotic administration for sepsis, severe sepsis, and septic shock patient were associated with the risk of mortality in the hospital.[16] In children patient, the delay of discovering critical value not only can cause death, but also development impairment such as neurological e.g. which caused by hyperammonemia that attacks the brain.[17] So, it is very important for the responsible physicians to know about their patient's critical laboratory results as soon as possible, because delay in knowing means delay giving a prompt treatment.

With the rush of doctors who are not always in the inpatient room, 55,6% of laboratory critical results have been reported to other health workers than straight to responsible clinicians. Howanitz *et al.,* demonstrate there are different mindsets between doctors and nurses about the urgency of critical value reporting. The nurse assumes that critical value reporting is not important to the patient's medication, while the doctor thinks conversely. Thus, education for health workers about awareness of critical value reporting to the responsible clinicians is needed for the safety of patients.[18] The socialization about the urgency of critical value reporting in Hospital X has been held as re-accreditation preparation. Nowadays, critical value communication is the part of accreditation procedure of medical laboratories

and including in universally agreed International Organization for Standardization (ISO) 15189:2012.[3]

The total percentage of timeliness of laboratory critical value reporting to responsible clinicians was increased from 84,34% to 94,43% after re-accreditation (Table 3). Statistical analysis reveals re-accreditation increase the timeliness of reporting as high as three times. Despite the highest enhancement of the timeliness of critical value reporting's percentage was happened in May 2019 (picture 1) from 84,47% to 96,49%, the timeliness of laboratory critical value reporting was always >90% after re-accreditation. It could be influenced by the internal regulation publication about critical value in April 2019 and re-education about the importance of laboratory critical value reporting for the safety of patients. The intervention of training to increase knowledge, practice and attitude of staff towards compliance of critical value reporting to the clinician could increase the timeliness. The study in India shows the timeliness of critical value reporting was 97,22% before training and became 100% after the training.[19] Study in a University Hospital, Saudi Arabia shows the percentage of laboratory critical value reporting within 30 minutes had high compliance (99,37%) as they already stick to the College of American Pathologists (CAP) Laboratory Accreditation Program.[20] It seems accreditation and the sequence like training could bring a good impact to the timeliness of laboratory critical value reporting.

The limitation of this research is using secondary data which the accuracy depends on the data maker. The other limitation is we do not have data from the emergency department which could be the best source of laboratory test result which has critical value. This study could be expanded further with more complete data or to be performed in another hospital which could provide evidence about the benefit of re-accreditation in the Hospital.

In conclusion, our study found there is significant differences of timeliness laboratory critical value reporting before and after re-accreditation. Hospital re-accreditation and the sequence like education could increase the timeliness of the laboratory critical value reporting. It is very crucial to report the laboratory critical value result as soon as possible because it is inseparable with patient safety.

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Priority setting in responding crisis: a hospital leaders' perspective at the early stage of COVID-19 pandemic

DOI: https://doi.org/10.22435/hsji.v12i2.5295

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Received: August 25, 2021; Revised: September 29, 2021; Accepted: October 15, 2021

Abstract

Background: The COVID-19 pandemic hit Indonesia when hospitals were striving to adjust to a changing environment after a new health insurance system implementation, a government's effort to achieve Universal Health Coverage. As a result, the pandemic forced hospitals to exploit their resources. Due to limited resources, setting accurate priorities is highly important to secure hospital operations and maintain its track towards the expected goals. This study aims to explore how deep the crisis impacts hospitals and how hospital leaders in Indonesia set their priorities in responding to the impact of this pandemic.

Methods: This study used a descriptive and analytical approach. Data were collected through an online survey from hospital leaders and several documentary sources.

Results: The results show that almost all hospital directors consider patient visits and hospital finance the most significant impacts of the COVID-19 pandemic. However, government hospital directors emphasize different areas compared to non-government hospital directors; the former sets their priorities on the hospital's human resources, quality of service, and operations, while the latter focuses on the impact of patient visits and hospital finance.

Conclusion: Although directors of government and non-governmental hospitals have a different emphasis, their priority is the same, maintaining hospital sustainability to provide quality services to people. ***(Health Science Journal of Indonesia 2021;12(2):88-96)***

Keywords: COVID-19 pandemic, hospital leaders' perspective, impacts, Indonesia, priority setting.

Abstrak

Latar belakang: *Pandemi COVID-19 melanda Indonesia ketika rumah sakit berusaha menyesuaikan diri dengan lingkungan yang berubah setelah penerapan sistem jaminan kesehatan baru sebagai upaya pemerintah untuk mencapai Universal Health Coverage. Akibatnya, pandemi memaksa rumah sakit untuk mengeksploitasi sumber daya mereka. Sumber daya yang terbatas membuat penetapan prioritas yang akurat menjadi sangat penting untuk menjamin keberlangsungan operasional rumah sakit dan memastikan rumah sakit bergerak menuju tujuan yang diharapkan. Penelitian ini bertujuan untuk mengeksplorasi seberapa dalam dampak krisis ini terhadap rumah sakit dan bagaimana pemimpin rumah sakit di Indonesia menetapkan prioritasnya dalam merespon dampak pandemi ini.*

Metode: *Penelitian ini menggunakan pendekatan deskriptif dan analitik. Data dikumpulkan melalui survei online dari pimpinan rumah sakit dan beberapa sumber dokumenter.*

Hasil: *Hasil penelitian menunjukkan bahwa hampir semua direktur rumah sakit menganggap kunjungan pasien dan pembiayaan rumah sakit mendapat dampak paling signifikan dari pandemi COVID-19. Namun, direktur rumah sakit pemerintah menekankan bidang yang berbeda dibandingkan dengan direktur rumah sakit non-pemerintah. Direktur rumah sakit pemerintah menetapkan prioritas mereka pada sumber daya manusia rumah sakit, kualitas layanan, dan operasi, sedangkan direktur rumah sakit non-pemerintah fokus pada dampak kunjungan pasien dan keuangan rumah sakit.*

Kesimpulan: *Meskipun direktur rumah sakit pemerintah dan non-pemerintah memiliki penekanan yang berbeda, tetapi prioritas mereka sama yaitu menjaga keberlanjutan rumah sakit untuk memberikan pelayanan yang berkualitas kepada masyarakat.* ***(Health Science Journal of Indonesia 2021;12(2):88-96)***

Kata kunci*: pandemi COVID-19, perspektif pemimpin rumah sakit, dampak, Indonesia, penetapan prioritas.*

Delivering quality health services while having limited financial and human resources has become a tough challenge for hospitals after the Covid-19 pandemic. Resources, in fact, are not unlimited and barely meet all needs,[1] thus priority setting is obligatory. The COVID-19 pandemic, which began in Wuhan, China, at the end of 2019, was identified in Indonesia in early 2020. The pandemic spread rapidly and resulted in a high upsurge in the death rate worldwide.[2]

The pandemic has not only caused a health crisis, but also impacted the global economy.[3] Various efforts to deal with the virus transmission, especially by limiting human mobility, have enormously impacted numerous fields,[3] including hospitals that have been directly affected. Studies worldwide report that hospitals experienced problematic situations in various areas, such as the declining of patient visits, financial losses, increasing mortality and pressures on healthcare workers, and disruption to hospital operations and service quality.[4–9] This crisis then forced the hospitals to exploit all of their resources, thus threatening their sustainability.[9–11] Due to increasingly limited resources, carefully setting priorities is very important for the continuity of hospital operations and ensuring the hospital's progress in the expected direction.[9,11]

In fact, until August 2020, many hospitals in Indonesia only had limited resources, merely sufficient to meet the minimum hospital standards. It is shown from the hospital accreditation results, around 60% of hospitals in Indonesia had *dasar* (basic), *perdana* (initial), and even not-accredited status.[12] Under this circumstance, any disturbance to the organization, such as late payment claims from BPJS to hospitals in 2018 and 2019, in some cases could substantially impact the operational activities and threaten hospital operations.[13,14] In reality, the disturbances caused by the COVID-19 pandemic have a huge direct influence on all aspects of hospital resources, primarily financial and human resources.[10] In addition to the large costs incurred, a significant number of health workers who died raises concerns about the hospital's sustainability.[15]

Before the COVID-19 pandemic hit, hospitals in Indonesia were undergoing a major change in implementing a new health insurance system, the National Health Insurance as an effort to achieve Universal Health Coverage. Due to standardized rates and quality of the new insurance system, the hospitals that previously only focused on providing services,[16] had to carefully calculate the costs because they could no longer compensate service fees incurred on service rates. Unfortunately, the COVID-19 pandemic hit Indonesia just as hospitals in Indonesia began to adjust. This pandemic may endanger the sustainability of hospitals that are also at the forefront of achieving universal health coverage. Therefore, an empirical study needs to be carried out to find out how far COVID-19 affects hospitals and how hospital leaders in Indonesia set priorities in responding to the impact of this pandemic. Understanding hospital leaders' response and their perspective on the effect of the COVID-19 pandemic on hospitals will help generate the hospital's intra- and inter-organization policy to support the hospitals to continue operating and progressing towards the expected goals.

METHODS

This study applied a descriptive-analytic approach. Data was collected from hospital leaders through online surveys and several documentary sources. The online surveys were distributed on November 2020 through the WhatsApp group for alumni of the Postgraduate Program in Hospital Management, Universitas Brawijaya, Indonesia, which covers hospital directors and managers. The surveys were also forwarded to alumni colleagues who work as hospital directors. The online survey consists of close and open-ended questions. The close-ended questions aimed to measure the severity of the impact of the COVID-19 pandemic on hospitals in five areas, namely patient visits, finance, human resources, service quality, and hospital operations. Meanwhile, the open-ended questions aimed to explore what and why certain areas became top priorities for hospital leaders to resolve. Secondary data related to the COVID-19 condition were written based on government reports, official government websites, international organization reports, scientific literature, and online news articles. An ethics clearance was obtained from the Postgraduate Program in Hospital Management, Faculty of Medicine, Universitas Brawijaya, Malang Indonesia No.409.1/EC/KEPK-PPS/MMRS/2020 and informed consent was obtained from all respondents included in this study.

RESULTS

As many as 30 people, respondents of this study were directors of hospitals that have different characteristics. Most respondents (73.3%) were directors

of non-government hospitals. The classes and numbers of the hospital beds were relatively varied, although most were class C (46.7%) and D (36.7%) hospitals, with the number of beds ranging from 51 to 200 beds (76.6%). Of all respondents, most (63.3%) were directors of COVID-19 referral hospitals. The characteristics of respondents' hospitals are presented in Table 1.

Table 1. Characteristics of respondents' hospital

Characteristics		Frequency n=30	Percentage %
Ownership	Government	8	26.7
	Non-Government	22	73.3
Class	Class A	1	3.3
	Class B	4	13.3
	Class C	14	46.7
	Class D	11	36.7
Bed number	Up to 50 Bed	1	3.3
	51 to 100 Bed	13	43.3
	101 to 200 Bed	10	33.3
	201 to 300 Bed	4	13.3
	More than 300 Bed	2	6.7
COVID-19 Referral	Referral	11	36.7
	Non-Referral	19	63.3

The impact of the COVID-19 pandemic on hospitals

The research results revealed that the COVID-19 impacted the hospitals in various aspects and at different levels. Most hospital directors (93%) stated that patient visits to hospitals were significantly affected (moderate and severely affected) by the Covid-19 pandemic. It is related to the majority (77%) of directors' statements that this pandemic had a significant impact on the hospital's financial condition. Similarly, hospital human resources and service operations were also significantly affected. Meanwhile, although the biggest proportion was unaffected (33%), the directors' response regarding the impact of the pandemic on service quality was fairly equal, starting from not being affected to being severely affected. A more detailed description of the directors' response is presented in Figure 1.

The cross-tabulation results (Figure 2) show a similar response between government and non-government hospital directors on the impact of the COVID-19 pandemic, namely in the aspects of patient visits and hospital financial conditions (Figures 2a and 2b).

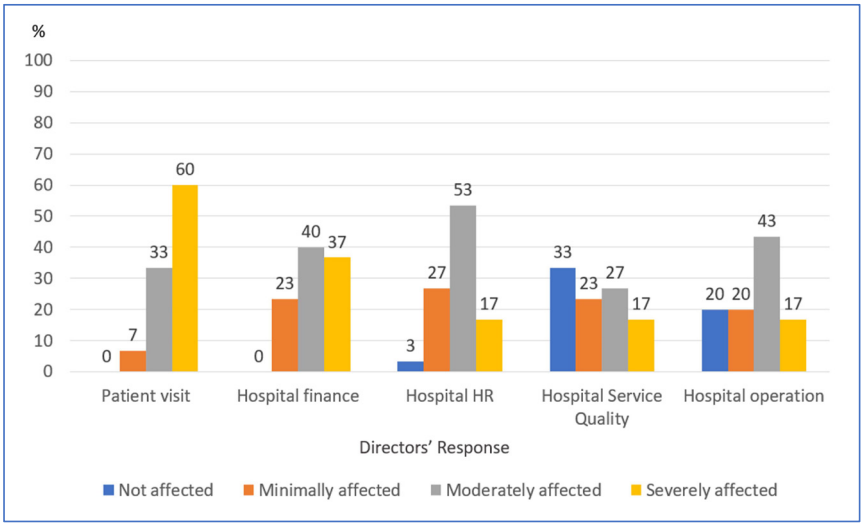

Figure 1. Directors' response regarding COVID-19 impact on hospitals

All directors of government hospitals (100%) and almost all directors of non-government hospitals (91%) stated that patient visits were affected and severely affected by the pandemic. Meanwhile, most of the directors of government hospitals (75%) and non-government hospitals (77%) also expressed a similar impact of this pandemic on hospital finance. Figures 2c, 2d, and 2e revealed that the responses of the directors of government and non-government hospitals were quite diverse regarding the pandemic impact on human resources, service quality, and hospital operations. The proportion of government hospital directors who thought that COVID-19 had no significant impact on the quality of hospital services and operations was almost the same as the proportion of directors who thought the opposite.

Meanwhile, slightly more non-government hospital directors (59%) considered that the quality of their hospital services was not significantly affected. In contrast, most non-government hospital directors (64%) believed that the pandemic had a significant impact on hospital operations. Different responses between government and non-government hospital directors were noticed in the pandemic impact on hospital human resources. Most government hospital directors (63%) stated that this pandemic had no significant impact on hospital human resources, while most non-government hospital directors (82%) argued contradictorily.

Although the response of government hospital directors about COVID-19 pandemic impact on hospitals on patient visit and finance aspects was similar to those of non-government hospital directors, the results of this study indicated that their priorities were different (Figure 3). Most government hospital directors (62.5%) stated that human resources, quality of services, and hospital operations were their priorities, while the rest (37.5%) prioritized visits and finance. In contrast, non-governmental hospital directors preferred visits and finance as their priorities (59.1%) than those who prioritized human resources, quality of service, and hospital operations (40.9%).

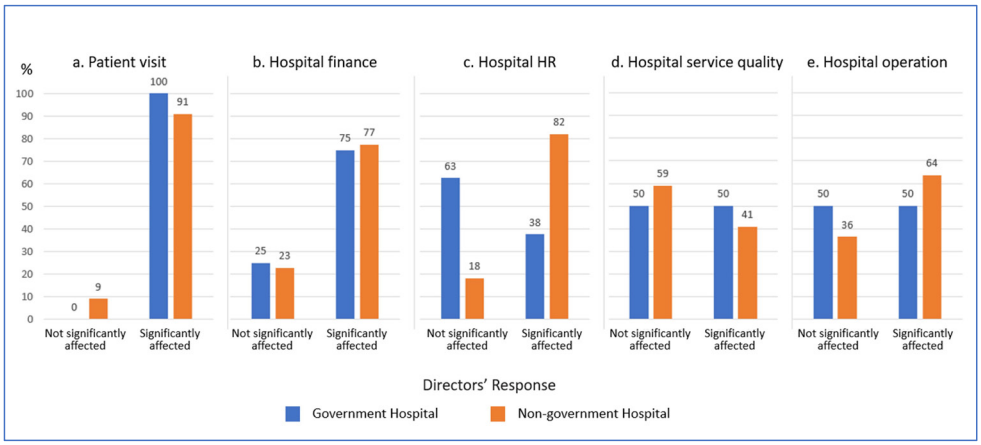

Figure 2. Response of the Directors of Government and Non-Government Hospitals on the impact of COVID-19 on hospitals

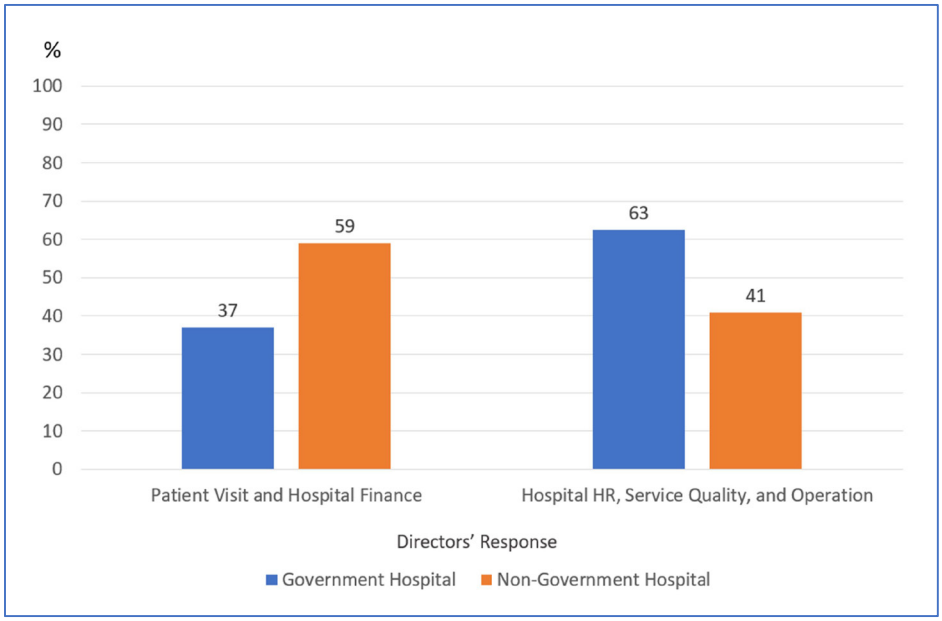

Figure 3. The main priorities of government and non-government hospital directors on the impact of COVID-19 on hospitals

Reasons for selecting impact priorities

The reason of the government hospital directors to prioritize solving problems on human resources, quality of service, and hospital operations seemed related. One of the hospital directors argued that COVID-19 exposure on staff had a far-reaching impact on the hospital. In fact, hospital human resources are the primary executor to carrying out hospital service activities. According to the directors, the key to resolving other existing problems was fixing the hospital service operational issues. Also, the hospital service operation is under the control of hospital managers as hospital policymakers, so they can overcome those difficulties. The hospital director also stated the priority issues affecting hospital operations and service quality were the ease of obtaining personal protective equipment and health protocol application. Meanwhile, some hospital directors who prioritized finances and hospital patient visits argued that patient visits significantly affected hospital revenues. Further, the director said that efforts to overcome decreasing patient visits were not easy, so they must be prioritized. Also, other directors stated that patient fear was the cause of the decreasing patient visits.

Meanwhile, the determination of the impact on patient visits as the priority by non-government hospital directors was mainly based on the impact size on the hospital's financial condition. The non-government hospital director stated that patient visits were the hospital and staff income source. The director's primary consideration in dealing with the pandemic impact on the patient visit was to immediately restore hospital's financial stability because the impact affected the performance and sustainability of hospital operations. Others argued that they prioritized overcoming patient visits because the efforts to gainpatient visits were not easy since it required time and resources. The directors stated that gaining patient visits was constrained by the lack of communication space between hospital and public and the growing stigma in the public that hospitals were a prone place for COVID-19 transmission. Situations become increasingly difficult because people believed that many patients were *"di-COVID-kan"* by hospitals to get financial benefit from treating COVID-19 patients. The term *"di-COVID-kan"* means the patients are forced to admit that they are diagnosed as COVID-19 patients although they are not. Figure 4 presents a map of the reasons for non-governmental hospital directors in setting patient and financial visits as top priorities.

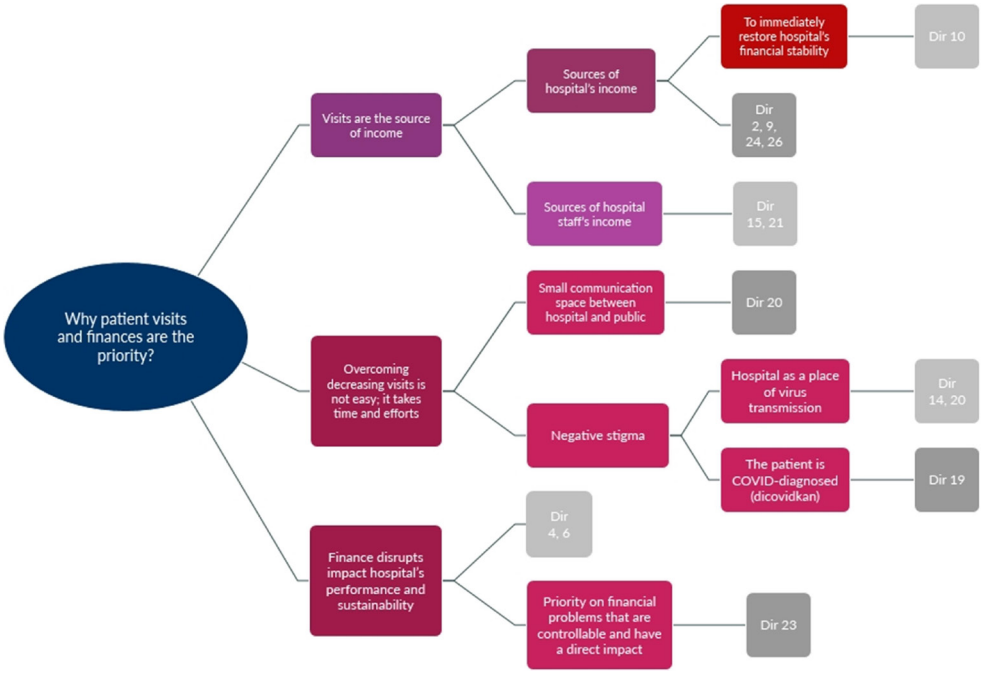

Figure 4. Reasons of non-government hospital directors on determining patient visits and finances as top priorities

Meanwhile, several non-government hospital directors prioritized aspects other than patient visits and finances. They select human resources and service operations which in turn aim for the continuity of hospital operations. Some directors' focuses were meeting the needs for medical equipment and materials for COVID-19 screening, protecting staff and patients, and optimizing adaptation and innovation efforts. The aims of directors that set priority on fulfilling COVID-19 screening materials and medical devices were to ensure smooth, quick, and precise services, in addition to protecting the staff and patients. Further, the protection of patients and hospitals is the director's concern because patient care is the main goal of health services and the hospital staff is the primary executor in delivering services to patients. The hospital directors argued that when more human resources and patients were exposed and more resources were needed, it disrupted hospital sustainability. Figure 5 presents a reason mapping why non-government hospital directors set priorities other than patient visits and finances.

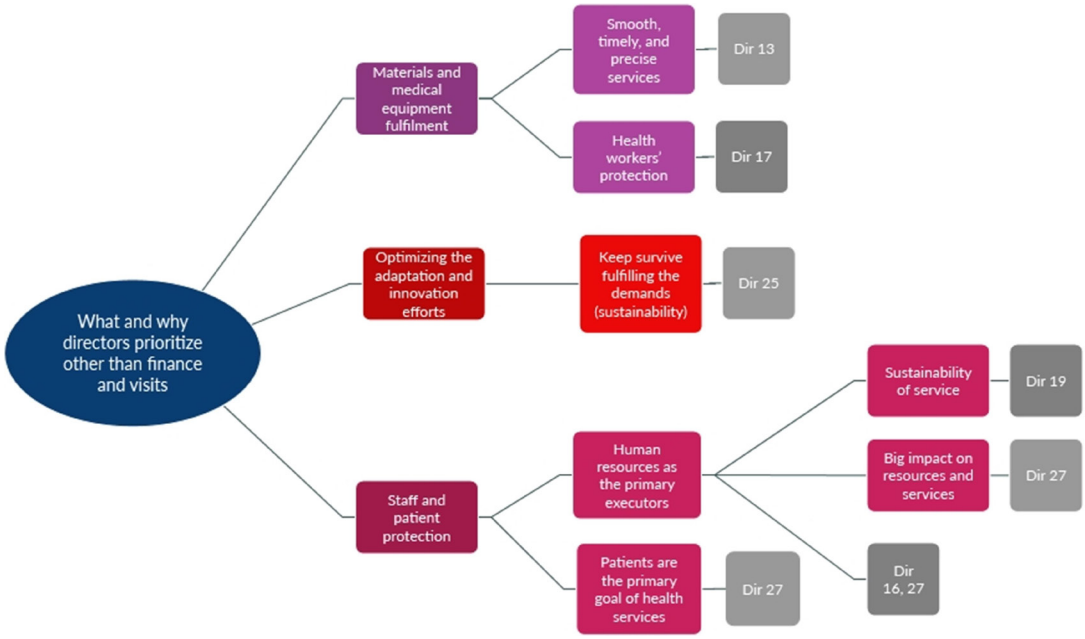

Figure 5. Reasons of non-government hospital directors on determining priorities other than patient visits and finances

DISCUSSIONS

According to all directors of the government hospitals and non-government hospitals, the most severe impact of COVID-19 is the decreasing patient visits and hospital financial problems. A decrease in hospital patient visits also means a reduction in revenue for the hospital. Moreover, decreasing visits occurred in almost all units, including outpatient, elective, and surgical services, which are significant income sources for hospitals.[6] Based on the statement of hospital leaders, this decrease in hospital income further disturbed many other aspects, such as decreasing income of health workers and disruption of service operations due to financial difficulties. This shows that the conditions are similar to hospitals around the world that also suffered from such impacts due to the pandemic.[4–9]

The decrease inpatient visits was caused by restriction or reduction in general public activity, which has even led to a world economic recession and impacted almost all forms of business.[3] In addition, the decrease in visits was caused by the Indonesian government policy at the beginning of the pandemic, which limited non-emergency hospital services.[17] This condition threatens the financial sustainability of Indonesian hospitals which were struggling to adjust to the changes in the new payment system.[16] In fact, for American hospitals that have long adapted to payment reforms, the crisis has still created financial challenges.[6]

Nonetheless, the study results revealed that the leading cause of the decrease inpatient visits was due to patient fear. It can be seen from the results of open-ended questions, which show that patient fear is a factor in decreasing patient visits. This

fear has arisen in Indonesia since the beginning of the pandemic.[18] This patients' fear resulted from the circulating stigma that a hospital is a place of COVID-19 transmission. The public thinks that contact with healthcare and healthcare workers is very risky of transmitting COVID-19.[19] However, government policies limiting hospital services for non-emergency cases in the early days of the pandemic may also become the cause. The service limitation reinforces the stigma for the public that hospitals are places of COVID-19 transmission. Besides, patient fears also come from the issue that health workers or hospitals are looking for profit by caring for COVID-19 patients.[20] It makes people afraid to obtain medication in the hospitals because they are scared of being "*di-COVID-kan*". This situation was worsened by statements from a government official and a member of *Dewan Perwakilan Rakyat* or the House of Representatives of the Republic of Indonesia regarding this problem,[21,22] so that public opinion seemed justified. Unfortunately, one of the directors mentioned that the hospital only has limited space to communicate and convince the public not to be afraid of going to the hospital.

This shows that the leading cause of the decreasing patient visits is the people's fear of going to the hospital, and this is mainly because of the circulating negative stigma. This critical situation should be taken into consideration by many parties, including government and hospital management. The government or its officials can provide support for hospitals in the form of forethought in making statements for the public and supported by clear policy formulation, which can strengthen public trust. At the same time, hospital management should be more active in communicating with the community to regain trust.[19,23]

All government hospital and non-government hospital directors agreed that the aspects affected mainly by the COVID-19 pandemic were patient visits and hospital finances, but they set different priorities. Government hospital directors focused more on dealing with human resource issues, service quality, and operational services in the hospital than problems on visits and finances. In contrast, non-government hospital directors preferred to prioritize patient visits and financial issues. It is possibly because government hospitals have a more secure financial condition. Besides income from patient visits, government hospitals obtain a cash flow from the government for human resource salaries and capital expenditure, such as hospital facilities and infrastructure and medical equipment.[24] On the other hand, non-government hospitals rely on revenue from hospital operating activities to finance their hospital operations.[24] Thus, it is understandable that non-governmental hospital directors prioritized patient visits and hospital finances.

Although government and non-government hospital directors set different priorities due to the pandemic impact, their priority setting is for the hospital operation continuity. The directors' attention on protecting the human resources aims to secure the main components of hospital service providers so that the hospital can survive and continue to operate to serve patients even in the pandemic condition. Likewise, the directors who prioritized patient visits and finances argued that patient visits were the source of hospital revenue. Financial disruption will impact the hospital's performance and its continuity. The current difference in prioritization indicates that it is not merely due to the difference in profit orientation between government hospitals and non-government hospitals but also on maintaining hospital operations.

This study has limitations. This study shows the views of hospital leaders at the time of collecting data which was in the early stage of the pandemic. Thus, careful consideration is needed in understanding and using the conclusions of this study. As the pandemic situation continues changing rapidly, further study will be needed to explain the changing phenomena. Researchers can consider the urban-rural and geographical distribution of the respondent and hospital location in collecting data and discussing the result as those differences may affect the response of hospital leaders; thus it may potentially give a different picture.

In conclusion, this study shows that the impact of the COVID-19 pandemic is inevitable for hospitals. The heaviest impacts revealed by the hospital directors are the decreasing patient visits and financial problems. Other areas affected are human resources and hospital service operations. Hospital directors set priorities differently based on the areas affected. Government hospital directors prioritize the impact of human resources and service operations, while non-government hospitals tend to focus more on the impact of patient visits and hospital finances. However, the reason for setting these priorities in general is for securing the hospital operations to continue providing health services for the country.

Acknowledgment

The authors would like to express their gratitude to Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia for funding this research through *Hibah Penelitian Dosen Muda* or Research Grant for Junior Lecturer with No. 6748/SK/UN10.F08.06/PN/2020.

Conflict of Interest

All authors declare that there are no significant competing interests that might have affected the performance or presentation of the work described in this manuscript.

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Factors associated with measles antibody titers in children aged 12-36 months in Indonesia: an analysis of National Health Research 2013

DOI: https://doi.org/10.22435/hsji.v12i2.5356

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Abstract

Background: The immunization program in Indonesia has been implemented since 1956 started to eradicate smallpox and expanded until 1980, including Measles. The timely and complete implementation of basic immunization is the main strategy to protect the population, including outbreak prevention. The purpose of this study is to determine the level immunity of Measles antibody as the outcome of completed basic immunization and its contributors in children aged 12-36 months.

Methods: This study is a secondary data analysis of the Indonesia Basic Health Survey (RISKESDAS) 2013. The analysis was carried out on a serological sample of the antibody titer of children aged 12-36 months, totaling 229 samples. The sample inclusion criteria were children who had complete sociodemographics data, basic immunization records and Measles antibody titer data. Measles examination was carried out using the Enzyme-Linked Immunosorbent Assay (ELISA) method.

Results: Incomplete immunization, being a boy, and lack of cleanliness in the family room were significantly associated with lower measles antibody levels in children. Having each variable controlled, completeness of immunization (OR=1,99; p=0.018; 95% CI=1.124-3.544) and gender of boy (OR=2.0; p=0.016; 95% CI=1.137-3.515) remain as significant variables for antibody's titer.

Conclusion: The completeness of immunization has a significant association towards titer antibody of Measles in children. Immunization completeness is an actual effort to reach herd immunity in children and to prevent measles outbreak in the community. Adequate health promotion is needed to change people's behavior to believe in the safety and importance of implementing complete basic immunization for children even in pandemic conditions. ***(Health Science Journal of Indonesia 2021;12(2):97-103)***

Keywords: antibody titer, immunization, children aged 12-36 months, Indonesia, measles

Abstrak

Latar belakang: *Program imunisasi di Indonesia telah dilaksanakan sejak tahun 1956 yang dimulai dengan pemberantasan cacar yang diperluas hingga tahun 1980, termasuk campak. Pelaksanaan imunisasi dasar yang tepat waktu dan lengkap merupakan strategi utama untuk perlindungan penduduk, termasuk pencegahan Kejadian Luar Biasa (KLB). Tujuan dari penelitian ini untuk mengetahui tingkatan kekebalan antibodi Campak sebagai hasil dari kelengkapan imunisasi dasar dan faktor yang berkontribusi pada anak usia 12-36 bulan.*

Metode: *Penelitian ini merupakan analisis data sekunder Riset Kesehatan Dasar Indonesia (RISKESDAS) 2013. Analisis dilakukan pada sampel serologi titer antibodi anak usia 12-36 bulan yang berjumlah 229 sampel. Kriteria inklusi sampel adalah anak yang memiliki data sosiodemografi lengkap, catatan imunisasi dasar dan data titer antibodi Campak. Pemeriksaan campak dilakukan dengan metode Enzyme-Linked Immunosorbent Assay (ELISA).*

Hasil: *Imunisasi yang tidak lengkap, berjenis kelamin laki-laki, dan kurangnya kebersihan di ruang keluarga berhubungan bermakna dengan rendahnya tingkat antibodi campak pada anak. Setelah masing-masing variabel terkontrol, kelengkapan imunisasi (OR=1,99; p=0,018; 95% CI=1.124-3.544) dan jenis kelamin laki-laki (OR=2.0; p=0.016; 95% CI=1.137-3.515) merupakan variabel yang tetap berhubungan dengan titer antibodi secara signifikan.*

Kesimpulan: *Kelengkapan imunisasi memiliki hubungan yang bermakna terhadap titer antibodi Campak pada anak. Kelengkapan imunisasi merupakan upaya nyata untuk mencapai herd immunity pada anak dan mencegah wabah campak di masyarakat. Promosi kesehatan yang memadai diperlukan untuk mengubah perilaku masyarakat agar percaya akan keamanan dan pentingnya pelaksanaan imunisasi dasar lengkap bagi anak meskipun dalam kondisi pandemi.* ***(Health Science Journal of Indonesia 2021;12(2):97-103)***

Kata kunci: *titer antibodi, imunisasi, anak usia 12-36 bulan, Indonesia, campak*

Immunization intends to provide toddlers' immunity. The immunization policy began in 1956 to eradicate smallpox. It expanded until 1980, including several vaccination types, i.e., BCG, DPT, Polio, and Measles. Hepatitis B immunization had become part of the national program in 1997. Basic Immunization Program in Indonesian toddlers started soon after birth and reached nine months, followed by repeated immunizations at specific periods (Regulation of the Minister of Health No.12 / 2017). The Indonesian Basic Health Research (RISKESDAS) shows no significant change in the prevalence of children receiving complete basic immunization. In 2013, it was reported that only 60% of children aged 12 months had completed the necessary immunizations, while the results of the 2018 survey the prevalence decreased slightly to 57.9%. Incomplete basic immunization coverage experienced a small increase from 32% to 32.9% from 2013 to 2018 and there were still 9.2% of children who did not receive immunizations based on the survey in 2018.[1,2]The global spread of the COVID-19 pandemic has been shown to significantly impact routine immunization services disruption. A rapid study conducted by UNICEF and the Indonesian Ministry of Health in April 2020 found that 84% of all health facilities reported interruption of immunization services. This disruption occurred at various levels of service where there was a decrease in demand due to fear of contact with COVID-19. In addition, there has also been a shift in focus on resources for controlling COVID-19. It was also reported that the limitations of personal protective equipment (PPE) in carrying out safe immunization were one of the problems that disrupted immunization services.[3] This further exacerbates the risk of children getting incomplete immunizations.

Due to the high prevalence of incomplete immunization in children, this has implications for the risk of disease exposure in children under five. In which malnutrition can be one contributor to this condition. Malnourished as a consequence of inadequate intake of food and other multiple predecessor factors in children are at a high risk of child mortality. It is commonly seen in low- and middle-income countries.[4,5] There is a two-way causal relationship between malnutrition and infection. Malnutrition caused by inadequate intake increases susceptibility to infectious diseases, while the condition might worsen infant nutritional status by reducing appetite, repetitive intestinal infection, and nutrient malabsorption. Although it is debatable whether malnutrition increases the incidence of infection or whether it only increases the severity of the disease, studies showed malnourished children are at a higher risk of death after infection.[6,7] Therefore child immunity is very important and can be invested early years of life through the maternal nutritional status.[8]

Nutrition is an essential determinant of the immune response, while malnutrition mostly causes immune deficiency worldwide. Lack of amino acids and carbohydrate intakes are associated with a significant decrease in cellular immunity. Specifically, on the phagocyte function, the complement system, secretory immunoglobulin, antibody concentrations, and cytokine production. Single nutrient deficiency produces an immune response, even when a nutritional deficiency is relatively mild. Micronutrients such as zinc, selenium, iron, copper, vitamins A, C, E, and B-6, and folic acid are essential for immune response. Excessive nutrition and obesity also reduce immunity. Babies with low birth weight have prolonged cellular immunity disruption, which can be partially restored by providing a different diet plus zinc.[9]

Inadequate nutritional intake reduced the body's immunity and body response to form antibodies, especially at newborn and young child of 12–36-month-old. The body's vulnerability at these age groups should be maintained since the fetus. Maternal micronutrient supplementation could prevent the adverse effect of the birth outcome, such as preterm birth and neonatal mortality[10–13] Furthermore, improved breastfeeding practices at postnatal and optimal nutrition intervention would prevent child's immunity and reduce deaths from infection.[14]

We selected children aged 12-36 months to assume that these subjects have completed the necessary immunization and measles booster and the body's immune response against measles formation. Based on the above evidence, to date, there are still limitations to studies using antibody titers in survey data to emphasize the importance of a comprehensive basic immunization program for children in Indonesia. Therefore, this study aims to determine the level of measles immunity in children aged 12-36 months and the factors associated with it.

METHODS

Design and Sample

Riskesdas has been carried out every five years since 2007. In the 2013 survey, data collection was conducted in the period of May-June, in 33 provinces and 497 districts/cities. This survey measures the coverage of health indicators in Indonesia. It measures the content of health indicators—secondary data analysis conducted to produce this article.

Measures

RISKESDAS 2013 blood sampling represented the provincial level. Probability proportional to size with replacement in selecting 177 districts/cities sampling is applied, then census blocks chosen by systematic sampling. The biomedical sample size which includes 1,000 Census Blocks was 49,931 people.[15] Our study consisted of a secondary analysis based on data from 229 children aged 12-36 years. The sample inclusion criteria were children who had complete sociodemographic and basic immunization records, public health and also Measles antibody titer data.

Measles examination was carried out using the Enzyme-Linked Immunosorbent Assay (ELISA) method using a commercial NOVALISA kit, which read at a wavelength of 450/620 nm. Measles IgG antibody titers were divided into two positive categories if the titer is> 220 mIU / ml and negative if it is ≤ 220 mIU / ml. The negative group titers with equivocal values (titers 120 - 220 mIU / ml) have been repeated and included.[16]

The dependent variable is the measles antibody titer (protective/non-protective). In contrast, the independent variables included age, sex, prior immunization status (complete/incomplete), nutritional status (WAZ, HAZ, and WHZ), frequency of illness in the past month (ARI, Diarrhea, and Pneumonia), anemia status (Fe levels in the blood), environmental health status, and settlement status (rural-urban).

Analytic strategy

Data were managed and analyzed using the statistical software SPSS Statistics for Windows, version 21.0 (SPSS Inc., Chicago, Ill., USA). Analysis was performed for univariate, bivariate of Chi-square analysis, and multivariate using stepwise logistic regression. Following are the operational definitions of the variables used in this study.

Operational definition of variables included in this analysis

Terminology	Definition	Category
Batita or children under three years old	Children aged 12-36 months. We adjusted a little bit of this terminology as we included children aged 36 months in the data collected.	1=12-23 months 2=24-36 months
Antibody titer	The level of immunity of Measles at the plasma blood of children	1=protected 2=unprotected
Immunization	The vaccination exemption, namely Measles, DPT, and Hepatitis	1=yes 2=no
Immunization status	Completeness of the primary immunization accepted by the children, taken from child's KIA book record	1= completed 2=uncompleted and unimmunized
Nutritional status	Anthropometric measurement results of weight by age (WAZ or wasting) and height by age (HAZ or stunting) using the cut-off point <-2 SD as malnourished	1=well-nourished 2=malnourished
Disease frequency	Having a history of acute respiratory infection (ARI) or diarrhea or pneumonia at the last month	1= yes 2=no
Anemia status	Level of hemoglobin in the blood using the cut-off point<12 mg/dl	1= anemia 2=not anemia
Environmental health status	The availability of cleaned water and household's clean space in the house	1=yes 2=no
Residential	Urban and rural (based on the CBS criteria)	1=urban 2=rural
Mother's education	Mother's length of education from not schooling up to the highest level of education achieved	1=below high school 2=high school or above

Ethical Clearance

This study is a secondary data analysis from the 2013 RISKESDAS Survey. Ethical approval was granted by the National Ethical Committee (ethic number: 01.1206.207). Informed consent is signed up before the data collection by all study participants. For children younger than 15 years old, parental consent was mandatory.

RESULTS

There were 229 children aged 12-36 months with complete measles antibody titer data analyzed in this study—the frequency distribution for each variable presented in Table 1.

Table 1. The distribution of demographic and child health status

No	Characteristics (N=229)	n	%
1	Titer antibody (protective)	141	61.6
2	Immunization (completed)	147	64.2
3	Not wasted (WAZ)	176	76.9
4	Not stunted (HAZ)	136	59.4
5	No history of ARI	127	55.5
6	No history of Diarrhea	190	83.0
7	No history of Pneumonia	223	97.4
8	Not Anemia	150	65.5
9	Boys	122	53.3
10	Age of 24-36 month	151	65.9
11	Mother's education (high)	70	30.5
12	Urban residence	108	47.2
13	Clean space of the household	172	75.1
14	Clean water available	171	74.4

Of the 229 children, 61.6% had protective measles antibody status and 64.2% had complete immunization status. The proportion of illness history is relatively good, except for ARI experienced by almost half of the total sample (45.5%). Anemia in children under the age of three years reached 34.5%. Maternal education was still relatively low; only about 30% of mothers were high school graduates.

Table 2. Analysis of association between independent variables and measles titer antibody

No	Demography and Health Status	Measles Titer antibody		
		OR	95% CI	P
1	Incomplete immunization	1.91	0.982-3.701	0,05
2	Wasted	0.59	0.220-1.583	0.25
3	Stunted	0.72	0.353-1.469	0.37
4	Ever ARI	0.68	0.450-1.681	0,87
5	Ever Diarrhea	0.85	0.366-2.034	0.72
6	Ever Pneumonia	4.59	0.352-59.885	0.24
7	Anemia	0.86	0.431-1.737	0.68
8	Boys	2.45	1.243-4.843	0.01
9	Age of 12-23 month	1.57	0.807-3.063	0.18
10	Low mother's education	0.68	0.339-1.368	0.28
11	Rural residence	0.99	0.517-1.920	0.99
12	Clean family room	2.21	1.027-4.740	0.04
13	Clean water available	0.59	0.270-1.277	0.18

The bivariate analysis results showed children with incomplete immunization status had two times the risk of lower antibody titers (OR = 1.91; p = 0.05). No association between nutritional status and antibody titer status, nor was illness history. Table 2 shows family room cleanliness is significantly related to Measles antibody titer (OR = 2.21; p = 0.04). Boys have twice antibody titers than girls (OR = 2.45; p = 0.01). The regression analysis runs in the stepwise method, as presented in Table 3.

Fit model shows that having each variable controlled, completeness of immunization influences quality of Measles antibody titer (OR = 1.99; p = 0.01; 95% CI = 1.124-3.544). Boys' measles antibody titer is twice that of girls. No interaction between the completeness of immunization with the sex of the child. Statistically estimated calculation results show that Logit antibody titer = -1,057 +0,691 complete immunization + 0.693 male sex.

The model showed a significant number of Omnibus test p = 0.002, which completeness of immunization and sex could explain 7.6% (based on Nagelkerke R-square) effect on measles antibody variable in children. However, the accuracy of predicting the two variables against the Measles antibody titer was 61.6%.

Table 3. Multivariate regression of risk factors and measles antibody

Factor	Estimated				
	Reg Coeff (β)	Se of β	p-value	Odds Ratio of β	95% CI of β
Constant	-1.057	0.241	0.000	0.347	
Incomplete immunization	0.691	0.293	0.018	1.996	1.124-3.544
Boys	0.693	0.288	0.016	2.000	1.137-3.515

DISCUSSIONS

Completeness of vaccination has a significant effect on a toddler's antibody titer. Results of this study show completeness of immunization are closely related to protective measles antibody titers. There are two aspects in a child's immune system against the Measles vaccine, namely: 1) completeness of immunization shows the discipline of parents to access immunization services so that the child's immunity is protected, and 2) the possibility of antibody titers in Measles vaccine due to booster treatment.

Results of previous studies indicate, in general, mothers knew the benefits of immunization even though they do not fully understand, so mothers try to immunize their toddlers. Yet, those who are socio-economically capable always try to vaccinate their children to the fullest.[17] Besides, higher maternal education leads to better literacy skills and health-seeking behaviors, which increases immunization awareness for their children.[18]

A child's immunization completeness depends on the mother's knowledge and education. Unfortunately, this analysis results do not show any differences in children's antibody titers between mothers with low education and mothers with high education. A relatively small number of samples might cause this. Studies in Indonesia and several countries show maternal education as a determining variable in vaccination and child health. Higher the mother's education leads to higher understanding and awareness about the prevention of infectious diseases by immunization.[19–22]

Primary immunization is a mandatory program globally. The immunization program in Indonesia requires children to complete essential vaccination at the age of 9 months, followed by a measles immunization booster at the age of 18 months.[23] Maternal antibodies are transferred from the mother to protect their child's immune system from the late pregnancy period until the first month after birth or during the child's immune system maturation.[24] Therefore, vaccination is essential to acquire immunity. The health workers implemented immunization to the children through the integrated health post for child health or Posyandu.

A study of multilevel analysis in Indonesia showed the rise of immunization coverage from 47,5% to 61,5% in 2008 and 2013.[19] The 2018 RISKESDAS showed 32.9% of under-fives-year-old children in Indonesia did not get complete immunizations, and 9.2% were not immunized at all.[2] Unfortunately, according to the WHO recommendation (>80%) has not reached the basic immunization completeness coverage. Low immunization coverage has been shown by several studies, among others due to young mother's age, low parental education, limitations on access to health workers and health services, as well as the presence of certain negative beliefs. [19,25] Also, an analysis of data from IDHS 1997 showed that freeing immunization and health services charge did not guarantee mothers would bring their children getting immunized. Mothers' education is a confounder for children immunization.[26]

Vaccine safety is among the main issues for children not being immunized in developed countries such as America.[27] Besides, also the increasing refusal of vaccines based on religious beliefs. Incorrect interpretation of parents or religious leaders leads to clashes between religion and vaccination. Proper communication to illuminate the essence of the theological perspective on vaccination[28] is necessary to solve this issue. Studies on the incompleteness of immunization in Indonesia also underscore the problem of rural-urban disparities, where immunization coverage is lower in rural areas.[25]

Sex difference in measles antibody titers is challenging to explain. A GAVI report shows no difference in immunization coverage between boys and girls, except when gender inequalities existed (e.g., giving priority to boys); on the contrary, gender bias related to immunization inequality is apparent in India. Studies in six regions show that girls and those living in rural areas are less protected by vaccines because they have lower coverage than boys and those living in urban areas.[29]

A previous study from the 2013 RISKESDAS biomedical data analyzed the DPT antibody titer in under-five children in Indonesia found incompleteness on the 3-dosage of DPT's immunization was around 28%, while protective titers for tetanus and diphtheria was 18-30% and for pertussis was only 10%. This study provided a critical recommendation related to the immunization records that should be filled and appropriately stored.[30] The incompleteness of the immunization record caused inaccurate reporting of immunization coverage from surveys conducted in the community.

We used a cross-sectional dataset that cannot answer whether the dependent and independent variables

become our study limitation. Our small sample represented the national biomedical sub-sample of the RISKESDAS 2013. Therefore, future research is needed with a larger sample size to support better generalizability. Nevertheless, this is the only data related to immunization and antibody titer for measles in Indonesia.

In conclusion, immunization completeness and Measles's booster received are significantly protect antibody titer of children. Fully immunized children are more protected and have better Measles antibody titers than those who are incomplete. To avoid Measles and preventable diseases, the completeness of immunization is an important indicator. This study provides recommendations for policymakers in Indonesia to evaluate the ongoing immunization program, maximize health promotion, to educate the public on the importance of necessary immunization completeness. With the condition of the COVID-19 Pandemic which is exacerbating the challenge of providing complete immunizations to children. The reactivation of routine immunization programs must be supported by an effective communication strategy. Adequate health promotion is needed to increase knowledge and change the attitude and behavior of the community to believe in the safety and importance of carrying out complete basic immunization for children even in pandemic conditions.

List of abbreviations

BCG: Bacille Calmette Guerin vaccine; DPT: a class of combination vaccines against three infectious diseases in humans: diphtheria, pertussis (whooping cough), and tetanus; WAZ: Weight for Age Z Score; HAZ: Height for Age Z Score; WHZ: Weight for Age; ARI: Acute Respiratory Infection; IDHS: Indonesia Demographic Health Survey; WHO: World Health Organization; GAVI: The Global Alliance for Vaccines and Immunizations

Acknowledgment

Our gratitude goes to the Head of the National Institute of Health Research and Development Ministry of Health for his permission to use this RISKESDAS data.

Authors contributions

NKA and PPA have contributed the same authorship as the first writer. Conceptualization: VS, NKA. Data curation: NKA, PPA. Formal analysis: NKA, PPA. Funding acquisition: NKA. Methodology: NKA, VS, PPA. Project administration: NKA. Writing - original draft: NKA, PPA. Writing - review & editing: VS, SI, PPA. The Authors declare that there is no conflict of interest.

Conflict of interest

The authors have no conflicts of interest associated with the material presented in this paper.

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Spatial variation of tuberculosis risk in Indonesia 2010-2019

DOI: https://doi.org/10.22435/hsji.v12i2.5467

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Received: October 11, 2021; Revision: December 7, 2021; Accepted: December 10, 2021

Abstract

Background: As the second-highest country in tuberculosis (TB) cases globally, Indonesia has experienced an increasing trend of notification rate in the last ten years; however, the 34 provinces may have different risks. This study aims to examine TB risk variation across Indonesia in 2010-2019**.**

Methods: A descriptive analysis was conducted on TB routine data of 2010-2019 from the Ministry of Health. Cases included all types of TB patients. Total cases, incidence rate (IR), and standardized morbidity ratio (SMR) were calculated for each province and national level during the period. Distributions of IRs and SMRs were displayed on maps.

Results: During 2010-2019, 3,866,447 TB cases occurred in Indonesia, and the national IR was 1,523 per 100,000 populations. The highest proportion of cases and IR were in West Java (20.6%, 314 per 100,000); while the lowest were in North Kalimantan (0.2%, 3 per 100,000). Higher risks of TB occurred in DKI Jakarta (SMR 1.9), Papua (1.7), North Sulawesi (1.7), Maluku (1.5) and West Papua (1.5) among others. The smallest SMRs were found in Bali and Yogyakarta (0.5).

Conclusion: TB risk varied across Indonesia in 2010-2019, with a higher risk in DKI Jakarta and several provinces in eastern Indonesia. Given the underreporting nature of routine data, a validation is required when using the finding of this study in the local-level intervention. ***(Health Science Journal of Indonesia 2021;12(2):104-10)***

Keywords: tuberculosis, TB, standardized morbidity ratio, spatial variation, risk

Abstrak

Latar belakang: *Sebagai negara dengan jumlah kasus tuberkulosis (TB) terbesar kedua di dunia, Indonesia menunjukkan tren peningkatan notification rate di sepuluh tahun terakhir. Akan tetapi, risiko TB di 34 provinsi bisa saja berbeda-beda. Artikel ini bertujuan mengkaji variasi risiko TB di Indonesia pada tahun 2010-2019.*

Metode: *Data rutin TB tahun 2010-2019 dari Kementerian Kesehatan dianalisis secara deskriptif. Kasus TB didefinisikan sebagai semua tipe pasien TB. Total jumlah kasus, incidence rate (IR), dan standardized morbidity ratio (SMR) dihitung untuk tiap provinsi dan tingkat nasional selama periode tersebut. Sebaran IR dan SMR diplot di atas peta.*

Hasil: *Selama 2010-2019, terdapat 3.866.447 kasus TB dan IR nasional 1.523 per 100.000 populasi. Proporsi kasus dan IR terbesar ada di Jawa Barat (20,6%, 314 per 100.000) dan terkecil di Kalimantan Utara (0,2%, 3 per 100.000). Risiko TB lebih tinggi di antaranya terjadi di DKI Jakarta (SMR 1,9), Papua (1,7), Sulawesi Utara (1,7), Maluku (1,5) dan Papua Barat (1,5). Standardized Morbidity Ratio terendah ditemukan di Bali dan Yogyakarta (0,5).*

Kesimpulan: *Dapat disimpulkan bahwa risiko TB beragam di seluruh Indonesia selama 2010-2019, di mana DKI Jakarta dan beberapa provinsi di timur Indonesia memiliki risiko lebih tinggi. Mengingat adanya kurang lapor dalam data rutin, validasi diperlukan jika menggunakan temuan studi ini dalam intervensi di tingkat lokal.* ***(Health Science Journal of Indonesia 2021;12(2):104-10)***

Kata kunci: *tuberkulosis, TB, standardized morbidity ratio, variasi spasial, risiko*

Tuberculosis (TB) is in second place after HIV as a major infectious disease in the world. In 2015, there were 10.1 million total TB prevalence cases and 1.3 million TB deaths.[1] It is estimated that around 10 million people had tuberculosis (TB) in 2019. More than half were men aged 15, followed by women (32%) and children (12%). Death due to TB is estimated at 1.2 million people in 2019.[2] The regions with the most TB cases in 2019 were Southeast Asia (44%), Africa (25%), Western Pacific (18%) and the rest in the Eastern Mediterranean, Americas and Europe. Two-thirds of the world's TB burden is located in eight countries, or so-called high TB burden countries (HBC). Indonesia (8.5%) is in second place after India (26%) and before China (8.4%).[2]

In Indonesia, TB is also a national health problem. The 2013-2014 national TB prevalence survey reported that pulmonary TB confirmed by bacteriological methods was 759 per 100,000 population aged 15 years (95% CI 589-961). The burden of TB disease is higher in men, increasing with age and more in urban areas.[3] The prevalence of the Indonesian population diagnosed with pulmonary TB by a general practitioner or specialist in the last 1 year maximum is 0.42% according to the results of the 2018 Basic Health Research (Riskesdas).[4] Through the National TB Control Program, Indonesia has a target of TB elimination in 2035 and Indonesia free of TB in 2050. It is said that TB is eliminated if the number of TB cases is 1 per 1,000,000 populations.[5]

Standardized morbidity ratio (SMR) is defined as the ratio of observed cases in a study population to expected cases in that population.[6] It can be used as one of the epidemiology measures other than incidence, prevalence, odds ratio, relative risk, attributable risk and the likes. The SMR is a ratio where the denominator is the expected cases calculated based on the multiplication of the rates in a general population with the number of a study population. It has not been widely used in Indonesia as a measure of disease frequency yet. As a product of indirect standardization by incorporating the number of population in specific areas, the SMR is more objective to examine the disease distribution spatially.

TB risk shows variations across the spatial landscapes, even within one country. A study in Ethiopia reported that multidrug resistant tuberculosis (MDR-TB) cases were clustered around the border regions of Ethiopia-Sudan and Ethiopia-Eritrea, where many seasonal migrants resided.[7] Moreover, Diah et al (2017) reported that among eleven districts in Kedah State, Malaysia, the highest risk of TB occurred in Kota Setar, while the lowest in Kulim.[8]

There is an increasing trend in notification rates in Indonesia according to the 2020 Global TB Report.[2] However, the risk of TB in 34 provinces may vary. Literatures reporting TB risk variation across different geographical areas in Indonesia in a long time span are still limited. The purpose of this study is to examine the spatial variation of TB risk in Indonesia during the 2010-2019 periods.

METHODS

It is a descriptive analysis of annual TB case data in Indonesia for the 2010-2019 periods. The unit of analysis is provincial level.

Data Source

The number of TB cases was obtained from routine data collected every three months by the Ministry of Health. Tuberculosis cases were defined as new and relapsed patients of either pulmonary or extra pulmonary TB. Data for 2011-2016 are district/city level data, while 2017-2019 are individual cases originating from the Tuberculosis Information System (*Sistem Informasi Tuberkulosis, SITB*). Total cases for provincial and national levels for ten years were calculated from these two sources. The population data were obtained from supporting data in routine program data and population projections by the Central Statistics Agency (*BPS*) (https://sensus.bps.go.id/topik/tabular/sp2020/83/175748/0).

Incidence rate (IR)

The national incidence rate of TB was obtained by dividing the total number of national cases during 2010-2019 by the median of Indonesian population in the same period. A similar calculation was used to compute the IR for each province.

Standardized morbidity ratio (SMR)

The difference of TB cases observed in a province with the expected TB cases if that province has the same rate with the national level during 2010-2019 was identified with standardized morbidity ratio (SMR)[9] following the formula as follow:

$$Yi = [Oi/Ei]$$

Y is the SMR in province *i*, *O* is the number of TB cases occurring in that province, and *E* is the number of TB cases expected to occur in that province over a ten-year period. The expected number of TB cases (*E*) is calculated by multiplying the median population of each province by the crude national TB IR.[7] An SMR >1 means the risk of TB in a province is greater than in the national population because there are more TB cases in the province than anticipated based on the national IR. If an SMR <1, it indicates a lower TB risk than the national level; and an SMR equals to 1 means the TB risk in the province is the same as the national population.[9] The IR and SMR distributions of 34 provinces were then mapped in choropleth maps created in QGIS 3.16.5.

RESULTS

At the national level, there were 3,866,447 TB cases, with an average of 386,645 cases per year during 2010-2019 (Table 1). The largest proportion of cases by province was in West Java (20.6%) and the smallest in North Kalimantan (0.2%). The national IR during the study period was 1,523 per 100,000 populations. West Java and North Kalimantan have the highest and lowest IRs, 314 and 3 per 100,000 populations, respectively. The majority of provinces with high IR were located in Java Island, and North Sumatera as well as South Sulawesi (Figure 1).

The distribution of SMR of TB in ten year period across Indonesia was shown in Figure 2. According to the SMR, several provinces were identified as having greater TB risk compared to the national risk. The risk of TB is higher in DKI Jakarta (SMR = 1.9), Papua (SMR = 1.7), North Sulawesi (SMR = 1.7), Maluku (SMR = 1.5) and West Papua (SMR = 1.5) among others; while the lowest SMRs were found in Bali and Yogyakarta (SMR = 0.5) (Figure 2)

Table 1. Distribution of observed and expected cases, proportion, incidence rate, and SMR of TB by province in Indonesia, 2010-2019

No	Province	Population (median)	Observed cases	% cases	IR (per 100K)	Expected cases	SMR
1	Aceh	4,875,203	59,662	1.5%	24	74,254	0.8
2	North Sumatera	14,005,850	242,786	6.3%	96	213,321	1.1
3	West Sumatera	5,149,845	80,029	2.1%	32	78,437	1.0
4	Riau	6,357,668	70,187	1.8%	28	96,833	0.7
5	Riau Islands	2,007,348	35,674	0.9%	14	30,574	1.2
6	Jambi	3,408,180	38,433	1.0%	15	51,910	0.7
7	South Sumatera	8,029,618	119,201	3.1%	47	122,298	1.0
8	Bangka Belitung	1,377,031	17,088	0.4%	7	20,973	0.8
9	Bengkulu	1,852,096	23,203	0.6%	9	28,209	0.8
10	Lampung	8,047,623	97,806	2.5%	39	122,572	0.8
11	Banten	11,900,844	181,861	4.7%	72	181,260	1.0
12	DKI Jakarta	10,157,015	291,505	7.5%	115	154,700	1.9
13	West Jawa	46,552,872	797,082	20.6%	314	709,040	1.1
14	Central Jawa	33,731,500	436,957	11.3%	172	513,760	0.9
15	DI Yogyakarta	3,648,850	30,049	0.8%	12	55,575	0.5
16	East Jawa	38,656,890	486,858	12.6%	192	588,778	0.8
17	Bali	4,175,400	32,457	0.8%	13	63,595	0.5
18	West NT	4,775,000	61,668	1.6%	24	72,727	0.8
19	East NT	5,098,423	63,040	1.6%	25	77,653	0.8
20	West Kalimantan	4,693,750	61,954	1.6%	24	71,490	0.9
21	Central Kalimantan	2,432,977	28,398	0.7%	11	37,056	0.8
22	South Kalimantan	3,952,304	59,825	1.5%	24	60,197	1.0
23	East Kalimantan	3,463,150	51,822	1.3%	20	52,747	1.0
24	North Kalimantan	670,000	6,960	0.2%	3	10,205	0.7

No	Province	Population (median)	Observed cases	% cases	IR (per 100K)	Expected cases	SMR
25	North Sulawesi	2,396,321	61,421	1.6%	24	36,498	1.7
26	Gorontalo	1,134,049	22,694	0.6%	9	17,273	1.3
27	Central Sulawesi	2,858,645	41,565	1.1%	16	43,540	1.0
28	South Sulawesi	8,458,274	147,833	3.8%	58	128,827	1.1
29	West Sulawesi	1,283,160	17,441	0.5%	7	19,544	0.9
30	Southeast Sulawesi	2,460,331	40,911	1.1%	16	37,473	1.1
31	Maluku	1,699,245	39,489	1.0%	16	25,881	1.5
32	North Maluku	1,154,331	17,052	0.4%	7	17,581	1.0
33	Papua	3,178,600	83,179	2.2%	33	48,413	1.7
34	West Papua	876,719	20,357	0.5%	8	13,353	1.5
	Indonesia	253,856,079	3,866,447	100.0%	1.523	3,866,447	1.0

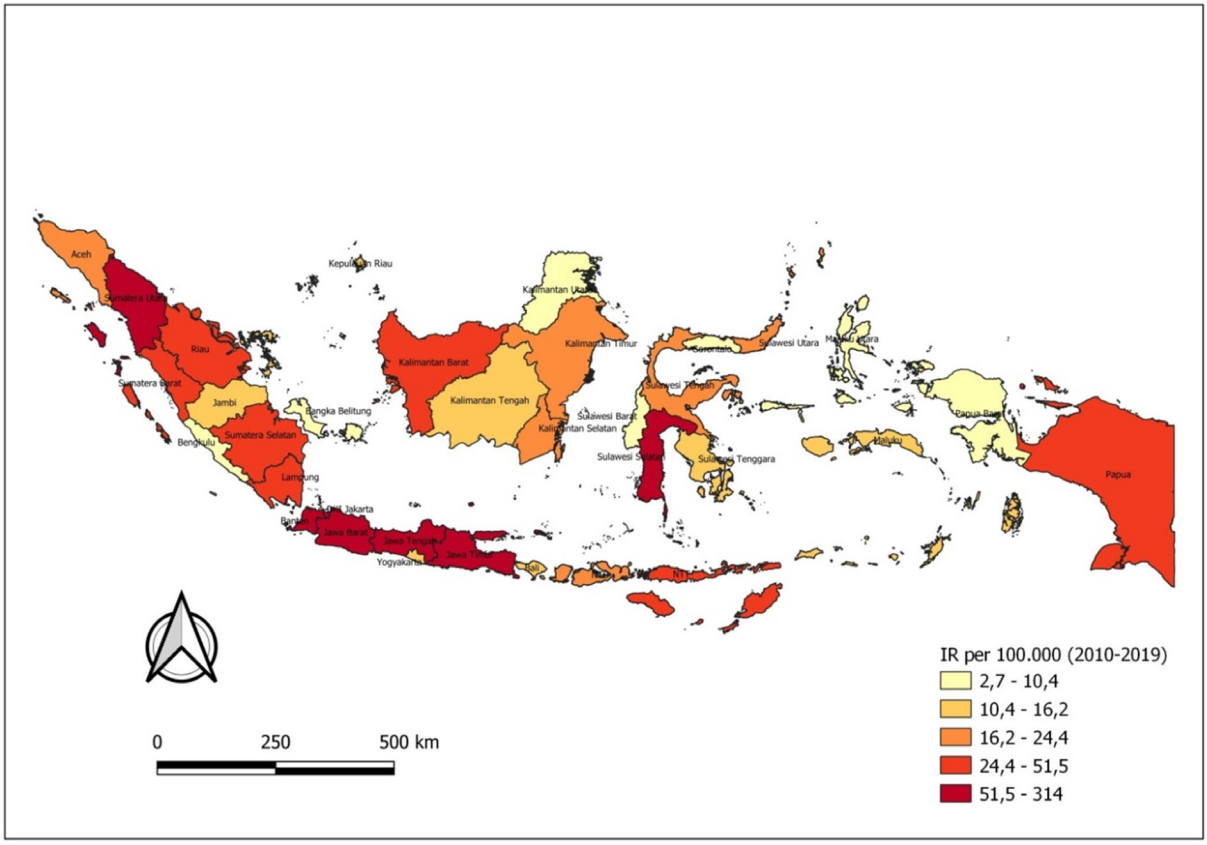

Figure 1. Distribution of TB incidence rate (IR) in Indonesia, 2010-2019

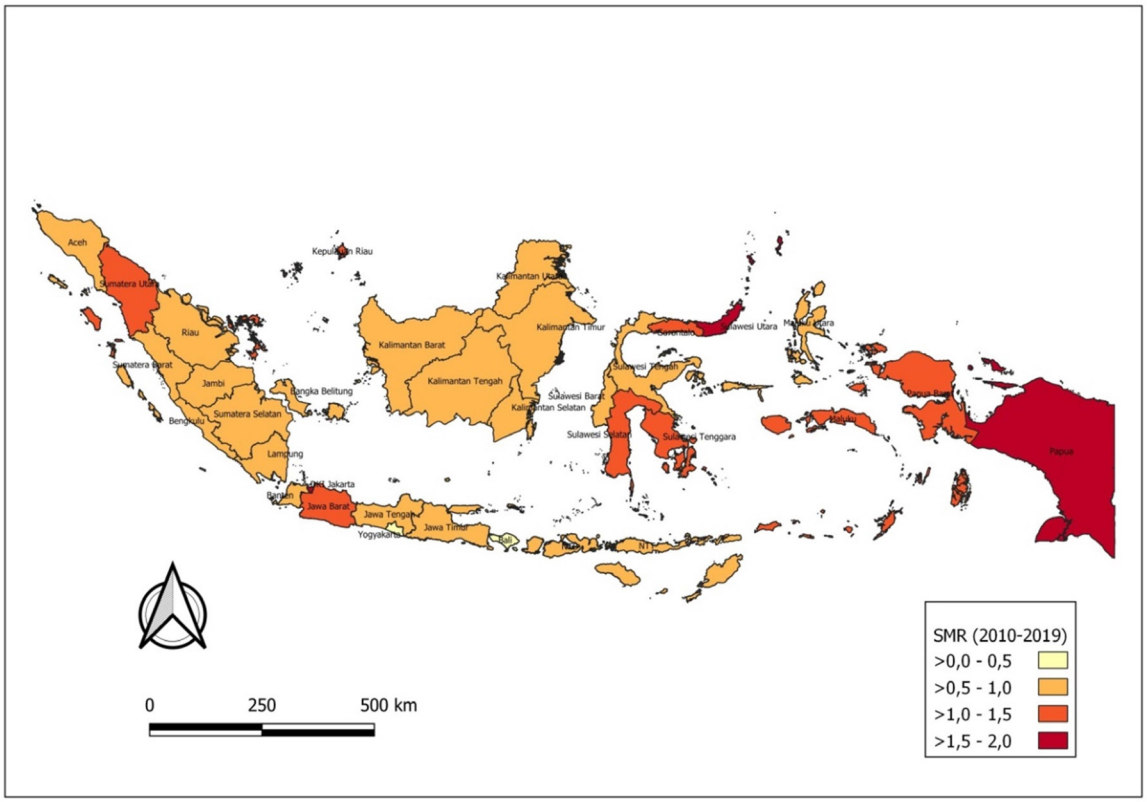

Figure 2. Distribution of SMR of TB in Indonesia, 2010-2019

DISCUSSIONS

This study shows that the risk of TB varies among Indonesia's 34 provinces during the 2010-2019 periods. It means there have been disparities in TB burden across the country, which can be related to aspects, such as health, environment, and socioeconomic.

Several factors can explain the differences in TB risk. Low socioeconomic groups have a greater risk of developing TB due to unhealthy housing environments, for example, overcrowding, lack of ventilation, and lack of safe cooking fuel facilities. They also tend to be malnourished and consume alcohol.[10] These groups include marginalized populations such as prisoners, who, while living in cramped cells, are also vulnerable to HIV coinfection and to the use of unsafe injecting needles for drugs.[10] Ethnic differences also correlate with TB risk, with indigenous groups or foreign-born immigrants having a higher risk.[10,11] This is related to socio-economic factors as well as genetic factors.[10,12,13] In addition, the health system can also play a role; for example, web-based reporting can increase TB notifications or delays in diagnosis or treatment will affect the TB infection rate at the household level.[10] In terms of the environment, climatic factors, such as air temperature, humidity, and duration of sunlight affect the incidence of TB in an area.[14,15]

The high number of excess TB cases in DKI Jakarta can be attributed to urban characteristics. Based on the 2013-2014 Tuberculosis Prevalence Survey, the prevalence of TB in urban areas was higher than that in rural areas. One possible explanation is the in-house density is higher in the cities rather than in the villages. It is also supported by the finding of a study by the Ministry of Health, which showed that more TB cases were found in residences with housing density less than 8m^2/person.[3] Another possibility is that case finding and reporting in DKI Jakarta were more intensive which lead to higher SMR. In this study, the cases reported in the province were almost twice as high as the cases anticipated by TB program coverage. This may support the notion that SMR can be utilized to compare the actual TB program's performances (observed cases) with the program's target (expected cases).

The higher risk of TB in Papua Province can be attributable to HIV coinfection. The province is one of the areas with the greatest number of cumulative

HIV cases until 2020.[16] Regions with a high burden of TB generally also have a high prevalence of HIV, especially among young men and women. At the individual level, the number of TB cases is quite high among HIV patients. Sociodemographic and clinical factors may influence TB risk in people with HIV in areas with a high TB prevalence.[17] Similarly, one study showed that HIV coinfection among TB patients was higher in Merauke General Local Hospital, Papua, than in other study areas in Indonesia.[18]

Bali and DIY were among the lower TB-risk provinces, and it may be linked to less intensive case finding and reporting. In that sense, the coverage of TB programs to diagnose cases in the population and notify them into the available TB surveillance system is less than what the program had targeted.

The disparity of TB burden has also been reported in global literatures. A research in China stated that TB incidence occurred more frequently in the northwestern and southern provinces[19], and spatiotemporal TB clusters appear in several provinces at different times.[20] Other studies also found that provinces located in central and eastern Iran had TB clusters with the highest rates in Khuzestan Province[21];and TB notification rates varied by geographic region in India.[22] These studies showed that disparities in TB risks within a country is not exclusive to Indonesia alone.

In disease mapping, SMR is useful to identify high risk areas. The Standardized Morbidity Ratio is a conventional method for estimating relative risk[8] and is calculated through an indirect standardization process. As a product of standardization, SMR is more appropriate for comparing health status between populations because the difference in the population structures (e.g. age groups and sex) has been controlled. It is different from using crude rates for comparison, which will lead to wrong conclusions when the populations being compared have different compositional characteristics. However, the SMR value is a hypothetical value, which means the ratio does not describe actual morbidity in a population and should not be used as a substitute for crude rates when assessing disease burden in that population. In addition, SMR cannot be used to compare among many populations and can only be used to compare each population with one standard.[9,23] Despite its easy application, SMR has not been widely used in the Indonesian literature, but already in literatures from other countries, for example Malaysia[8] and Ethiopia.[7] In the latter study, once the high and low risk areas were recognized with the SMR, the underlying factors were examined.

This study has several limitations. The use of routine data has the potential of underreporting because the incoming data only come from patients or people accessing health facilities, so that the estimated TB risk may not reflect the actual conditions in that area. In addition, this study has not explored the relations between several known TB risk factors, including indoor pollution, smoking behavior, diabetes, HIV, socioeconomic level, and climate.[10,14,15,24,25]

In conclusion, TB risk varied across Indonesian provinces during 2010-2019. Provinces with higher TB risk compared to the national risk were DKI Jakarta and Papua; while Bali and DI Yogyakarta were among the lower risk provinces. Given the underreporting nature of routine data, validation is required when using the finding of this study in the local-level intervention.

Acknowledgment

This article is part of the Study of Climate Change Impacts on Health in Indonesia, a collaborative work of Ministry of Health, UNICEF as the funding agency, WHO and SPEAK Indonesia; and was presented in The 4th Public Health International Conference-Fakultas Kesehatan Masyarakat Universitas Sumatera Utara 2021.

Author contribution

Main contributors: TP, AS. Conceptualization: TP, AS. Data curation: TP, AS, OSS, HL, IP, Sul, TTP. Formal analysis: AS, TP. Funding acquisition: AA. Methodology: TP, AS. Visualization: GV, Writing – original draft: TP, AS. Writing – review and editing: TP, AS, OSS, AA, HL, Sul, TPP, IP.

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The relationship of smoking duration, sleep disorders, and nutritional status of Indonesian adult men: data analysis of the 2014 Indonesian Family Life Survey

DOI: https://doi.org/10.22435/hsji.v12i2.5243

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Received: July 14, 2021; Revised: October 4, 2021; Accepted: December 7, 2021

Abstract

Background: In Indonesia, the prevalence of smoking is increasing from year to year and can cause various health problems, such as sleep disorders and affect a person's nutritional status. So, in this study, the relationship between smoking duration, sleep disturbances, and nutritional status in men aged 26–45 years will be investigated using secondary data from the 2014 Indonesia Family Live Survey (IFLS).

Methods: The 2014 secondary data from the fifth waves of the IFLS were used for analysis. All 5,379 data of men aged 26–45 years who provided anthropometric, smoking duration, and sleep disorders were included in the study. The Chi-Square test was used to examine the relationship between smoking duration, sleep disorders, and nutritional status in men aged 26 – 45 years. Furthermore, the Multinomial Logistics Regression test is carried out to determine the variables that have the strongest influence.

Results: Based on the results of statistical tests conducted, it was found that the majority of respondents had a smoking duration of 11-20 years, of which 27.2% of respondents did not experience sleep disorders and 25.4% had sleep disorders. The nutritional status of respondents with a smoking duration of 11-20 years is normal as many as 35% of respondents and at least 0.5% of respondents have underweight nutritional status with smoking duration <5 years. Furthermore, the test results of the relationship between smoking duration and sleep disturbances obtained p-value = 0.03 and the relationship between smoking duration and nutritional status obtained p-value <0.01.

Conclusion: Smoking duration was associated with sleep disorder and overweight nutritional status in men aged 26 – 45 years. ***(Health Science Journal of Indonesia 2021;12(2):111-6)***

Keywords: smoking duration, sleep disorder, nutritional status, tobacco use, sleeping sickness

Abstrak

Latar belakang: *Di Indonesia, prevalensi merokok semakin meningkat dari tahun ke tahun dan dapat menyebabkan berbagai permasalahan kesehatan, seperti gangguan tidur serta mempengaruhi status gizi seseorang. Sehingga pada penelitian ini akan diteliti hubungan antara durasi merokok, gangguan tidur, dan status gizi pada pria berusia 26–45 tahun menggunakan data sekunder dari Indonesia Family Live Survey (IFLS) tahun 2014.*

Metode: *Analisis dari data sekunder gelombang kelima IFLS tahun 2014. Semua 5.379 data pria berusia 26–45 tahun yang memiliki kelengkapan data antropometri, kebiasaan merokok, dan gangguan tidur diikutkan dalam penelitian. Uji Chi-Square digunakan untuk menguji hubungan antara durasi merokok, gangguan tidur, dan status gizi pada pria berusia 26 – 45 tahun. Selanjutnya uji Regresi Logistik Multinomial dilakukan untuk mengetahui variabel yang memiliki pengaruh paling kuat.*

Hasil: *Berdasarkan hasil dari uji statistik yang dilakukan, didapatkan bahwa mayoritas responden memiliki durasi merokok selama 11-20 tahun, dimana sebanyak 27.2% responden tidak mengalami gangguan tidur dan 25.4% mengalami gangguan tidur. Status gizi paling banyak yang dimiliki oleh responden dengan durasi merokok selama 11-20 tahun adalah normal sebanyak 35% responden dan yang paling sedikit sebanyak 0.5% responden memiliki status gizi underweight dengan durasi merokok <5 tahun. Selanjutnya hasil uji hubungan antara durasi merokok dengan gangguan tidur didapatkan nilai p-value=0.03 dan hubungan antara durasi merokok dengan status gizi didapatkan nilai p-value<0.01.*

Kesimpulan: *Durasi merokok berhubungan dengan gangguan tidur dan status gizi overweight pada laki-laki usia 26 – 45 tahun.* ***(Health Science Journal of Indonesia 2021;12(2):111-6)***

Kata kunci: *durasi merokok, gangguan tidur, status gizi, penggunaan tembakau, penyakit tidur*

Smoking habit is very dangerous for health because cigarettes contain many chemicals that are harmful to the body such as nicotine, tar, and carbon monoxide.[1,2] Smoking is a lifestyle that is considered attractive by the people of Indonesia. Indonesia is the country with the largest cigarette consumption in the world, which is the fourth after China, the United States and Russia. Smokers can be found in almost all age groups, but the majority are adults.[3] Based on World Health Organization, as many as 34.8% (59.9 million) of the adult population in Indonesia currently consume tobacco cigarettes. Based on the results of Riskesdas in 2007 and 2013 cigarette consumption continued to increase for the male population aged 15 years and over, namely in 2007 by 65.6% to 66% in 2013.[3] The prevalence of smokers in Indonesia in men is always higher than women. Smoking can also cause other effects for smokers themselves, one of which is sleep disorders.[4,5]

Sleep disorders are a person's inability to obtain adequate quality and quantity of sleep.[6] Sleep disturbances can be caused by several factors, such as stress, medication side effects, poor diet, and consumption of caffeine, nicotine, and alcohol. A person who experiences sleep disturbances for a long period of time, causing a continuous lack of sleep hours, will certainly experience health problems that can reduce mental health.[2] This sleep disorder will also cause disturbances in intellectual abilities, motivation, emotional instability, and depression. The physical effects given by the occurrence of sleep disturbances can be in the form of fatigue, muscle pain, exacerbating the condition of hypertension, blurred vision, and reduced concentration.[7] There are various forms of sleep disorders, namely insomnia, hypersomnia, parasomnia, narcolepsy, and delirium. Insomnia is a sleep disorder that affects the quantity and quality of a person's sleep.

Nutritional status is influenced by direct and indirect causes. Several direct causes include food intake and the presence or absence of infectious diseases, while indirect causes include household consumption patterns and availability, lifestyle, health services, environmental, socio-economic and political conditions. One of the causes that are quite serious is a bad lifestyle. An example of a lifestyle that indirectly affects nutritional status is smoking.[8,9] Previously, similar research was conducted by Anggraeny in 2019 and Roshifanni in 2016 but the research that had been carried out only had a small number of samples and only in certain groups. This cannot be used to describe the general condition, especially regarding smoking habits and their impact on Indonesia. Therefore, the use of secondary data from IFLS was chosen because secondary data has a larger number of respondents and respondents are also taken from 13 provinces in Indonesia. Other than that, the number of respondents in more secondary data is also useful for strengthening the evidence of this study. So this study was conducted to determine the relationship between smoking duration, sleep disorders, and overweight nutritional status in men aged 26-45 years from the fifth wave of the IFLS.

METHODS

This study is involving the analysis of secondary data from the fifth wave of the IFLS. The IFLS data set consists of anonymous data available for research under the guidelines of the Research and Development (RAND) Corporation. The population of this study was men aged 26-45 years. There were 50148 participants in total. Participants who provided personal data, sleep disorders, and smoking habits were further analyzed. We excluded participants who had incomplete data on the dataset obtained from interviews using the questionnaire, we only included participants who did not have missing data. After the criteria were applied, 5.379 participants were included in this study. The participant's smoking duration will be divided into 4 categories, namely <5 years, 5-10

years, 11-20 years, and >20 years. The body mass index (in kg/m²) was classified into 3 groups (<18.5 underweight, 18.5 – 25 normal, and >25 overweight). Enumerators performed anthropometric data. All data were obtained using a questionnaire that was asked and filled indirectly by the interviewer. The data were analyzed using the Statistical Program for Social Science (IBM SPSS) and STATA version 12. STATA 12 was used to clean the existing data in the dataset and combine several datasets to collect the variables to be studied according to the respondent's code so that there was no missing respondent data. Normality test using Kolmogorov-Smirnov to see the normality of the data. Data analysis consisted of univariate and bivariate analyses. Univariate analysis was carried out to present data descriptively with the distribution table of the characteristics of the subject while bivariate analysis to analyze the influence of the dependent variable used the Chi-Square test with a significance of <0.05. And will also be followed by a multivariate test using multinomial logistic regression. This research has been approved by the Health Research Ethics Commission, Faculty of Medicine, Airlangga University with letter number number 121/EC/KEPK/FKUA/2021.

RESULTS

The first test conducted in this study was to determine the distribution of the characteristics of the respondents in the study. Characteristics of respondents include age, sleep disturbances, smoking duration, and nutritional status. The following characteristics of respondents in the study are presented in Table 1.

Table 1. Characteristic of study participants

Variable	All (N= 5379)	
	Freq	**%**
Age (years)		
26-34	2641	48.9
35-45	2756	51.1
Sleeping Disorder		
No	2866	53.1
Yes	2531	46.9
Nutritional 5Status		
Underweight	599	11.1
Normal	3513	65.1
Overweight	1285	23.8
Smoking Duration (years)		
<5	254	4.7
5-10	1071	19.8
11-20	2828	52.4
>20	1244	23

Table 1 explained that in this study, the majority of participants were aged 35 – 45 years old, as many as 2756 (51.1%) and the remaining 2641 (48.9%) participants aged 25 – 35 years old. Based on the sleeping disorders, as many as 2531 (46.9%) participants have a sleeping disorder and as many as 2866 (53.1%) participants do not have a sleeping disorder. Furthermore, the nutritional status of participants in this study was as many as 599 (11.1%) were underweight, 3513 (65.1%) normal, and 1285 (23.8%) overweight. For the smoking duration, the majority of respondents had a smoking habit for 11-20 years as many as 2828 respondents, the second highest smoking duration is for >20 years with a total of 1244 respondents, 1071 respondents have a smoking duration of 5-10 years and 254 respondents <5 years have a smoking habit.

Table 2. The association between smoking duration, sleeping disorder, and nutritional status

Variable	Smoking Duration (years) n(%)				p-value
	<5	5-10	11-20	>20	
Sleeping disorder					
No	146(2.7)	559(10.4)	1463(27.2)	698(13)	0.03*
Yes	108(2)	512(9.5)	1365(25.4)	546(10.2)	
Nutritional Status					
Underweight	27(0.5)	148(2.8)	314(5.8)	110(2)	<0.01*
Normal	146(2.7)	674(12.5)	1882(35)	811(15.1)	
Overweight	81(1.5)	249(4.6)	632(11.8)	323(6)	

*The test was performed using the Chi-Square test with α=0.05

Table 3. The results of the multivariate test of the dependent variable with the independent variable

Variable	**Smoking Duration (years)**								
	5 – 10			11 – 20			>20		
	Sig	OR	95% CI	Sig	OR	95% CI	Sig	OR	95% CI
Sleeping Disorder									
No[a]									
Yes	0.139	1.232	0.935-1.625	0.08	1.262	0.973-1.636	0.668	1.062	0.808-1.395
Nutritional Status									
Underweight	0.478	1.176	0.752-1.840	0.603	0.893	0.582-1.369	0.179	0.731	0.463-1.155
Normal[a]									
Overweight	0.01	0.666	0.489-0.906	0.001	0.605	0.454-0.805	0.31	0.718	0.531-0.970

[a]Reference group

Table 2 showed that smoking duration associated with participants sleeping disorder and nutritional status. Sleeping disorder has p-value 0.03, which means that there was an effect of smoking duration on sleeping disorder. And also nutritional status has p-value <0.01 so that means smoking duration affect nutritional status.

The multivariate test was carried out with the aim of knowing which variables had the greatest influence. Based on the results in Table 3, it can be seen that the nutritional status variable is overweight that chooses a relationship with smoking duration. The duration of smoking associated with overweight nutritional status is 5 – 10 years and 11 – 20 years with p-value <0.01.

DISCUSSIONS

Overall, findings from this study indicate an association between smoking duration, sleep disorders, and nutritional status in men aged 26-45 years. The results of this study are in line with previous research that there is a relationship between smoking and sleep disorders.[2,4,6,10,11] Smoking was one of the triggers for sleep disorders. Cigarette consumption causes the release of noradrenaline and increased nerve activity. The release of noradrenaline also affects the synthesis of melatonin in the brain, so that sleep-wake regulation is disrupted. The nicotine in cigarette smoke stimulates the body to release adrenaline which causes an increase in heart rate and blood pressure.[12] But, sleep disorders can not only be caused by smoking, many other factors can be the cause. Sleeping disorder can be caused by several factors, namely extrinsic and intrinsic factors. Extrinsic factors can be in the form of an uneasy environment when going to sleep. While the intrinsic factors include pain, itching, certain diseases that make anxiety, anxiety, depression, stress, irritability and anger that are not channeled.[13] This sleep disorder will also cause disturbances in intellectual abilities, motivation, emotional instability, and depression. The physical effects given by the occurrence of sleep disorders can be in the form of fatigue, muscle pain, worsening hypertension conditions, blurred vision, and reduced concentration.[7]

Smoking can also affect appetite. The nicotine in cigarettes can have a suppressive effect on appetite, thereby reducing appetite and reducing food intake in smokers. A decrease in appetite can have an impact on the level of food consumption which causes the food intake needs of smokers to be insufficient.[14] Of course, if this happens for a long time, it will have an impact on nutritional status and health conditions, such as the emergence of malnutrition, diabetes, hypertension, and other non-communicable diseases. In addition, nicotine can also cause insulin resistance, fat accumulation, and can increase the hormone cortisol. Smoking has a negative relationship with weight gain but has a positive relationship with belly circumference in men. Smokers found a higher waist circumference ratio than non-smokers. This is due to the anti-estrogenic effect and the increase in the hormone cortisol due to the nicotine content in cigarettes.[15] Cigarettes also have a dual effect, namely smoking can increase energy expenditure and reduce appetite, and both of these effects will disappear when smokers stop smoking. The impact of smoking will indeed be felt or seen after 10 - 20 years after use. Based on the results in table 2, it was found that the duration of smoking was related to the nutritional status of the respondents with a p-value <0.01. The nicotine content in cigarettes will cause the release of neurotransmitters such as dopamine, norepinephrine, and serotonin which can suppress appetite.[14] This is in line with research conducted by Huriyati & Amareta in 2020 where the p-value was obtained 0.001 for the relationship between smoking and energy consumption levels.

As seen in Table 2, the majority of respondents have normal nutritional status with a smoking duration of 11-20 years. This is contrary to the results of previous research. This can be due to the IFLS data collection for smoking durations, only asked whether the respondent has a smoking duration regardless of the frequency and timing of the smoking duration. So, it does not rule out that respondents who have a smoking duration are not in the frequency of heavy smoking and have recently had this habit. Cigarettes also have a dose response effect, which means that the younger a person starts smoking, the more difficult it will be to quit smoking and the greater the effect because more toxins will accumulate in the body.[16,17]

This study had several strengths. One of the strengths of this study is the number of respondents involved 5.379 people, more than other studies. In addition, IFLS 5/2014 is the latest survey conducted by IFLS so that the data presented will be representative of the condition of society to date. However, some limitations were also observed. The use of secondary data causes limitations in terms of variables and completeness of data from each respondent. So that the selection of the variables under study adjusts to the data available in IFLS 5.

In conclusion, this study using secondary data analysis from the fifth wave of the (IFLS) showed that there was a relationship between smoking duration, sleep disorders, and overweight nutritional status in men aged 26-45 years.

Acknowledgment

This research is part of the Riset Kolaborasi Indonesia (RKI) in 2021 which was carried out with researchers from two leading universities in Indonesia, namely Universitas Hassanuddin, Makassar and Diponegoro University, Semarang. The authors are thankful to RAND Corporation for giving a permission to access the secondary data used in this study.

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Intake of kidney bean (*phaseolus vulgaris*) extract as postpartum blues management

DOI: https://doi.org/10.22435/hsji.v12i2.4938

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Received: May 24, 2021; Revised: November 23, 2021; Accepted: December 6, 2021

Abstract

Background: Postpartum blues is common in postpartum Mother with more prone to crying, more anxious, often unstable and more emotional than usual. Zinc supplementation is one of the methods needed for postpartum blues conditions. Kidney bean (Phaseolus vulgaris) extract has the highest zinc content. This study aimed to examine the effect of intake kidney bean extract (Phaseolus vulgaris) as a zinc source as management mother with Postpartum Blues

Methods: Quantitative study with an experimental study design (Quasi Experiment Design) with a Pre and Post-test Control Group Design. The instrument used to measure the mood of a mother after childbirth was EPDS (Edinburgh Post-Partum Depression Scale). The total sample was 68 mothers who experienced postpartum blues in Ngerandu Ponorogo primary health care. The Mann-Whitney was used to analyse and find out the difference in mood improvement before and after the intervention in the experimental group and the control group.

Results: The results showed that there was a statistically significant difference in mood levels of mothers with postpartum blues before and after intervention (p value of 0.001 (<0.005). This result indicated that intake of kidney bean (Phaseolus vulgaris) extract had an effect on the mood level of mothers with postpartum blue.

Conclusion: Intake of kidney bean (*phaseolus vulgaris*) extract on the incidence of postpartum blues possibly improvement mood in the experimental group after the treatment for 1 month. ***(Health Science Journal of Indonesia 2021;12(2):117-24)***

Keywords: kidney bean (phaseolus vulgaris) extract, postpartum blues, postpartum mother

Abstrak

Latar belakang: *Postpartum blues umum terjadi pada ibu postpartum dengan tanda sering menangis, khawatir yang berlebihan, emosional yang tidak stabil. Suplementasi zinc merupakan salah satu metode yang dibutuhkan untuk kondisi postpartum blues. Ektrak kacang merah (phaseolus vulgaris) memiliki sumber nutrisi zinc yang tinggi, Penelitian ini bertujuan untuk menguji efek konsumsi ekstrak kacang merah (Phaseolus vulgaris) sebagai sumber zinc sebagai manajemen ibu dengan postpartum blues*

Metode: *Penelitian kuantitatif dengan design Quasi Experiment pre dan post control grup. Instrumen pengukur mood ibu setelah melahirkan adalah EPDS (Edinburgh Post-Partum Depression Scale). Total Sampel 68 ibu yang mengalami postpartum blues di Puskesmas Ngerandu Ponorogo. Analisis statistik menggunakan Mann-Whitney untuk menemukan perbedaan perubahan mood ibu postpartum blues sebelum dan sesudah dilakukan intervensi pada grup intervensi dan kontrol.*

Hasil: *Hasil menunjukkan bahwa terdapat perbedaan signifikan tingkat mood ibu dengan postpartum blues sebelum dan sesudah dilakukan intervensi (p : 0,001 (<0,005). Hasil mengindikasikan bahwa konsumsi ekstrak kacang merah (phaseolus vulgaris) memiliki efek pada tingkat mood ibu yang sedang mengalami postpartum blues.*

Kesimpulan: *Konsumsi ekstrak kacang merah (phaseolus vulgaris) pada ibu postpartum blues memungkinkan untuk perubahan mood pada grup intervensi setelah diberikan treatment selama 1 bulan.* ***(Health Science Journal of Indonesia 2021;12(2):117-24)***

Kata kunci: *ekstrak kacang merah (phaseolus vulgaris), postpartum blues, ibu postpartum*

After going through the labor process, some women usually experience psychological changes. Psychological changes in the postpartum period consist of three forms, including postpartum blues, postpartum depression and postpartum psychosis. But in general, psychological problem often experienced is postpartum depression (PPD).[1] Women who experience postpartum blues are usually more prone to crying, more anxious, often unstable and more emotional than usual. Postpartum blues usually occur on days 3 to 5 after childbirth. According to Miller, the incidence of postpartum blues was not related to psychiatric history, environmental stress, cultural context, composition or parity. But these factors usually showed an effect when Postpartum Blues changed into depression.[2]

Globally the PPD prevalence is 35%, and in the United States it is around 21%. However, it is different from poor countries like South Africa wherein the prevalence is around 35%. PPD prevalence is 19% in Saudi Arabia, 11.2% in China and 27% in Japan.[3] Physiologically, the cause of postpartum blues consists of several factors. First, nutritional deficiencies and metabolic imbalances. Second, a decrease in hormone levels, namely progesterone and estrogen which occurs quickly after delivery. Third, there is an alteration in the hypothalamic-pituitary-edemocortical mechanism (HPA axis).[4] In Indonesia, many incidents of postpartum blues are not documented. Not much has been done by health care facilities so that the data obtained from the results of previous research by Mursidin, it was found that 53.3% reported the incidence of postpartum blues in an "M" Hospital that needed special support and education, so that it did not develop into postpartum depression. Partum blues has a negative impact on maternal health and the mother's treatment of her baby.[5]

Kidney bean (Phaseolus vulgaris) is a member of leguminosae, phase-oleae, subfamily Papilionoideae. Most often, beans are usually used as dryseeds include one most of them is Kidney bean (Phaseolus vulgaris). Nutrition of Kidney bean (Phaseolus vulgaris) is a good source protein, starch, fiber, vitamin and mineral. Kidney bean (Phaseolus vulgaris) have the highest mineral content compared to other beans. Kidney bean (Phaseolus vulgaris) has important sources of iron, zinc, copper, phosphorus, and aluminum and other minerals are also significantly found amounts in Kidney bean (Phaseolus vulgaris). The level of zinc range of 10,1 – 10,9 µg/g.[6] (Phytic acid is classified as an anti-nutritional substance because it forms complex bonds with iron or other minerals such as zinc, magnesium and calcium since kidney beans have high viscosity and low absorption properties. It is seen that the zinc content of food and starch made of kidney beans have a quite significant advantage because these are viscous components.[7]

One micronutrient that plays an important role in depression is zinc. Zinc acts as a micronutrient that plays an important role as a neuroreceptor and neurotransmission. Zinc has a direct and indirect effect on the balance of glutamatergic.[8] Zinc increases the constant dissociation of opioid receptors for naloxone. Zinc also affects the muscarinic acetylcholine receptors in the brain. These receptors are widely found in the cerebral cortex and hippocampus, where there is a high zinc concentration. Zinc is also needed in the formation of proteins needed for the formation of Gamma Aminobutyric Acid (GABA) and other neurotransmitters.[9] In humans, low zinc levels are associated with a person's mood disorders. This relationship seemed consistent at various ages, from young adult, adult, to old age.[10] Some studies showed a tentative relationship between zinc and mood regulation among infants and children.[11] Other studies showed that almost all pregnant women have a zinc deficiency. It can be indicated in the study conducted by Shah who found zinc levels among pregnant women.[12] Postpartum depression is often referred to as postpartum blues.[13] Women who experience it often experience fear and anxiety related to labor and their new role as a mother or parent.[14]

There was a relationship between low zinc levels and mood disorders. This relationship seemed consistent at various ages, from young adult, adult, to old age.[15] Some studies that examined the role of zinc showed that zinc played an important role in reducing stress in old age. Lower plasma zinc concentrations were associated with a number of lower psychological variables, such as cognitive status, mood and stress, especially in areas with low zinc intake, limited versions of foods high on zinc.[16] In addition to psychological variables, low concentrations of zinc plasma can be influenced by the increased zinc needs of nursing mothers but insufficient fulfillment and absorption in the body that is not perfect. According to previous research, it was found that socioeconomic has an influence on serum zinc levels in the body.[17] The results of the study stated that zinc levels in the body of someone who has a lower socioeconomic status compared to someone who has an upper middle socioeconomic level, because someone who has a low socio-economic level will consume more foods that are nutritionally unbalanced, such as foods that are rich in nutrients. carbohydrates, unsaturated fatty

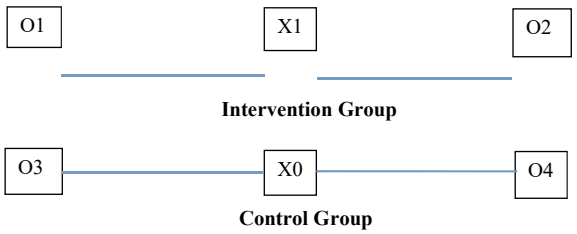
acid, because these foods have a low marketability value compared to other nutritious foods. Economic factors can influence zinc levels.[18] Formal education can be a nutrition-sensitive intervention that supports the improvement and impact of special nutritional action. Food intake is highly dependent on education level and the economic. In rural areas, low economy status or poverty occupies the first position in society that causes lack of nutrition. Educational factors and low economic status will influence each other in influencing nutritional intake.[19]

This study aimed to determine the effect of the intake of kidney bean *(Phaseolus vulgaris*) extract as a zinc source as management postpartum blues. The results of this study are expected to provide information regarding the management of postpartum women who experience postpartum blues with a used herbal extract which is rich in zinc and minimal side effects and alternative herbal interventions related to postpartum blues.

METHODS

Study Design

This was a quantitative study with an experimental study design (quasi experiment design) with a Pre and Post-test Control Group Design. Pre-test was conducted in the intervention group (O1) and followed by treatment (X1), and a post-test was conducted in the intervention group after a period of time (O2). Pre-test was also conducted in the control group (O3) without treatment (X0) and followed by a post-test in the control group (O4).[20]



Respondents

The sample of this study was 68 mothers who experienced postpartum blues in the work area of Ngrandu Ponorogo Community Health Center. Respondents were divided in two group the intervention group and control group with 34 respondents in each group. The method of sampling used here was non random sampling according to the established inclusion and exclusion criteria. The inclusion criteria for this study were the postpartum mothers, mothers who experienced the postpartum blues and the exclusion criteria was mothers who have confirm Schizophrenia disease.

Instrument

The instrument used in this study was EPDS (Edinburgh Post-Partum Depression Scale). EPDS (Edinburgh Post-Partum Depression Scale) is a measuring tool to assess the mood of a woman after childbirth. The instrument consists of 10 measurement items. EPDS (Edinburgh Post-Partum Depression Scale) is assessed by a score with a maximum score of 30. A score of 10 or more indicates possible depression.[21] EPDS (Edinburgh Post-Partum Depression Scale) has been validated and used widely. Has a level of reliability from moderate up to height also has a good correlation with measuring instruments other than depression. Intake of nutrients especially micronutrients assessed with questionnaire semi-quantitative food frequency. An instrument for characteristic respondent uses general questionnaire.

Intervention

All postpartum mother was assessed their characteristic (age, education, parity, employment, family income, husband support, and family smoking status) with a questionnaire and then the respondent was determined with assessed all postpartum women with instrument EPDS (Edinburgh Post-Partum Depression Scale). Respondents consisted of two groups. The first group is the intervention group consisting of 34 postpartum mothers with postpartum blues and the second group is the control group which consists of 34 postpartum mothers with postpartum blues. The intervention group was given kidney bean extract (*phaseolus vulgaris*) as a source of zinc 1000 mg. Respondent was given 120 capsules, which was taken 3 times a day (morning, afternoon, evening). Take a capsule with water, 1-2 hours after eating and don't take foods or drinks that contain high calcium and phosphorus because it can inhibit the absorption of zinc. The control group were given a placebo. Respondent was given 120 capsules, which was taken 3 times a day (morning, afternoon, evening). Before the intervention, mothers with postpartum blues in both groups were measured first of micronutrient content especially zinc with

questionnaire semi-quantitative food frequency. The Intervention was carried out for 1 month in both groups. After that both groups were measured back the scale of mood mother with postpartum blues using instrument EPDS (Edinburgh Post-Partum Depression Scale) and zinc level with questionnaire semi-quantitative food frequency. To find out the respondent's compliance, the researcher called and gave the respondent a control sheet regarding the research. In addition, researchers also work with guardians so that they are always reminded when they are taking medicine.

Data Collection

After the data was collected, before being processed the data is edited first by researchers to avoid mistakes or doubts in order to get quality data. In this study, researchers examined the completeness of the questionnaire, the clarity of writing answers, relevance, and consistency with the questions. After the researcher checks the filling of the questionnaire, the incomplete, unclear, irrelevant or inconsistent questionnaire with the questions will be clarified to the respondent. The goal is to make it easier for researchers to analyze data.

The coding process was provided a code on the respondent's questionnaire sheet to facilitate data analysis and processing. At this stage the researcher gave code A followed by the serial number of the respondent (A1,2,3, ...) for the intervention group, and code B followed by the serial number of the respondent (B1,2,3 ...) for the control group. The researcher then changed the data in the form of letters into numeric data in the form of scores of respondents' answers based on the provisions set by the researcher to facilitate analysis and speed up data entry.

Scoring is done by giving a value to the data according to a predetermined score based on the measuring instrument made then giving the total score of all the answers. The score on the data in this study is 1-10 according to the anxiety scale observation sheet.

At this stage the researcher processes the data by entering data from each respondent into a computer program. The data is entered according to the respondent's number on the questionnaire and the number on the observation sheet and the respondent's answer, then it is entered into a computer program in numerical form according to the answer score that has been determined when coding. This cleaning stage aims to provide data from possible data that do not meet the requirements or are missing with the help of software. Researchers recheck the data that has been entered. After confirming there are no errors, the next stage is carried out, namely data analysis according to the type of data.

Data analysis

The normality data were analyzed using the Shapiro-Wilk test, characteristic respondent analysis with descriptive analysis, and Food Frequent with AKG. The effect treatment kidney bean on postpartum blues was analyzed by independent t-test for data that were normally distributed and would be tested with the Mann-Whitney test if the data were not normally distributed.[22]

Ethical Clearance

This Research passed an ethical clearance from the KEPK Poltekkes Kemenkes Semarang with number 060/EA/KEPK/2020.

RESULTS

The general respondent characteristics such as age, education, parity, employment, family income, husband support, smoker's family of the respondent are presented in Table 1. Most respondents had at risk age, low education level, parities, unemployment status, family income below upah minimum regional UMR, came from smoker's family in the intervention group. On these results, it shows that from each of the respondents both from the intervention group and the control group there is no significant difference from age, education, parity, employment, family income, husband support, smoker's family.

The dietary pattern consumption among respondents with the incidence of postpartum blues can be seen in Table 2. Result of dietary pattern consumption respondent before intervention in zinc, iron, cooper, folate, calcium, Vitamin $B_{6,}$ and Vitamin B_{12} are shown that the nutritional intake below RDA (Recommended Dietary Allowances). After intervention for 1 month, component of zinc, iron, copper, folate increased in both groups, but still below RDA (Recommended Dietary Allowances) except zinc, and iron content. According to RDA (Recommended Dietary Allowances) Normal zinc and iron level is 10 mg and 26 mg. In this result mean zinc level before intervention is 9,1 mg and after intervention 11,6 mg and mean of iron level before intervention is 20,9 mg and after the intervention is 26,0 mg.

Table 1. General characteristics of respondents based on psychological factor, postpartum blues incidence and zinc levels

Characteristic	Experiment Group		Control Group	
	n	%	n	%
Age				
At risk	22	64.7	20	58.8
No Risk	12	35.3	14	41.2
Education				
Low	26	76.4	24	70.5
High	8	23.6	10	29.5
Parity				
Primipara	20	58,8	16	47,0
Multipara	14	41,2	18	53,0
Employment				
Employed	10	29.5	14	41.2
Unemployed	24	70.5	20	58.8
Family Income				
Below Regional Min. Wage	25	73.5	21	61.8
Comply with Regional Min. Wage	9	26.5	13	38.2
Husband Support				
Yew	27	79.4	27	79.4
No	7	20.6	7	20.6
Family smoking status				
Smoker	20	58.8	21	70.5
Nonsmoker	14	41.2	13	38.2

Source: Primary Data of 2020

Table 2. Dietary pattern consumption among respondents with incidence of postpartum blues

Dietary Pattern	Before Intervention				After Intervention			
	Intervention Group		Control Group		Intervention Group		Control Group	
	Min	Max	Min	Max	Min	Max	Min	Max
Zinc (mg)	7,9	10,3	**7,2**	11,6	10,8	12,4	8,2	10,8
Iron (mg)	16,5	27,4	12,9	20,6	22,4	29,7	11,2	23,9
Copper (mg)	0,6	1,9	0,9	1,8	1,2	2,1	0,5	1,5
Folate (µg)	104,2	210,3	110,4	220,9	135,7	248,9	127,6	217,8
Calsium (mg)	700,5	900,6	864,9	1001,3	578,8	957,9	678,9	895,4
Vitamin B_6 (mg)	0,6	1,0	1,2	1,5	0,4	1,4	0,9	1,3
Vitamin B_{12} (mcg)	1,3	2,0	0,7	1,3	1,2	1,8	0,8	1,0

Source: Primary Data of 2020

Paired T test pre and posttest in the intervention group can be seen in Table 3. The result showed that average pretest intervention in intervention group value was 6.4 and average posttest after intervention was 5.9. P value in this test was 0,001 ($p<0,05$), which means can be concluded that significantly on the score of EPDS (Edinburgh Post-Partum Depression Scale) tools before and after intervention, this means there is a change in EPDS score before intervention and after intervention in intervention group. The average pretest in control group value was 3.8 and the average posttest after being given a placebo was 4.4. P value in this test was 0,062 ($p>0,05$), which means can be concluded that no significant change in the score means of EPDS (Edinburgh Post-Partum Depression Scale) tools before and after being given a placebo in control group.

Table 3. Paired T test pre and post test in the intervention and control group

Intervention Group	Mean	p
Pretest Intervention Group	6.4	
Posttest Intervention Group	5.9	0,001
Control Group		
Pretest Control Group	3.8	0,062
Posttest Control Group	4.4	

Effect of the intake of kidney bean (*phaseolus vulgaris*) extract as a zinc source as management postpartum blues can be seen in Table 4. On equal variance assumed obtained t value is 5.476 and significance level p = 0.03. These significant results indicate p < 0.05, which means that there were differences in score of EPDS (Edinburgh Post-Partum Depression Scale) in intervention group and control group. This result can be said that score of EPDS (Edinburgh Post-Partum Depression Scale) were fundamentally different between intake of kidney bean (*phaseolus vulgaris*) extract group than the placebo group.

Tabel 4. Independent samples test

	F	Levene's Test of Equality of Variences	t-test for Equality of Means			
		Sig	t	df	Sig. (2-tailed)	
Skor EPDS	Equal Variances assumed	.932	.104	5.476	82	0,03
	Equal variances not assumed			7.875	86.432	0,03

DISCUSSIONS

In this study, there was an effect of intake of red bean extract (*phaseolus vulgaris*) as a source of zinc for the management of postpartum blues. The EPDS score in Table 4 shows that there is a significant effect of p=0.03. Postpartum blues is common in postpartum mothers with more prone to crying, more anxious, often unstable and more emotional than usual.[23] Supplementation is one of the methods needed for postpartum blues condition. Kidney bean (*phaseolus vulgaris*) extract has the highest zinc content. This study examines the effect of intake kidney bean extract as a zinc source as a management mother with postpartum blues.

The use of antidepressants and depression is bad for fetal growth and development. Depression in mothers is associated with preterm birth, low birth weight, impaired fetal growth as well as cognitive complications and emotional post-birth.[24] Antidepressant exposure is associated with preterm birth, reduced birth weight, pulmonary hypertension persistent and a visible postnatal adaptation syndrome correlated with autism syndrome. Paroxetine is related to heart formation disorders. According to previous research by Mubarak, nutritional Composition and Antinutritional Factors of Mung Bean Seeds (*phaseolus vulgaris*), stated that in Phaseolus aureus there is a zinc content of 1.40 mg of zinc in every 1 kidney bean seed (*phaseolus vulgaris*) extract.[25]

A study conducted in France on mothers postpartum on day 3 after delivery found that there were 30% of mothers who had an EPDS score of 9 and 19% had score 11.[21] Studies conducted in Italy found that about 15.7% of women on day 2 of delivery reported an EPDS score of more than 9. EPDS factors analyzed on day 2 indicated that there are 3 aspects that stand out, namely depression, anxiety and anhedonia.[2]

A phenomenon can be categorized as a problem in public health if the prevalence is more than 20% of the population.[2] Meanwhile in Indonesia, many postpartum blues incidents are not documented. Not much has been done by health care facilities, so from the data obtained from the results of previous research by Mursidin in 2017 it was found that 53.3% reported the incidence of postpartum. Incidence of postpartum blues need special support and education, so it does not develop into postpartum depression. Partum blues have a negative impact on the health of the mother and the mother's treatment of her baby.[5] The problem of zinc deficiency should be a common concern considering its important role in supporting one's health. Moreover, the prevalence of zinc deficiency is very high. This study as well as previous studies show that zinc levels in pregnant and lactating women are very low. However, the issue of zinc deficiency has not been discussed in detail especially as a public health nutrition problem. Which become Health nutrition problem is Lack of Protein/Less Energy Chronic Energy, Iron deficiency anemia, Vitamin A deficiency, Disorders Due to iodine deficiency, and obesity. With great view a zinc

deficiency problem, hence hypozinkemia should be candidates for public health nutrition problems. In line with that study taking extracts (Phaseolus vulgaris) as a source of zinc was effective against the incidence of postpartum blues compared to a control group given a placebo.

In this study, there was an effect of intake of red bean extract (*phaseolus vulgaris*) as a source of zinc for the management of postpartum blues. The EPDS score in table 4 shows that there is a significant effect of 0.03. Previous research about supplementation of iron, zinc, and magnesium on mothers with postpartum depression showed that giving it to mothers with postpartum depression can be an alternative treatment for postpartum depression patients.[2] Several studies have shown that zinc sources are involved in the pathophysiology and therapy of depression. Another study showed that only after successful antidepressant therapy, the lower blood concentration of zinc was normalized in a depressed patients.[16] Studies before conducted to assess work zinc as an antidepressant against mild stress Chronic / Chronic Mild Stress (CMS) and levels Brain-Derived Neurotrophic Factor (BDNF) protein as well as BDNF mRNA shows that zinc hydro aspartate (10 mg / kg BW) has an effective antidepressant that is very fast on CMS. Such zinc therapy has an effect after intervention a week. In long-term therapy, zinc was found to increase BDNF levels amounted to 17-39 percent in the mRNA level and hippocampal protein. That finding showed zinc acts as an antidepressant works very fast in dealing with CMS and increases BDNF.[29]

There was a Cohort study conducted on 66 mothers. They give the supplementation zinc and tested to the subjects in 3 different periods ie: a month before delivery, three days, and thirty days after delivery. The results showed that level of zinc is associated with symptoms of severe depression in mothers with postpartum blues. The relationship between zinc and DPP is suspected, related to each other through glutamate hyperactivity. Glutamate is an excitation neurotransmitter major in the central nervous system and binds with a variety of ionotropic and metabotropic receptors.[30]

With this study, it can be seen that consuming foods that contain higher zinc, such as kidney beans, which are easy to obtain and consume, can help reduce the incidence of postpartum blues. The limitations of this study, the respondent's food intake was only measured from a semi-quantitative meal frequency questionnaire so that it could not be strictly controlled for the intake of food. Although they have been informed not to consume foods or drinks that contain high calcium and phosphorus because they can inhibit the absorption of zinc, there are some respondents who unknowingly have consumed them even if only once.

In conclusion, this study showed a result that there was an effect of kidney bean (*phaseolus vulgaris*) extract on the decreasing incidence of postpartum blues. Effect of the intake of kidney bean (*phaseolus vulgaris*) extract as a zinc source as management postpartum blues can be seen. There was an improvement in the mood of women with postpartum blues in the experimental group after the treatment of the administration of kidney bean (*phaseolus vulgaris*) extract tablets for 1 month. Meanwhile, women with postpartum blues who were given placebo tablets showed a similar mood and there was no change in it so that they still felt anxiety.

It is recommended for mothers who experience postpartum blues to always eat foods that contain higher zinc, such as nuts. The results of this study can be used as a reference for further research literature.

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