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Correlation Between The Knowledge On Health Effects Of Smoking And Motivation On Smoking Cessation In Ex-Smokers Of Lung Department Patients, Siloam General Hospital, Lippo Village.

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Abstract

Introduction: Data from WHO showed that deaths caused by tobacco reaches approximately ± 6 million deaths annually. There are many information about the danger of smoking which spreading from various sources. The level of knowledge about the danger of smoking can be associated with motivation to stop smoking. Therefore, motivation toward smoking cessation arises if someone knows the benefits that can be taken, through an adequate knowledge.

Aim: To determine the relationship between the level of knowledge on the health effects of smoking with motivation to stop smoking in ex-smokers of lung department patients at Siloam General Hospital, Lippo Village.

Methodology: This is a cross-sectional study, analyzing 138 ex-smokers of Siloam General Hospital's lung department patients using consecutive sampling techniques.

Results: the results showed 73.2% of people have good knowledge about the danger of smoking and 26.8% are not. Then, 58% of people have high motivation to stop smoking and 42% have low motivation. The results of statistical test using Chi Square showed a significant relationship between the level of knowledge and the motivation to quit smoking (OR = 4.293 [95% CI: 1,921-9,594], *P*<.001). The results of the multivariate logistic regression test showed educational factors (*P*=0.014), and the frequency of smoking (*P*=0.007) also influence the motivation to stop smoking.

Conclusion : There's a significant relation between knowledge about the danger of smoking and the motivation to quit smoking.

Introduction

Tobacco use is a significant global problem and a major cause of a preventable fatal deaths. Smoking is the main form of tobacco use and has been accepted by the majority of Indonesians as a habit. According to World Health Organization (WHO) data, nearly 6 million deaths annually caused by tobacco. This number is expected to increase even more than 8 million deaths by 2030.[1] The incline in smoking prevalence is seen to be greater at a young age than in adult age.

Appeals regarding the danger of smoking that have been carried out by various aspects such as in advertisements, warning labels on the cigarette packages, increased cigarette costs, counseling about smoking-free and many more, but still it's underestimated and ignored by Indonesian smokers. Therefore, the prevalence of smoking in Indonesia is still very high.

Indonesia ranks at number three as a country with the largest cigarette consumption in the world after China and India. West Java's the highest in Indonesia (32.7%). While the lowest smoking prevalence goes to Papua's Province (21.9%).[1] There are 13 provinces out of 33 provinces which have a smoking prevalence higher than the national average. Globally, the impact of smoking accounts for 22% of all cardiovascular diseases and is also associated with hypertension and cerebrovascular disease. Between 56%-80% of all chronic respiratory diseases (including chronic bronchitis and emphysema) are caused by smoking. It is estimated that tobacco-related deaths

account for 10% or around 200,000 per year of total deaths in Indonesia. WHO estimates that most of deaths in Indonesia (61%) are caused by non-communicable diseases[2], and three conditions are included as causes of death due to non-communicable diseases are cardiovascular disease, malignant neoplasms, and chronic obstructive pulmonary disease. Smoking is claimed to be the cause of 90% of lung cancer in men and around 70% in women in Indonesia. Smoking often assumed to be a symbol of masculinity and courage. Judging from several studies related to the knowledge about danger of smoking, a person can be motivated to stop smoking by a high level of knowledge because it's one of the intrinsic factors that builds up a motivation.

Knowledge makes someone to have reason and foundation to make a choice, such as for being motivated. Lack of knowledge and motivation leads to inappropriate behavior because there is no basis for positive values from the knowledge they get. Someone's behavior and actions will be better if it's based on knowledge and motivation. The higher one's knowledge will contribute to the next behavior which will ultimately give an impact. Knowledge is also closely related to education, where it is expected that with higher education, a person will have broader level of knowledge. However, it needs to be emphasized, it does not mean that someone with low education has an absolute lower knowledge.[3]

Knowledge about smoking is the first step for smokers to be motivated on smoking cessation, if the knowledge in providing motivation is not good enough, it would makes that person not being able to stop smoking.[3]

Objective

Determining the relationship between the level of knowledge on the health effects of smoking with motivation to stop smoking in ex-smokers of lung department at Siloam General Hospital, Lippo Village.

Methodology

Design

The research is a categorical analytic with cross-sectional study design.

Sample

The samples are ex-smokers from lung department patients, Siloam General Hospital, Lippo Village that fulfill the inclusion criteria, which is a 15-64 years old patients. They agreed to participate in this research by signing an informed consent. The independent variable in this research was knowledge about smoking, and the dependent variable was motivation on smoking cessation. The other independent variables that are associated with the dependent variable were education and smoking frequency

Data Collection Method

This research data were collected using consecutive sampling method. Knowledge of smoking from each sample are assessed by International Tobacco Control's questionnaire containing 13 questions[4], while the motivation on smoking cessation containing 11 questions are assessed using ATC Center for Tobacco Treatment, Education, and Research Questionnaire (*Tobacco Use Context Section E number 11 and Tobacco Quitting History Section F*)[5]. The ways of working and data collection technique include :

1. Lung department patients in Siloam General Hospital (aged 15-64 y.o)
2. Samples taken by consecutive sampling
3. Fulfilled inclusion criteria
4. Informed Consent
5. Fulfilled questionnaire of knowledge about the danger of smoking (ITC) and the motivation on smoking cessation (ATC Center for Tobacco Treatment, Education, and Research).
6. Checking the completeness of the questionnaire.
7. Analysing data and result interpretation

Data Analysis

Data obtained were processed and analyzed using *Statistical Program for Social Science* (SPSS) 22.0

Result and Discussion

Samples included in this research were part of research target population. A total sample of 138 people were included in data processing. Data on age, sex, education, job, economics, knowledge about the danger of smoking, and motivation to stop smoking were recorded and shown in the

demographic of samples table (Table 1). This research obtained 97.1% men and only 2.9% of women, having an average age at 47 years.

The youngest was 18 years and the oldest was 64 years old. In this research, knowledge about the danger of smoking from each sample was assessed using a questionnaire consisting of 13 questions related to smoking (Table 2). Furthermore, the results of the questionnaire, the sample would be categorized as having a good level of knowledge if the results shown were ≥10, while it's categorized as having a level of poor knowledge if <10.

Table 1. Demographic characteristics of respondents

Characteristics (n=138)	Frequency	Percentage (%)
Age		
15-25 y.o	5	3.6
26-45 y.o	51	37
46-54 y.o	82	59.4
Sex		
Man	134	97.1
Woman	4	2.9
Age (start smoking)		
< 21 y.o	105	76.1
>21 y.o	33	23.9
Reasons to smoke		
Parents/ siblings	15	10.9
Friends	120	86.9
Mass media	3	2.2
Social media	0	0
Number of cigarettes consumed		
≥21 /day	44	31,9
<21 /day	94	68.1
Economics		
High (> UMK)	115	83.3
Low (< UMK)	23	16.7
Education		
College ✓	37	26.8
College ✗	101	73.2
Smoking time		
Several times/ day	9	6.5
Several times/ week	89	64.5
Every time with friends	40	29
Knowledge about smoking		
Good	101	73.2
Poor	37	26.8
Motivation on smoking cessation		
High	80	58
Low	58	42

After analyzing the knowledge survey data, it was found that more samples had good knowledge (73.2%) compared to poor knowledge (26.8%). The smallest value of knowledge about smoking was 6 and the greatest was 13 (100%). After processing the data, it showed that there were more samples who began smoking because of their friends' influence. For the education data, more samples showed that they do not attend college (26.8%) rather than the ones do (73.2%). From which the classification of smokers are categorized as a heavy smoker and a non-heavy smokers, this research have more a non-heavy smokers (68.1%) rather than the heavy ones (31.9%).

Table 2. Description of Smoking Knowledge Questionnaire

NO	QUESTIONS	RIGHT N (%)	WRONG N (%)
1.	Carbon Monoxide (CO) is a chemical included in cigarette smoke	104 (75.4)	34 (24.6)
2.	Nicotine is a chemical included in cigarette smoke	135 (97.8)	3 (2.2)
3.	Tar is a chemical substance in cigarette smoke that causes most of lung cancer	113 (81.9)	25 (18.1)
4.	Nicotine is the main substance in tobacco that makes people addicted to smoke	133 (96.4)	5 (3.6)
5.	Smoking cause stroke on smokers	128 (92.8)	10 (7.2)
6.	Smoking cause impotence on male smokers.	121 (87.7)	17 (12.3)
7.	Smoking cause vascular diseases on smokers.	126 (91.3)	12 (8.7)
8.	Smoking cause bladder cancer on smokers.	115 (83.3)	23 (16.7)
9.	Smoking can increases mouth and throat cancer on smokers.	119 (86.2)	19 (13.8)
10.	Smoking cause heart attack on smokers and second-hand smokers	136 (98.6)	2 (1.4)
11.	Smoking cause lung diseases in smokers (such as emphysema and bronchitis)	120 (87)	18 (13)
12.	Smoking can increases the risk of blindness on smokers	98 (71)	40 (29)
13.	A mother who smokes during pregnancy cause serious harm to the baby (such as premature)	121 (87.7)	17 (12.3)

The result of the questionnaire above shown in table 2 showed that the disease that seems to be very familiar to the patients is the one that says “smoking can cause a heart attack”, because 98.6% of all samples can correctly answer the question, and the second highest correct answer was the question that asks about nicotine in cigarettes smoke and the addictive ability (only 2.2%-3.6% of all people that don’t answer this correctly). The most wrong question is the one that says “smoking can increase the risk of blindness”. Most of the samples didn’t know that smoking can affect their eyes. For the motivation on smoking cessation, assessed by using ATC Center for Tobacco Treatment, Education, and Research Questionnaire consisting of 11 questions about the motivation to stop smoking.

From this research, it was found that most people tend to quit tobacco because they had a diseases. 58% of the samples showed a high motivation to quit tobacco (score ≥7), mostly by using “cutting down” technique, where they reduce the cigarettes they consume slowly. For the 42% of people that do not have a high motivation on smoking cessation, they have a

motivation score <7.

Statistical Analysis

Tabulation result shown in table 3 showed that 101 of 138 respondents had good knowledge about the danger of smoking , with 68 (67.3%) of them having a high motivation to stop smoking and 33 (32.7%) others had a low motivation. About 37 samples that had poor knowledge, 12 (32.4%) of them had a high motivation and 25 (67.6%) samples had low motivation. Data analysis Chi-Square showed p value = 0,000 supported by Odd and 95% CI = 1.921-9.594; which stated that there was a significant relation between knowledge about the danger of smoking and the motivation to stop.

Table 3. The Relation Between Knowledge about The Danger of Smoking and Motivation on Smoking Cessation

Variabel	Motivation to stop smoking		Total	*P* value	Odd Ratio	95% CI
	High	Low				
Knowledge about The danger of smoking						
Good	68 (67.3%)	33 (32.7%)	101	0.000	4.293	1.921-9.594
Poor	12 (32.4%)	25 (67.6%)	37			

Table 4. Chi-Square Analysis between the correlation of motivation on smoking cessation and variable

Variable	Motivation to stop smoking		Total	*P* value	Odd Ratio	95% CI
	High	Low				
Age				0.735	0.835	0.420-1.660
15-45	31 (55.4%)	25 (44.6%)	56			
46-64	49 (59.8%)	33 (40.2%)	82			
Sex				0.400	4.309	0.437-42.518
Man	79 (59%)	55 (41%)	134			
Woman	1 (25%)	3 (75%)	4			
Education				0.018	2.691	1.239-5.846
College ✓	33 (73.3%)	12 (26.7%)	45			
College ✗	47 (50.5%)	46 (49.5%)	93			
Age (start smoking)						
< 21	59 (56.2%)	46 (43.8%)	105	0.580		
					0.733	0.327-1.643
≥ 21	21 (63.6%)	12 (36.4%)	33			
Smoking Frequency					0.357	0.171-0.747
<21 (Non- Heavy smokers)	62 (66%)	32 (34%)	94			
				0.010		
≥ 21(Heavy smokers)	18 (41%)	26 (59%)	44			
Economics				0.700	1.326	0.540-3.258
>Minimum wage	68 (59%)	47 (41%)	115			
<Minimum wage	12 (52%)	11 (48%)	23			

For multivariate analysis that consists of 6 factors; education, economics, smoking frequency, age at starting smoking, sex, and age, there's only 2 factors that showed a significancy with the dependent variable (motivation to stop smoking), which are education and smoking frequency. It was found that education has a significancy with P = .014 and for smoking frequency; P =.007, shown in table 5, with a probability:

$$P(X) = \frac{1}{e^{-(1.711-(0.998x education)-(1.036x smoking frequency)}}$$

Table 5. Final Result of Multivariate Logistic Regression Analysis

Variables in the Equation

		B	S.E.	Wald	dF	Sig.	Exp(B)	95% C.I. for Lower	Upper
Step 1[a]	education	-.998	.407	6.010	1	.014	.369	.166	.819
	smoking frequency	-1.036	.386	7.204	1	.007	.355	.166	.756
	Constant	1.711	.684	6.252	1	5.535			

Discussion

Based on demographic characteristics of the respondents in table 1, it shows that samples in this research are mostly men 134 (97.1%), while women are only 2.9%. The samples which is an ex-smokers who are a lung department patients in Siloam General Hospital, Lippo Village are mostly 47 years old or so, range in age from 18-64 years old. Table 1 shows that 80 samples were highly motivated to stop smoking, which 68 of them had good knowledge about smoking (said to be good if ≥ 10 questions were correct), and the remaining 12 people had poor knowledge (if <10 questions were correct).4 It also showed from 58 samples with low smoking cessation motivation, 33 of them have a good knowledge and 25 of them have bad knowledge. Chi Square test results obtained P<.001 and Odd Ratio 4.293 with 95% CI 1.921-9.594 which can be interpreted that there is a significant correlation between knowledge about the danger of smoking with one's motivation to stop smoking. 95% Confidence Interval (1.921-9.594), which means that the confidence interval does not contain value = 1, so it shows the relationship between knowledge about smoking with smoking cessation motivation at a significance level of 5%.

In accordance with the results of the knowledge questionnaire regarding the danger of smoking in Table 2, it is found that 29% of the samples are wrong in answering questions about smoking can increases risk of blindness on smokers. Tobacco smoking is the prime modifiable risk factor for age related macular degeneration. Evidence indicates that more than a quarter of all cases of age related macular degeneration with blindness or visual impairment are attributable to current or past exposure to smoking.[6] But, there's still many samples who don't know about this information.

As a matter of fact, some of the respondents' knowledge, are somehow still low regarding the danger of smoking, eventhough there are many information spread from tv, newspaper, pictorial health warning, to counselling. This research proved that eventhough those are important but environmental are also really important in influencing someone's motivation to stop smoking such as their family and friends.[7]

This study's result is parallel with the result of International Tobacco Control Four Country Survey' study conducted on 9058 active smokers, aged > 18 years, who consumed at least 100 cigarettes and still smoked in the past 1 month, the results showed that knowledge is closely related to the intention of the smokers to stop smoking with P =0.001. However, it is also said that one's knowledge about the danger of smoking, cannot or is not enough to be the only trigger for someone to stop smoking.[8]

Data analysis for this research uses Chi Square because the research is categorized as an unpaired comparative analytic. So it

cannot be analyze with other tests such as T-Test or Man-Whitney test.

In this study, the results of the Chi Square test for the correlation between the knowledge on health effects of smoking and motivation on smoking cessation in ex smokers of lung department patients, aged 15-64 years who have high and low motivation to stop smoking in Siloam General Hospital can be seen in table 3.

Usually, people who are addicted to cigarettes said that it is very difficult to let go and not consume cigarettes daily. In this study, respondents told that the reasons that smoking is a difficult thing to let go are because smoking gives benefits such as to relieve stress, distract mind, and replace hunger. However, there are also respondents that said it's only because of his habit and assumptions, it doesn't really replace hunger etc. This relates to knowledge as an understanding that is possessed by humans both in terms of theoretical and practical, it can undergo transformation at any time if it's used properly. Proved by this study, where the samples that have good knowledge and understanding about the danger of smoking have higher motivation to quit smoking compared to the sample group that has poor knowledge.

In a study at the Centers for Disease Control and Prevention in the US, it was said that those who started smoking regularly before age 18 having an intention to quit (OR, 0.66; 95% CI, 0.60-0.72) and had a lower chance of adjusting on smoking cessation (OR, 0.75; 95% CI, 0.69- 0.81) than those who started smoking at the age of 21 or more. People who start smoking regularly at age 18 to 20 also have lower intention to quit (OR, 0.73; 95% CI, 0.66-0.81) and a smaller chance on succeeding smoking cessation (OR, 0.83; 95% CI, 0.75-0.90) than those starting from age 21 or older.[9] So it can be concluded, people who do not smoke before the age of 21, are expected to have greater intentions and motivation to stop smoking. In this study, age at starting smoking was divided into 2 groups, namely <21 years and 21 years.[10] It can be seen in table 4 where the results are stated to be insignificant because the value of P<0.581 where P>0.05 so that there is no relationship between the age of smoking and the motivation to stop smoking.

In a study conducted by Henni Barus of 106 active smokers students majoring in FKM and FISIP UI regarding the relationship between sex and motivation to stop smoking, P =0.46 was obtained, which shows the two variables were not significantly related.[11] Similarly, in this study no significant relationship was found between sex and motivation to stop smoking, showed in table 4. However, this might occur because the sample is uneven where there are more samples taken from men; 134 people than women who were only 4 people.

Based on Henni Barus' research on the relationship between smoking frequency and motivation to stop smoking, P=0.129 was obtained, which means the two do not have a meaningful correlation.[10] In contrast to this study, the final P value between the frequency of smoking (calculated from the number of cigarettes consumed per day) and the motivation to stop smoking, obtained a significant P=0.010 which means there is a significant correlation between the two variables. This study illustrates that someone with a lower smoking frequency has a higher motivation on smoking cesation and vice versa. Then for the relationship between age and motivation to stop smoking the results obtained is a P=0.712 so that means no significant correlation was found between the variables. In this study the age range is divided into 2 groups which are included in the inclusion of 15-45 years and 46-64 years and the results show P=0.735 which means there is no significant relation as in previous studies.

Based on research conducted by Indah Oktarita on 80 public transport drivers who have ever stopped smoking in the Indralaya city area, Indonesia as a respondent regarding the economic relationship with the motivation to stop smoking showed P= 0.028 where it's P<0.05 so that means that there are a correlation between the respondent's economic and motivation to

quit smoking.[12] The study illustrates that someone who has a lot of income certainly does not think too much about spending to buy cigarettes. This make the respondents' motivation to stop smoking low. However, in this study, P =0.700 was obtained which indicates that the two variables are not significantly related.

Education is one of the variables studied and can be an indicator that affects motivation on smoking cessation. In this study it was found that there was a significant relationship between education and motivation because P=0.018 was obtained. Sulastri, et al (2009) research on smokers' compliance to DKI Jakarta regulations showed that the higher the level of education, the higher the smokers' compliance to DKI Jakarta regulations. Thus, education affects one's motivation.

In a study conducted at Santun Untan High School students, Pontianak by Alex regarding the relationship of the level of knowledge about Pictorial Health Warning (PHW) on cigarette packaging (which is one of the indicators of knowledge about smoking) with motivation to stop smoking shows that there is no significant relationship; P=0.759.[13] Contrast results showed in this study, there were a significant relationship between the knowledge of the dangers of smoking and motivation to stop smoking; P<.001.

In a study that also conducted by Henni Barus, described the results of the relationship between knowledge about danger of smoking with the motivation to quit showed P=0.054 so there was no significant relationship. The results in this study are different, which sateted before that it was found that there are a significant relationship between the knowledge of the dangers of smoking and motivation to stop smoking giving a P<.001.[11]

The final results of multivariate logistic regression analysis in this study can be seen in table 5, which is useful for predicting outcomes and assessing which variables are the strongest and most significant, showed that there are only 2 variables that have a significant relationship with motivation on smoking cessation, namely education (P= 0.014) and the frequency of smoking; measured by the number of cigarettes consumed per day (P=0.007) so it can be interpreted that this variables are proved to be an independent variables that significantly influenced the motivation to stop smoking.

The limitation in this research is the number of confounding variables that cannot be controlled which can be the factors that influenced the dependent variable so that the main independent variable (knowledge about the danger of smoking) is not the only one that can be significantly related to the dependent variable (motivation to quit smoking). Then the samples taken are not balanced between men and women. More men (97.1%) studied than women (2.9%) so it is less evenly distributed. Weakness in this study also can be seen in the questionnaire where translation is done but has not been validated internally or externally, also the subject of this study is different from previous studies because this study conducted on ex-smokers while in previous studies conducted on active smokers. Therefore there are differences that might lead into a bias. But because this study is still limited in Indonesia, it is hoped that the results of this study can contribute to providing data or an overview of the correlation between knowledge and motivation so this issue will become more concern in Indonesia.

Conclusion

The results show a significant relation between knowledge about the danger of smoking and motivation to stop smoking. 73.2% samples have a good level of knowledge about the danger of smoking and 58% samples have a high motivation on smoking cessation.

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A Systematic Review of Coronavirus Disease 2019 with Respiratory Distress Syndrome in Adult: Focus on Risk Factors, Mechanism, Diagnosis, and Treatment

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Abstract

Context: Coronavirus disease 2019 (COVID-19) is a newly discovered disease, caused by SARS-CoV-2 and currently has become a pandemic. Acute respiratory distress syndrome (ARDS) is the most common complication in COVID-19. There were numerous conflicting results among articles related to it. The aim of this study is to ascertain the most compelling evidence about ARDS in COVID-19.

Evidence Acquisition: This systematic review was registered in PROSPERO (CRD42020180379). A systematic search was conducted in PubMed, PubMed central, and Google Scholar on April 16, 2020. Two reviewers independently searched and selected the articles. The risk of bias was evaluated using the Newcastle-Ottawa Quality assessment tool.

Results: A total of 1,647 articles were screened, 9 articles were included. Patients were classified as having various degrees of ARDS, the diagnosis of COVID-19 was confirmed by PCR nasopharyngeal swab. Risk factors of ARDS in COVID-19 reported were older age, male gender, and pre-existing medical conditions. Cytokine storm was thought to play a role in the mechanism of ARDS. The main treatment for COVID-19 was supportive and symptomatic. To date, there is no antiviral treatment recommended for COVID-19 and the given treatment for ARDS in COVID-19 was similar to other pneumonia-induced ARDS. No additional therapy specific for ARDS in COVID-19 has been proposed.

Conclusion: Our synthesis of the literature showed that there was no good evidence in the mechanism and treatment of ARDS. Further translation research in the mechanism of ARDS and continuing with clinical trials evaluating drug efficacy for ARDS in COVID-19 is needed.

Introduction

Since December 2019, the world has been introduced to a new type of viral pneumonia, Coronavirus disease 2019 (COVID-19).[1] Out of all complications, acute respiratory distress syndrome (ARDS) was the most prevalent.[1–5] Study from Xiaobo Yang, et al reported that 67% of critically ill COVID-19 patients had ARDS.[2] ARDS increased the need of mechanical ventilation and intubation, although some studies also suggested the usage of extracorporeal membrane oxygenation (ECMO). In addition, ARDS increased mortality risk; most patients who died from COVID-19 developed ARDS.[2] Recently, many articles have been published in relation to ARDS in COVID-19. There is still conflicting data about the risk factor, mechanism, diagnosis, and treatment of ARDS in COVID-19 since its outbreak.

The aim of this systematic review is to summarize the literature and evaluate the strength of the evidence of risk factor, mechanism, diagnosis, and treatment of COVID-19 and ARDS.

Material and Methods

Search Strategy

This systematic review was registered at PROSPERO (International database of prospectively registered systematic reviews) (CRD42020180379) [6]

A literature search was performed on electronic databases, including PubMed, Pubmed Central and Google Scholar. A literature search was conducted on April 16, 2020, using keywords listed in Table 1. The results, obtained from the database corresponding to clinical questions using Boolean operators, are presented in Table 1.

The literature search process was performed within the limits of the literature research, whereas the titles and abstracts were selected from each database. Studies were included in this review if they met the following inclusion criteria: representation for clinical questions (P: adult with COVID-19; I: adult with respiratory distress syndrome; C: adult without respiratory distress syndrome; O: risk factors, mechanism, diagnosis, and treatment), type of the study was either a review article, case report, observational study and clinical trial, and if the full-text article was available. The diagnosis of COVID-19 made by molecular test using reverse transcription polymerase chain reaction (RT-PCR) as the golden standard. Sample must be obtained from nasal and throat swab or other respiratory tracts. The outcome may be within any time period. Studies that included pregnant women population or articles that were not in English were excluded.[7]

Two independent reviewers (AK and CJ) selected the articles, extracted the data, and analyzed the data. Any discrepancies were resolved by consensus between the reviewers or after discussion with a third author (DAH). The reviewers evaluated the title and abstract for all studies that were identified through the PRISMA search strategy. Full texts were evaluated when there was insufficient information in the title and abstract to make decisions about inclusion and exclusion. References in reviewed and excluded articles were examined to identify studies that may not have been identified through the primary search strategy. The search was limited to English. A list of potential studies for inclusion in the systematic review was generated through the process.

Data Extraction

Extracted data included details regarding authors, last five years of publication, country of study population, inclusion/exclusion criteria (patient characteristics), and description of outcomes. Data were also extracted regarding COVID-19 (confirmation cases by PCR swabs), study outcomes (e.g., risk factors, mechanism, diagnosis, and treatment) and secondary outcomes (survival, length of stay, and ventilator dependence).

Multiple article checks were performed in the three databases. The appropriate study

was read in full paper and appraised. A critical appraisal was made based on the Oxford's Center for Evidence-Based Medicine assessing the validity, importance, and applicability of each article. A flow diagram describing the study selection process is shown in Figure 1. [8,9]

Outcome Definitions

Primary outcomes include risk factors, mechanism, diagnosis, and treatment. The secondary outcomes consist of survival, length of stay, and ventilator dependence.

Quality Assessment

The Newcastle-Ottawa Quality (NOQ) assessment of observational trials was used to measure the risk of bias in this systematic review. Two independent researches (AK and DAH) assessed methodological quality and standard of outcome reporting in the included studies. Disagreement between was solved by consensus and if no consensus exists, the opinion of a third reviewer (CJ) was sought. The quality of evidence assessed using the GRADE (Cochrane Group) analysis of findings was not done. [10,11]

Results

Literature search

A total of 1,663 articles were identified through the search strategy. Figure 1 presents the PRISMA diagram (Preferred Reporting Items for Systematic Reviews and Meta-Analysis).[9] After duplicates were removed, the two primary reviewers (AK and CJ) screened titles and abstracts for 1,647 articles. The remaining 54 full texts were reviewed for its eligibility. Most articles were excluded because they did not include information on outcomes selected for our reviews or did not include comparison groups. Ultimately, 9 articles were selected[5,12–19] with a total of 1,121 patients. Overview of the included studies were presented in Table 2.

<<Figure 1 here>>

Primary Outcomes

Risk Factors

Risk factors of developing ARDS in COVID-19 are age, particularly those who are older than 65 years old, male gender, patients' symptoms on arrival including higher temperature and dyspnea, pre-existing medical conditions such as hypertension, diabetes, other cardiovascular diseases, and lung disease. Some laboratory values were also identified to be a risk factor, namely lymphocytopenia, elevated total bilirubin, urea, D-dimer, interleukin-6 and neutrophilia.[2,5,15,16,18–20] Further information regarding risk factors are listed in Table 2. It is important to note that patients who developed ARDS and did not receive antiviral therapy were treated with methylprednisolone because they had higher score of Pneumonia Severity Index (PSI) and had a significant elevation in some laboratory tests compared to patients without ARDS.[5]

Mechanism/ Pathophysiology

The coronavirus enters the body by binding to angiotensin converting enzyme 2 (ACE2) receptors. This receptor is located in many organs of the body, such as lung, heart and kidney.[13] The immune system is needed to eradicate virus from the body, but if the immune mediators are released uncontrollably, it can lead to organ damage.[15,19] Cytokine is one of the immune mediators; its level is highly elevated in COVID-19 patients. [14,19] This is also known as cytokine storm. Cytokine storm was thought to play a role in the development of ARDS in COVID-19 patients.[5,14,16,19]

A lung pathological study from ARDS secondary to COVID-19 displayed pulmonary edema and hyaline membrane formation.[16] Another study also reported that patients also established diffuse alveolar damage accompanied by cellular fibromyxoid exudating in their lungs.[20]

Diagnosis

An arterial blood gas (ABG) analysis should be done to diagnose ARDS.[13,16,20] Based on WHO definition, ARDS is categorized into three classifications, based on the degree of hypoxemia: mild (200 mm Hg < PaO_2/FIO_2 ≤ 300 mm Hg), moderate (100 mm Hg < PaO_2/FIO_2 ≤ 200 mm Hg), and severe (PaO_2/FIO_2 ≤ 100 mm Hg).[5,14] Beside ABG analysis, a study from Yingxia Liu, et al used Murray score to assess the degree of lung injury in ARDS. The greater the score, the more severe the ARDS.[13]

Treatment

The main treatment for COVID-19 is supportive and symptomatic by hydration and nutrition. Monitoring vital signs, oxygen saturation and intake-output balance are also needed.[2,16] To date, there is no specific antiviral treatment recommended for COVID-19, but most of the studies used oseltamivir and lopinavir/ritonavir.[2,5,13–16] Empirical antibiotics were also administered to patients in some studies.[5,14,16]

Regarding the management of ARDS in COVID-19 patients, identifying those who have high risk to develop ARDS and monitoring them closely were the most important. For monitoring, ICU admission was needed.[5,14] In order to suppress immune response, administration of steroids and even anti-IL-6 could be done.[2,5,14–16,19,20] Oxygen therapy was required and could be given through nasal prongs, face mask and high flow nasal cannula. Mechanical ventilation, noninvasive or invasive, might be needed for patients in critical condition. Prone position was also recommended to aid patients with ARDS. Extracorporeal membrane oxygenation (ECMO) might also be given to patients with refractory hypoxemia.[2,5,14–16,18–20] Table 2 shows the managements that had been done or recommendations from various studies.

Secondary outcomes

According to Chaomin Wu, et al study, 44 (52.4%) out of 84 patients[5], 26 (74.3%) out of 35 patients from Xiaobo Yang, et al study[2], six (50%) out of 12 patients from Chaolin Huang, et al study[14] and all 113 (100%) patients in Tao Chen, et al study[16] who developed ARDS did not survive. Patients with ARDS secondary to COVID-19 had higher mortality rates, especially those with advanced age. Not only increasing the mortality rate, ARDS also increased the burden on healthcare workers due to the prolonged length of hospital stays, and most patients who develop ARDS needed ICU admission and mechanical ventilation support.[5,14] Similar findings were found in one study from Yingxia Liu, et al: six (100%) out of six patients who developed ARDS required mechanical ventilation[2,5,13] and intubation.[18]

Quality Assessment

Table 3 summarizes the Newcastle-Ottawa Quality (NOQ) assessment of observational trials results for studies included in the review. No studies were rated “good”; all studies were rated “poor”.[2,5,14–16,20] The GRADE analysis was not done because this study will not continue to a meta-analysis study.

Discussion

This systematic review evaluated ARDS in COVID-19 infection. An important finding was that male patients older than 65 years old and those with preexisting medical condition, mainly hypertension, diabetes, chronic obstructive pulmonary disease and cardiovascular disease, seem to be at a higher risk of developing ARDS.[2,5,15,16,18–20] These findings were similar to the other meta-analysis about the severity factors of COVID-19. Study from Chaomin Wu, et al also analyzed the symptoms on the arrival of patients with ARDS and found that those who suffered from higher fevers (≥39°C) and had dyspnea had higher risk.[5] Some laboratory values could also be a predictor for ARDS, but from a total of 9 studies, only two studies analyzed this aspect.

Lymphocyte count were found to be lower according to Chaomin Wu, et al and Yulong Zhou study, with 0.67 (0.49-0.99) x 10^9/L and 0.65±0.339 x10^9/L, respectively.[5,15]

Immune system was figured out to play a major role in ARDS pathogenesis. It was

thought that there were two phases of immune response produced by SARS-CoV-2 infection: non-severe and severe phase (Figure 2). When the severe phase took place, it would induce cytokine storm.[21] Cytokine storm would cause more damage and eventually ARDS to occur.[5,15,16,19] Findings behind the mechanism of ARDS in COVID-19 patients were based on general knowledge and laboratory tests. Study from Chaomin Wu, et al postulates cytokine storms based on neutrophilia. [5] On the other hand, cytokine test was done by Tao Chen, et al.[16] Some studies also reported elevation of inflammation predictors and cytokines which supported the idea of cytokine storm.[1,13–15]

<< Figure 2 here>>

Even though some laboratory tests were elevated in patients who subsequently developed ARDS, the diagnosis of ARDS was still made based on the ABG analysis.[5,13,16,20] Aside from ABG analysis, study from Yingxia Liu, et al also used Murray score in order to assess the ARDS severity. It was found that the viral load was associated with the degree of severity.[13,22] One subject, a 63 year old male from Yingxia Liu, et al's study developed a very high viral load and suffered from fulminant myocarditis.[13] Thereby, this scoring might be helpful for assessing those who need closer monitoring.

Mainstay management of ARDS in COVID-19 was to identify the high risk groups and monitoring and oxygen support was also an important key in managing patients.[2,5,14,15,18–20] A study also suggested the use of ACE inhibitor or angiotensin receptor blocker drugs.[13] Most studies in this systematic review suggested the use of immunosuppressants, but there was no detailed recommendation regarding the dose and length of drug usage.[2,5,14–16,19,20] Study from Dennis McGonagle, et al also stated that IL-6 was greatly induced by SARS-CoV rather than by influenza A virus and human parainfluenza virus type 2. Viral replication might be increased or suppressed by IL-6, depending on the virus.[23] It was not yet clear whether IL-6 suppresses or initiates further viral replication in COVID-19. With regards to steroids use, some studies, international consensus and WHO did not recommend the use of glucocorticoids in ARDS patients.[24,25] Many articles discussed the management of ARDS, but none of them provided satisfactory evidence and recommendations, thus further study is needed.

ARDS patient survival was poor.[2,5,14,16] Even in Tao Chen, et al study, all ARDS patients died. However, sepsis was also developed, and it might be possible that the poor survival rate was due to the development of sepsis.[16] It was necessary to monitor those with ARDS and who were in more critical condition. Hence the hospital stay duration was longer and mechanical ventilation might be needed in ARDS patients.[2,5,13,14,26] The inflammatory markers to predict severe COVID-19 have been reported, for instances C-reactive protein, procalcitonin, lactate dehydrogenase, D-Dimer, and albumin.[27] To date in the recent meta-analysis, many efforts have been done to control the disease such as Remdesivir[28], Lopinavir/ritonavir[29] Dexamethason[30], and Tocilizumab[31-32]. Patients with comorbidities should continue their therapy.[33-35]

The limitation of this study is that there are no sufficient research references marked good. All studies included in our analysis were rated poor based on Newcastle-Ottawa Quality assessment. This was due to the comparability of the cohort studies included were scored zero, indicating poor quality studies. Only one study provided exposed and non-exposed table & discussion[15] but neither age nor sex and other confounders were found statistically significant, while other studies compared directly the population of the outcomes. Hence, they are not in accordance with the design study. This could be explained due to the limited time to collect and analyze the study about the newly discovered disease, COVID-19. As a result, this systematic review lacks satisfactory evidence. We strongly suggest further research about ARDS in COVID-19 adjusting to the

appropriate steps based on the used study design to produce a better-quality study. The overall included studies lacked evidence regarding the management of COVID-19 with ARDS. We suggest that future research and clinical trials focusing on this aspect provide better evidence in the future.

Conclusion

This systematic review evaluation consisted of risk factors, mechanisms, diagnosis, and treatment of ARDS related to COVID-19. The age, gender, comorbidities, presenting symptoms and some laboratory values were associated with higher risk of developing ARDS in COVID-19. Our synthesis of the literature shows that there is no good evidence in the mechanism and treatment of ARDS. Future translation research is needed to explore more in the mechanism of ARDS, evaluating the key player between inflammation, thrombosis, hypoxemia, and organ dysfunctions. Furthermore, clinical trials are needed to evaluate the drug or drug combinations targeting the key factors of ARDS.

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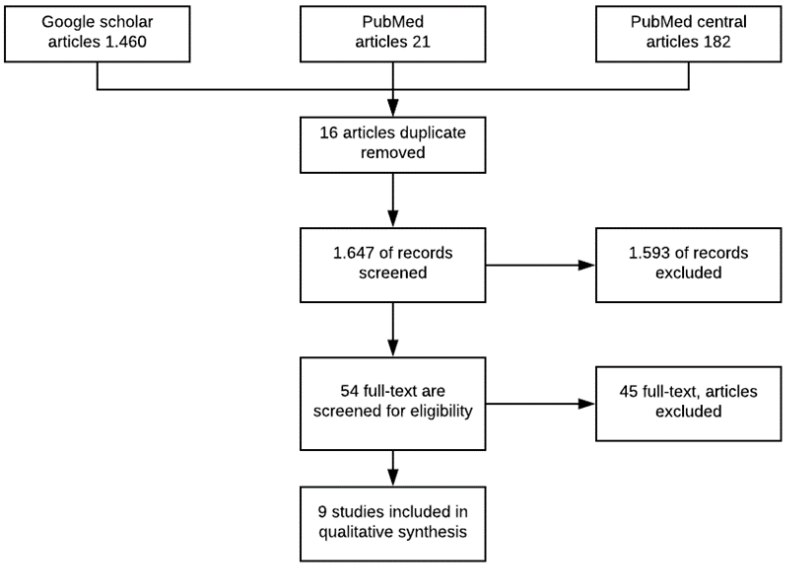

Figure 1. PRISMA Diagram

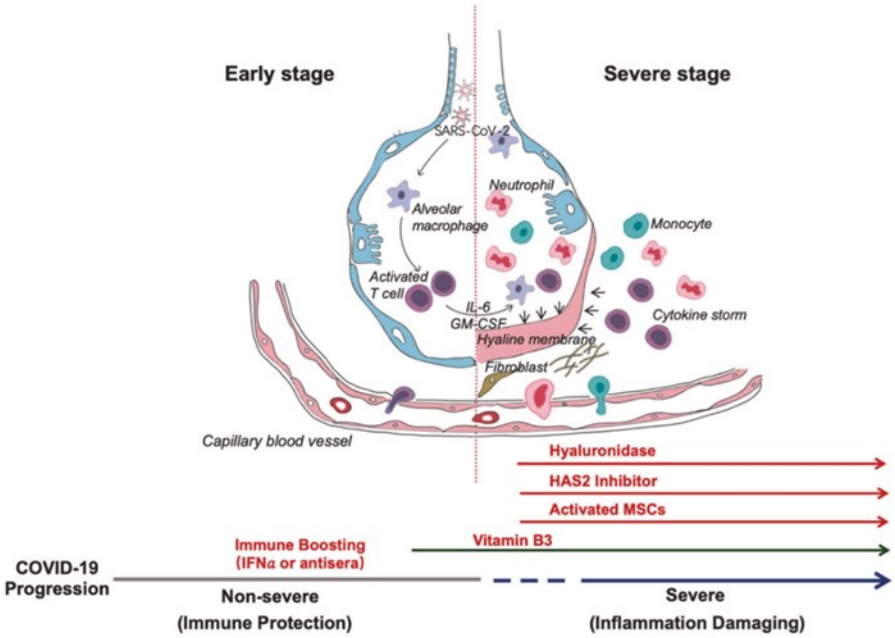

Figure 2. Immune Response Phase

Table 1. Literature search strategy

Database	Keyword	Result
PubMed	("COVID-19"[All Fields] OR "COVID-2019"[All Fields] OR "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "2019-nCoV"[All Fields] OR "SARS-CoV-2"[All Fields] OR "2019nCoV"[All Fields] OR (("Wuhan"[All Fields] AND ("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields])) AND (2019/12[PDAT] OR 2020[PDAT]))) AND ("respiratory distress syndrome, adult"[MeSH Terms] OR ("respiratory"[All Fields] AND "distress"[All Fields] AND "syndrome"[All Fields] AND "adult"[All Fields]) OR "adult respiratory distress syndrome"[All Fields] OR ("respiratory"[All Fields] AND "distress"[All Fields] AND "syndrome"[All Fields] AND "adult"[All Fields]) OR "respiratory distress syndrome, adult"[All Fields])	21
Pubmed central	("COVID-19"[All Fields] OR "COVID-2019"[All Fields] OR "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "2019-nCoV"[All Fields] OR "SARS-CoV-2"[All Fields] OR "2019nCoV"[All Fields] OR (("Wuhan"[All Fields] AND ("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields])) AND (2019/12[PDAT] OR 2020[PDAT]))) AND ("respiratory distress syndrome, adult"[MeSH Terms] OR ("respiratory"[All Fields] AND "distress"[All Fields] AND "syndrome"[All Fields] AND "adult"[All Fields]) OR "adult respiratory distress syndrome"[All Fields] OR ("respiratory"[All Fields] AND "distress"[All Fields] AND "syndrome"[All Fields] AND "adult"[All Fields]) OR "respiratory distress syndrome, adult"[All Fields])	182
Google scholar	COVID-19 AND Respiratory distress syndrome AND risk factor AND mechanism AND treatment	1460

Table 2. Characteristics of included studies

Author	Participants	Study type	Risk factor	Mechanism	ARDS Diagnosis	Treatment	Reference
Chaomin Wu, et al	201	Retrospective cohort	Older age Higher temperature and dyspnea on admission Comorbid Elevated total bilirubin, urea, D-dimer, interleukin-6 Higher neutrophil count Lower total lymphocyte count	Cytokine storm and cellular immune response	-	Oxygen support Empirical antibiotics Antiviral Antioxidant therapy: glutathione and N-acetyl-L-cysteine Methylprednisolone Immunomodulators	[5]
Xiaobo Yang, et al	52	Retrospective cohort	Age >65 years old Male	-	-	Mechanical ventilation Prone position Antiviral IV glucocorticoids	[2]
Yingxia Liu, et al	12	Retrospective cohort	-	-	Arterial blood gas analysis Murray score to assess the severity of lung injury in ARDS	Angiotensin-converting enzyme inhibitor and angiotensin receptor blocker may be used to treat COVID-19	[13]

Chaolin Huang, et al	41	Prospective cohort	-	-	-	Oxygen therapy ECMO for refractory hypoxemia Empirical antibiotic Corticosteroids	[14]
Yulong Zhou, et al	17	Retrospective cohort	Lower total lymphocyte count	-	-	Oxygen support Antiviral Corticosteroid	[15]
Tao Chen, et al	274	Retrospective cohort	Age >60 years old Male Comorbid (hypertension in particular)	Pulmonary edema with hyaline membrane formation Cytokine storm	Arterial blood gas analysis	Oxygen support, if fail, mechanical ventilation ECMO Antiviral Antibiotics Glucocorticoid	[16]
Xiao Tang, et al	148	Retrospective case-control	Older age	Diffuse alveolar damage, fibromyxoid exudation	Arterial blood gas analysis	Antiviral Oxygen support Mechanical ventilation ECMO Glucocorticoids Immunoglobulin Chinese traditional medicine	[20]
Wenlong Yao, et al	202	Retrospective cohort	Age ≥ 65 years old Male	-	-	Oxygen therapy Intubation Prone ventilation	[18]
Wen Jun Tu, et al	174	Retrospective cohort	Older age Male Comorbid	Interferon-γ-related cytokine storm	-	Methylprednisolone Invasive mechanical ventilation Antiviral Tocilizumab	[19]

Table 3. Newcastle-Ottawa quality assessment of observational trials

First author, year	Study design	Selection	Comparability	Exposure/Outcome	Total score	Result
Chaomin Wu, et al. 2020	Cohort	***	-	***	6	Poor
Xiaobo Yang, et al., 2020	Cohort	****	-	***	7	Poor
Chaolin Huang, et al., 2020	Cohort	***	-	***	6	Poor
Yulong Zhou, et al., 2020	Cohort	****	-	*	5	Poor
Tao Chen, et al., 2020	Cohort	**	-	**	4	Poor
Xiao Tang, et al., 2020	Case-control	***	-	***	6	Poor

Coronavirus Disease 2019 and Gastrointestinal Involvement: a Systematic Review

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Keywords: COVID-19; gastrointestinal symptoms; SARS-CoV-2.
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Abstract

Introduction: The World Health Organization (WHO) announced the Coronavirus 2019 (COVID-19) as a Public Health Emergency of International Concern (PHEIC) toward the end of January 2020. There is still limited evidence to explain the gastrointestinal involvement in COVID-19. In this study, we aimed to further investigate current evidence describing the gastrointestinal involvement in COVID-19 patients.

Methods: This systematic review has been registered in PROSPERO (CRD42020181584). A systematic search of literature for observational and randomized controlled trial was conducted in PubMed, PubMed central, and Google Scholar through April 16, 2020. Two reviewers independently searched and selected. The risk of bias was evaluated using the Newcastle-Ottawa Quality assessment tool.

Results: A total of 1,480 articles were screened from which 12 articles with 5584 subjects were selected. SARS-CoV-2 can invade human body by binding to angiotensin converting enzyme 2 (ACE-2) receptor which also located to small intestinal epithelial cells, crypt cells and colon. The virus itself may cause disorders of the intestinal flora. The diagnosis should be based on a set of symptoms diarrhoea, nausea, vomiting, abdominal discomfort or pain, combined with positivity of faecal PCR test. Treatment of COVID-19 mainly is supportive care. The probiotic may modulate the gut microbiota to alter the gastrointestinal symptoms and reduced enteritis, ventilator associated pneumonia, and reverse certain side effect of antibiotics.

Conclusion: Our synthesis of literature showed that there was no good evidence yet in overall area of gastrointestinal manifestations in COVID-19. Future research is needed to explore all areas, especially in mechanism and treatments

Introduction

On December 31 2019, Word Health Organization (WHO) mentioned a case of cluster pneumonia with unidentified etiology in Wuhan City, Hubei Province, China. This case continues to distribute and grow until there are reports of deaths and cases found outside of China. In early 2020, China has identified pneumonia of unknown etiology as a new type of coronavirus. The WHO suggested the disease name as COVID-19 and has announced this as a Public Health Emergency of International Concern (PHEIC) toward the end of January 2020. Then as of February 24, 2020, more than 80,000 confirmed cases including more than 2,700 deaths have been accounted for around the world, influencing at any rate 37 nations. On March 2020 Indonesia reported two cases of COVID-19 confirmation and WHO established COVID-19 as a pandemic.[1,2] As February 15th, 2020, WHO reported total 108,579,352 confirmed cases worldwide COVID-19 outbreak and in Indonesia reached 1,223,930 cases.[2]

COVID-19 is the seventh human coronavirus detected and appears to have major similarities with two other highly pathogenic human respiratory coronaviruses, severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002–2004 and Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012–2016. COVID-19, SARS-CoV and MERS-CoV belong to the betacoronovirus family, which potentially share a similar source in bats. Such betacoronaviruses cause respiratory symptoms and gastroenteritis in hosts of humans and animals. [3,4]

Patients typically present with fever and respiratory symptoms, nevertheless, some patients also have gastrointestinal manifestations with diarrhoea, vomiting and abdominal pain.[5] Based on several scientific studies, it was confirmed that COVID-19 could be transmitted human-to-human primarily via respiratory droplets when an infected person cough or sneeze, not through the air.[3] Studies have identified the SARS-CoV-2 RNA in anal / rectal swabs and stool specimens.[5,6,7] Therefore considerations must be given to the possibility of faecal-transmission in COVID-19 infection. There were many articles published recently, but the results were conflicting. The aim of this study is to know the current evidence of COVID-19 and gastrointestinal involvement. In this systematic review, we will evaluate current articles related to digestive symptoms and COVID-19.

Material and Methods

This systematic review is registered at PROSPERO (International database of prospectively registered systematic reviews) (CRD42020181584).)

A literature search was performed on electronic databases, including PubMed (https://www.ncbi.nlm.nih.gov/pubmed/?term=COVID-19+AND+gastrointestinal+involvement+AND+%22risk+factors+OR+clinical+manifestations+OR+diagnosis+OR++treatment%22) PubMed central

(https://www.ncbi.nlm.nih.gov/pmc/?term=COVID19+AND+gastrointestinal+involvement+AND+%22risk+factors+OR+clinical+manifestations+OR+diagnosis+OR+treatment%22) and Google Scholar

(https://scholar.google.co.id/scholar?as_ylo=2019&q=COVID19+AND+gastrointestinal+involvement+&hl=id&as_sdt=0,5).

A literature was conducted on April 16, 2020, using keywords listed in Table 1. The results obtained from database corresponded to clinical questions using the Boolean system presented in Table 1.

The literature search process was continued using the limits of the literature research and then the titles and abstracts were selected from each database. Studies were included in this review if met the following inclusion criteria: representation for clinical question (P: adult COVID-19; I: Gastrointestinal involvement; O: risk factors, mechanisms, symptoms and signs, diagnosis and treatment), type of study was review article, observational study and clinical trial, and if the full-text was available. Timing of outcome is any time. The studies were excluded the population is pregnant women or the articles were not in English language.

Two independent reviewers (MM and AK) selected the articles, extracted the data, and analysed the data. Any discrepancies were resolved by consensus between the reviewer. The reviewers evaluated the tittle and abstract for all studies that were identified through PRISMA search strategy. Full texts were evaluated when there was insufficient information in the title and abstract to make decisions about inclusion and exclusion. References in reviewed and excluded articles were examined to identify studies that may not has been identified through the primary search strategy. The search was limited to English language. A list of potential studies for inclusion in the systematic review was generated through the process.

Data extraction

Extracted data included details regarding authors, since 2019, country of study population, inclusion/exclusion criteria (patient characteristics), and description of outcomes. Data were also extracted regarding the COVID-19 (confirmation cases by PCR swabs), study outcomes (e.g. risk factors, mechanism, symptoms and signs, diagnosis, and treatment).

Multiple article checks were performed in the three databases. The appropriate study was the read in full paper and appraised. A critical appraisal was made based on a critical appraisal was mad based on the oxford's Centre for Evidence-based medicine which assesses the validity, importance and applicability of each article. A flow diagram describing the study selection process is shown in Figure 1.

Outcomes definitions

Outcomes included (1) risk factors: what is the risk factor for gastrointestinal involvement in COVID-19; (2) mechanism: How is the gastrointestinal be involved in COVID-19 pathogenesis; (3) diagnosis: How is COVID-19 diagnosed if there are no respiratory symptoms and (4) treatment: Is there any specific symptoms for gastrointestinal involvement in COVID-19 infection.

Quality assessment

The Newcastle-Ottawa Quality (NOQ) assessment of observational trials was used to measure the risk of bias in this systematic review. Two independent researchers (MM and AK) to assess methodological quality and standard of outcome reporting in the included studies. The quality of evidence was assessed using the GRADE (Cochrance Group) analysis of findings will not be done.

Results

Literature search

A total of 1,480 articles were identified through the search strategy. Figure 1 presents the PRISMA diagram (Preferred Reporting Items for Systematic Reviews and Meta-Analysis). After duplicates were removed, the two primary reviewers (MM and AK) screened titles and abstracts for 1,480 articles. For the articles that remained after the initial screened, 54 full text were reviewed for eligibility. Most articles are excluded because they did not include information on outcomes selected for our reviews or did not include comparison groups. Ultimately, 12 articles were selected (all articles index) with a total of 5574 patients. Overview of included studies were presented in table 2.

Overview of included studies

Table 2 provides the characteristic of included studies. There are 6 observational studies, 1 case report and 5 review articles.

Diagnosis of COVID-19 was using RT-PCR nasal or nasopharyngeal swab. Only two observational studies[27,28] and one case report[15] evaluate the gastrointestinal involvement using RT-PCR faeces. Only one study included children population.[28]

Primary outcomes

Risk factors

None of articles or studies reported the risk factors of gastrointestinal involvement in COVID-19. One observational study reported comorbidity related to gastrointestinal disease.[7] One review article evaluates the risk factor of COVID-19 infection in patients with existing gastrointestinal disease. Patients with comorbidities of inflammatory bowel disease especially in immunosuppressive agents, malnutrition, hypertension, diabetes, and on pregnant were at risk.[10]

Mechanisms

There were four observational studies[7,27,28,33] mentioned about the potential mechanism of gastrointestinal involvement in COVID-19. There were 4 review[2,5,10,23] and commentary[11] articles discussed the mechanism of COVID-19 infection.

Infectious virions are secreted to the virus-infected gastrointestinal cells. The genome sequences showed that SARS-CoC-2 shared 79.6% sequence identity to SARS-CoV, both encoding and expressing the spike (S) glycoprotein that could bind to the entry receptor ACE-2.[5] The receptor found abundantly expressed in glandular cells of gastric, duodenal, and rectal epithelial.[27] After the virus entry the mucosa, the gastrointestinal wall will increase its permeability. Enteropathic viruses may directly damage the intestinal mucosa and cause digestive symptoms.[11] The symptoms of diarrhoea will occur by invaded enterocytes malabsorption.[7]

The virus itself may cause disorders of the intestinal flora, which could result in digestive symptoms. Decreased expression of antimicrobial peptides and showed altered gut microbial composition.[2] The viral nucleic acids found in the faecal samples and anal swabs.[33] It can be last longer than it found in nasal and pharyngeal swab has become negative.[28]

Diagnosis

Gastrointestinal involvement in COVID-19 infection should be based on a set of symptoms diarrhoea, nausea, vomiting, abdominal discomfort or pain, combined with positivity of faecal PCR test. Duration time of positivity of the test 1-12 days. In one study faecal PCR test found positive in 39 (53.4%) patients. Furthermore, 17(23.29%) found still positive of faecal test after the respiratory sample has become negative.[27] The diagnosis in children is the same as do in adult.[28]

Treatment

Treatment of COVID-19 mainly is supportive care, some case was given broad spectrum antibiotics.[15] Management gastrointestinal involvement in COVID-19 infection mentioned in one study was probiotic treatment. The probiotic may modulate the gut microbiota to alter the gastrointestinal symptoms[23] and reduced enteritis, ventilator associated pneumonia, and reverse certain side effect of antibiotics.[2] Antiviral therapy with alpha interferon oral spray (8,000 Unit, two spray, there times a day) may be used in children, however further clinical trial was needed.[28]

Quality assessment

From six observational studies evaluated using Newcastle-Ottawa quality assessment, three was only one study "good"[7], the others two studies "fair"[27, 33] and the others three studies "bad" [28, 24, 17]

Discussion

To be best of our knowledge, this systematic review is the first evaluate the gastro-intestinal involvement in COVID-19. This review evaluated the whole aspects from the risk factors to treatment specific if COVID-19 had gastro-intestinal

involvement. The COVID-19 is the systemic disease and one of the involvements is in gastrointestinal tract.

From the published articles related gastrointestinal in COVID-19, none of the articles shared information about the risk factors of gastrointestinal involvement. Most of studies shared about severity cases of COVID-19 to become ARDS or death. COVID-19 patients who only complaint the gastrointestinal symptoms, should further be evaluated the risk factors of severity cases.

There are many reasons why COVID-19 appears to cause digestive symptoms. SARS-CoV-2 is similar to SARS-CoV and can invade the human body by binding to the human angiotensin converting enzyme 2 (ACE-2) receptor, which causes liver tissue injury by up- regulation of ACE-2 expression in liver tissue caused by compensatory proliferation of hepatocytes derived from bile duct epithelial cells. [7] COVID-19 patients could manifest with gastrointestinal involvement for instance nausea/vomit, diarrhea and abdominal discomfort/pain. Not rare, gastrointestinal symptom was the initial and the only symptom complaint by the patients. From the included studies, there were still limited data regarding the correlation between lung and gastrointestinal symptoms in COVID-19 patients. The explanation why several patients showed gastrointestinal symptoms only, should be answered in further observational studies focus on risk factors evaluation.

Coronavirus human transmissibility and pathogenesis mainly depend on the interactions, including virus attachment, receptor recognition, protease cleaving and membrane fusion, of its transmembrane spike glycoprotein (S-protein) receptor-binding domain, specific cell receptors (ACE2), and host cellular transmembrane serine protease (TMPRSS), with binding affinity of 2019-nCoV about 73% of SARS-CoV.[3,4,7,11] The S protein is responsible for facilitating entry of the CoV into the target cell. It is composed of a short intracellular tail, a transmembrane anchor, and a large ectodomain that consists of a receptor binding S1 subunit and a membrane-fusing S2 subunit. Receptor binding motif (RBM) in the S protein showed that most of the amino acid residues essential for receptor binding have sequence similarities between SARS-CoV and SARS-CoV-2, suggesting that the two CoV strains use the same host receptor for cell entry. Lu et al proved structural similarity between the receptor-binding domains of SARS-CoV and COVID-19 by molecular modelling which means COVID-19 could use ACE2 as the receptor. For SARS-CoV entry into a host cell, its S protein needs to be cleaved by cellular proteases at two sites, termed S protein priming, so the viral and cellular membranes can fuse. Specifically, S protein priming by the serine protease *TMPRSS2* is crucial for SARS-CoV infection of target cells and spread throughout the host. Hoffmann et al. investigated if SARS-CoV-2 entry is also dependent on S protein priming by TMPRSS2. [2,12,13,5]

The virus itself may cause disorders of the intestinal flora, which could result in digestive symptoms. Mechanistically, ACE2 has a RAS-independent function, regulating intestinal amino acid homeostasis, expression of antimicrobial peptides, and the ecology of the gut microbiome. ACE2 mutants could decrease expression of antimicrobial peptides and showed altered gut microbial composition. Therefore, we speculate that COVID-19 may have some relationship with the gut microbiota.[2]

Finally, the intestine is the largest immune organ in the body. Changes in the composition and function of the digestive tract flora affect the respiratory tract through the common mucosal immune system, and respiratory tract flora disorders also affect the digestive tract through immune regulation. The effect is called the “gut-lung axis” which may further explain why patients

with COVID-19 pneumonia often have digestive symptoms.[7]

Current recommendation by US CDC requires the use of BOTH nasal and throat swabs to obtain specimen from upper respiratory tract of potential case with COVID-19 for diagnostic testing using RT-PCR to confirm the cases. However, initial rapid guidelines from China only indicated the use of throat swabs. Yang et al (2020) specific for COVID-19 have found that testing of specimens obtained from nasal swabs, as well as from sputum, are more effective than throat swabs, for the detection of SARS-CoV-2 concluded that "sputum is most accurate for laboratory diagnosis of (COVID-19), followed by nasal swabs, while throat swabs was not recommended for the diagnosis." However, the authors recognized the limitation that preliminary investigations only found about a quarter of COVID-19 patients showed sputum production.[9]

A study by To et al (2020) have found that SARS-CoV-2 was detected in saliva samples from 11 out of 12 COVID-19 patients. This suggests that saliva samples could be a potential alternative or additional specimen for diagnostic testing, especially in scenarios with limited trained healthcare providers outside of the hospital setting, and with aim to reduce exposure risk during specimen collection.[14,9]

Gastrointestinal involvement of SARS-CoV-2 infection and isolation of SARS-CoV-2 from faecal samples of patients are in support of the importance of faecal–oral route in SARS- CoV-2 transmission.[5] The positivity of COVID-19 virus still remain although the improvement of lung lesion and the nasopharyngeal swab had become negative.

Currently, there is no validated treatment for COVID-19. The main strategies are symptomatic and supportive care, such as keeping vital signs, maintaining oxygen saturation and blood pressure, and treating complications, such as secondary infections or organs failure.[20] The antivirus such as lopinavir/ritonavir did work in early evidence[34], but not after large RCT came out. Remdesivir showed benefit in moderate and severe cases.[35] Controlling several comorbidities such as hypertension[36] and diabetes[37] showed benefit, but not in dyslipidemia using statin.[38] Others risk factors such as anemia[39] and thyroid disease[40] should also be managed.

Currently no direct clinical evidence proved that modulation of gut microbiota has the therapeutic role in treatment of COVID-19[41], but we suppose that targeting gut microbiota might be a new therapeutic option or at least adjuvant therapeutic choice. In early February, Guidance from China's National Health Commission (Version 5) recommend that in the treatment of severe patients with COVID-19 infection, probiotics can be used to maintain the balance of intestinal microecology and prevent secondary bacterial infection which showed that growing awareness of the importance of gut microbiota in COVID-19 infection has been accepted by Chinese government and first-line medical staff.[2]

There are several potential therapeutic approaches. Development of a spike1 subunit protein-based vaccine may rely on the fact that ACE2 is the SARS-CoV-2 receptor. Cell lines that facilitate viral replication in the presence of ACE2 may be most efficient in large-scale vaccine production.[22]

Conclusion

There is still limited evidence to evaluate gastrointestinal involvement in COVID-19. Further studies should evaluate the risk factors of with gastrointestinal involvement only in COVID-19 patients. The interaction between microbiota and local and systemic immune system, and the consequences of pro or prebiotic treatment that modulate systemic immune system should also be sought.

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Coagulopathy in COVID-19: A Systematic Review

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Abstract

Introduction: Corona Virus Disease 2019 (COVID-19) firstly appeared in Wuhan, China in December 2019 and defined as a pandemic in March 2020. COVID-19 divided into asymptomatic, mild, and severe symptoms. Coagulopathy may have happened in severe COVID-19 infection, it was also associated with high mortality in COVID-19 patients. Laboratory examination is the main protocol to identify coagulopathy, thereby it also determined the prognosis of COVID-19 patients with coagulopathy. Here, we review the current evidence describing the mechanism, diagnosis, treatment, and mortality of coagulopathy in COVID-19.

Method: We identify 8 studies and/or review articles evaluating coagulopathy in COVID-19 patients by searching PubMed and EMBASE databases.

Results: DIC is most commonly found in death with COVID-19, the risk of VTE also higher in severe COVID-19 because of immobility and long-term bed rest. Sepsis-induced DIC is associated with organ dysfunction as in the patient with viral infection as in COVID-19 infection. Sepsis-induce Coagulopathy (SIC) score, D-dimer, and prothrombin time (PT) measured at the time the patient classified as severe COVID-19. Higher D-dimer and FDP levels, longer PT and activated partial thromboplastin time (APTT) may have a poor prognosis. Treatment with Low Molecular Weight Heparin (LMWH) effective to reduced 28-day mortality in patients with SIC ≥ 4 and D-dimer > six-fold of the upper limit of normal.

Conclusion: Coagulopathy plays a big role to determine the prognosis of COVID-19 patients. Treatment with LMWH may give some benefits to COVID-19 patients.

Introduction

COVID-19 is a new type of pneumonia that began it spreads since December 2019, for the first time in Wuhan, China, caused by beta-coronavirus, Severe Acute Respiratory System Coronavirus 2 (SARS-CoV-2). Beta-coronaviruses also previously caused SARS and Middle East Respiratory Syndrome Corona Virus (MERS-CoV) that became outbreaks in 2003 and 2012, respectively.[1]

The clinical features of COVID-19 are divided into asymptomatic, mild symptoms (fever, cough, and fatigue), and severe symptoms (acute respiratory distress syndrome, metabolic acidosis, sepsis, and coagulopathy including disseminated intravascular coagulation (DIC) and venous thromboembolism (VTE)).[2] Organ dysfunction and coagulopathy were associated with high mortality in COVID-19 patients, 11.0% and 14.6%, respectively.[3,4] Patients with severe COVID-19 infection are at high risk for developing VTE because they usually became immobilized and in a state of acute inflammation that leading to hypercoagulation. On the other hand, DIC is one of the most common complications of sepsis that usually happen in severe pneumonia case.[5] In this systematic review, we will evaluate current articles related to coagulopathy and COVID-19.

Search Strategies

A comprehensive search of literature was conducted in the PubMed (NIH) and EMBASE databases (January 2019 to March 2020) using keyword combinations of the medical subject headings (MeSH) of 'coagulopathy', 'disseminated intravascular coagulation', 'consumptive coagulopathy', 'COVID-19', 'coronavirus disease 2019', and 'SARS-CoV-2'. Relevant reference lists were also manually searched.

Problems of COVID-19 Patients with Coagulopathy

Zhou et al. found risk factors of mortality in COVID-19 patients are older age, high Sequential Organ Failure Assessment (SOFA) score, and D-dimer greater than 1 μg/mL on admission (81% of non-survivor had D-dimer levels of > 1 μg/mL on admission). They also found that D-dimer levels and prothrombin time (PT) were associated with death.[6] Patients with a high level of D-dimer and sepsis associated with 28-day mortality in the emergency department.[7] Tang et al. also revealed that non-survivors had higher D-dimer and fibrinogen degradation product (FDP) levels, longer PT and activated partial thromboplastin time (APTT) than survivors on admission, so conventional coagulation tests in COVID-19 was associated with prognosis.[8]

Mechanism of Coagulopathy in COVID-19

DIC is most commonly found in death with COVID-19.[8] Sepsis-induced DIC is associated with organ dysfunction as in the patient with viral infection as in COVID-19 infection. In sepsis, the system of blood coagulation is shifted toward the hypercoagulable state which is acute inflammatory mediator induced tissue factor expression in CD14+ monocyte and endothelial cells.[9] Antithrombin also decreased in sepsis because of consumption by the formation of thrombin-antithrombin complexes and degradation by proteases that released from activated neutrophil, so free thrombin circulated and activate platelet and fibrinolysis pathway,[10] but the level of fibrinolytic activity is too low to counteract the systemic deposition of fibrin clots in SIRS.[11] High level of plasminogen activator inhibitor-1 (PAI-1) that originates from endothelial cells also has a big role in predicting multiple organ dysfunction in sepsis-induced DIC.[12]D-dimer and FDP is elevated in all patients who were died in the late stages of COVID-19. Risk of VTE also higher in severe COVID-19 because of immobility and long-term bed rest.[13] On the other hand, severe COVID-19 cause hypoxia that increased risk of thrombosis because of increased blood viscosity and hypoxia-inducible transcription factor-dependent signaling pathways.[14]

Diagnosis of Coagulopathy in COVID -19

The earlier phase of sepsis-induced DIC can be detected using International Society on Thrombosis and Hemostasis new scoring system, named "sepsis-induced coagulopathy" (SIC) (Figure 1).[15] Tang et al started to use this scoring when the patients classified as severe COVID-19 that define by meeting any one of these: respiratory rate ≥ 30 breaths/minute, arterial oxygen

saturation ≤ 93% at rest, and PaO2/FiO2 ≤ 300 mmHg.[13]Beside SIC, D-dimer and PT also measure at the time the patient classified as severe COVID-19. In the previous study, they used ISTH diagnostic criteria for DIC (Figure 2) and found that 71.4 % non-survivor and 0,6% survivor matched in ≥ 5 points or the grade of overt-DIC.[16] DIC was detected in median time of 4 days after admission to hospital.[8] Platelet count may not be sensitive to detect coagulopathy in COVID-19, due to the reactively increased thrombopoietin following pulmonary inflammation.[17] ISTH recommended to measure fibrinogen level besides of D-dimer, PT, and platelet count in the guidance of DIC, this

recommendation can be used in COVID-19 infection.[18] Tang et al. found that D-dimer and PT level increased, and fibrinogen level decreased at days 10 and 14 in non-survivors.[8] Other researcher noted that for early identification of severe COVID-19 cases, monitoring the level of D-dimer and FDP can be helpful as their levels higher in severe COVID-19 infections than in milder forms.[10]

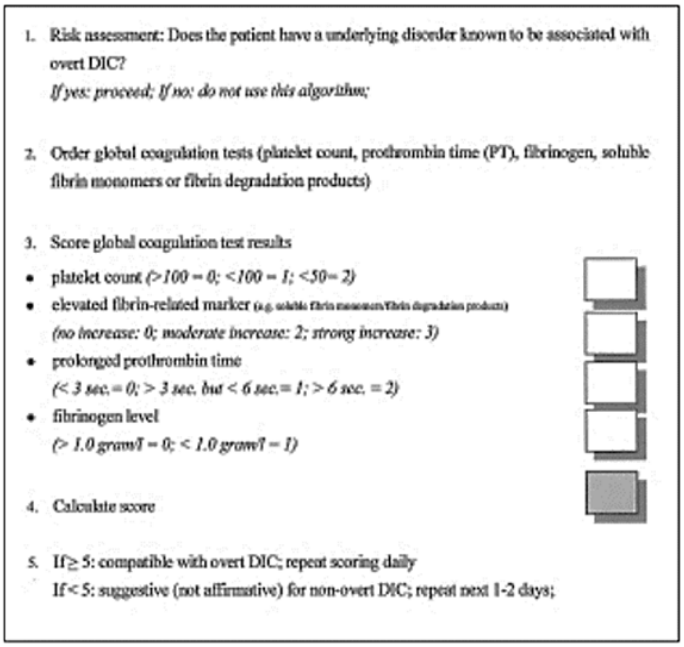

Figure 1. International Society on Thrombosis and Hemostasis (ISTH) diagnostic algorithm for the diagnosis of overt DIC[16] cited from Taylor J, et al. Thromb Haemost. 2001;86(5):1327–30.

Table 1. ISTH SIC Scoring System[15]

Item	Score	Range
Platelet count (x10^9/L)	1	100-150
	2	<100
PT-INR	1	1.2-1.4
	2	>1.4
SOFA score	1	1
	2	≥ 2
Total score for SIC	≥ 4	

Treatment of Coagulopathy in COVID-19

In Tang and colleagues' study that included 449 patients with severe COVID-19 infection, 99 of them were treated with heparin, mainly low molecular weight heparin (LMWH) for 7 days at prophylactic doses. The result was no difference in 28-day mortality between patients who received LMWH and those who did not. So, if there isn't any contraindication (active bleeding and platelet count less than $25x10^9$/L), prophylactic doses LMWH should be given in all patient including non-critical patients who required hospital admission for COVID-19 infection. In those with SIC score ≥ 4 and D-dimer > six-fold of the upper limit of normal, anticoagulant therapy (LMWH) associated with decreased mortality.[13] Besides that, LMWH also has other benefits such as against VTE in critically ill patients and its anti-inflammatory properties in COVID-19 infection where pro-inflammatory cytokines raised.[19–21] All immobilized and severely ill patients with COVID-19 should receive thromboprophylaxis unless there is any contraindication (for CrCl >30: LMWH or Fondaparinux subcutaneous (s.c) according to the license, for CrCl < 30 or acute kidney injury (AKI): unfractionated heparin 5000 unit s.c twice daily or three times daily or dose-reduced LMWH). ISTH has an algorithm to manage coagulopathy in COVID-19 based on simple laboratory markers (D-dimer, PT, platelet count, and fibrinogen). (Figure 2)[18]

Liu et al. suggest the use of anticoagulant in the early sign of elevated D-dimer in COVID-19 patients, they found that Dipyridamole (DIP), an antiplatelet, has the effectiveness to prevent hypercoagulability if given early in severe COVID-19 infection. It also has other benefits in COVID-19 infection such as broad spectrum of antiviral,[22] anti-inflammatory effect,[23] and anti-fibrotic effect.[24] DIP prevent the increased of D-dimer levels and increased platelet and leukocyte count.[22] Recent data showed data immune-thrombosis played a big role other than DIC.[25] In order to that modulation of inflammation could make a difference. Steroid and anti Il-6 could give several benefits in particular conditions.[26-28] By giving tocilizumab, anti Il-6 blocker for instance could improve inflammation parameters.[29] Several parameters D-Dimer and CRP had been proved as several severity markers in COVID-19.[30] These showed interaction between inflammation and thrombosis. Responses of inflammation to COVID-19 also influence by gut microbiota.[31] By modulating angiotensin-converting enzyme 2 may give benefit.[32] Others part also should concomitantly be controlled for instances the cardiovascular risk factors which also played extensive roles in COVID-19.[33,34] People have these cardiovascular risk factors should continue their medications[35-37], because in some particular conditions could give benefits to survival of COVID-19 when got infected.

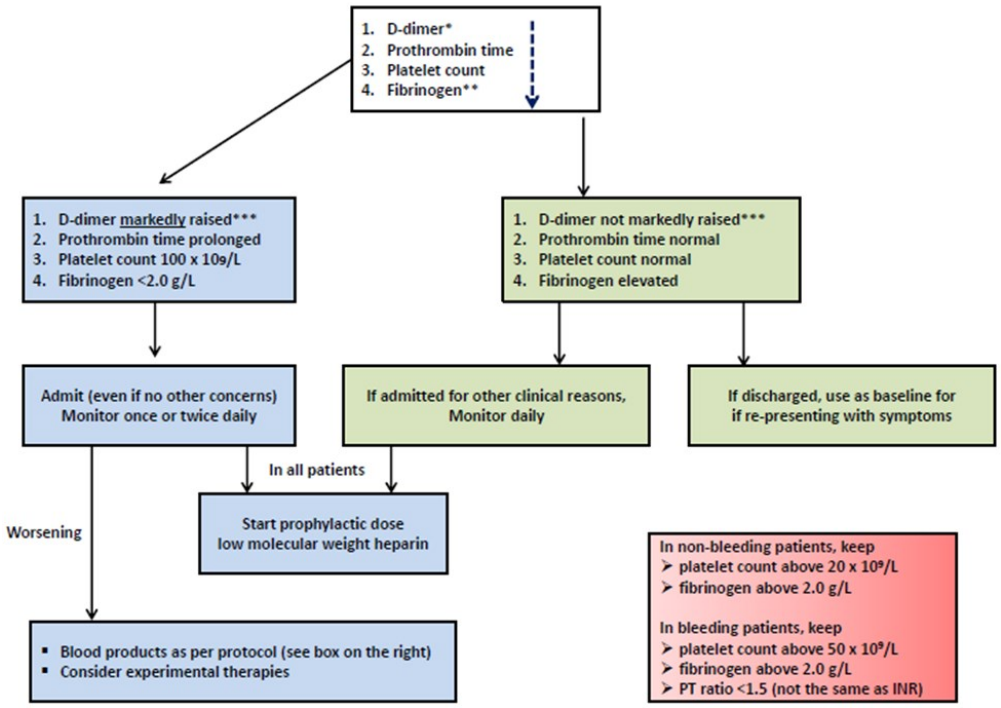

Figure 2. Algorithm for Management of Coagulopathy in COVID-19 Based on Simple Laboratory Markers. Cited from Thachil J, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. J Thromb Haemost [Internet]. 2020;n/a(n/a):0–2.

* The list of markers is given in the decreasing order of importance
** Performing fibrinogen assays may not be feasible in many laboratories but monitoring the levels can be helpful after patient admission
*** Although a specific cut-off cannot be defined, a 3 to 4 folds increase in D-dimer values may be considered significant

Conclusion

Coagulopathy plays a big role in determinate the prognosis of COVID-19 patients, DIC mostly appeared in died patients. D-dimer levels and FDP can be used to evaluate prognosis. In the guidance for DIC, D-dimer level, PT, platelet count, and fibrinogen measurement are recommended by ISTH and can be used in COVID-19 patients. LMWH in prophylactic doses should be given in all patient including non-critical patients who required hospital admission for COVID-19 infection if they didn't have any contraindications. Treatment with LMWH gave some benefits in COVID-19 patients, especially reduced mortality in patients with SIC score ≥ 4 and D-dimer levels >six-fold of the upper limit of normal.

Authorhsip contributions

Concept: A.K; Design: S.W.; Data Collection or Processing: S.W, A.K.; Analysis or Interpretation: S.W. , A.K.; Literature search: S.W., A.K., Writing: S.W, A.K.

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Late Intra-Uterine Fetal Demise with Fetal Hydrops: Challenges of Management Planning in Indonesia

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Abstract:

Intra-Uterine Fetal Demise (IUFD) is defined as death of human conception at age of 20 weeks' gestation or older or with a minimum 500-g birthweight before complete delivery from the mother and induced termination involved. In 2015, Indonesia has contributed a stillbirth rate of 13 out of 1,000 total births in which 17.1% of the cases were caused by congenital anomalies. Fetal Hydrops as a pathological condition in which there is an accumulation of fluid in fetal soft tissues and serous cavities. With the advancements of sonographic technology, identification of fetal hydrops has become uncomplicated. However, what remains a challenge is to investigate etiology and determine management. In order to plan proper management, the etiology of fetal hydrops must first be determined to predict the prognosis of fetal hydrops. In Indonesia; limited facilities and experts combined with high costs in etiology determination and management have complicated the matter. Furthermore, the strong influence of several Eastern communities' norms and religious views have further complicated both physicians and patients in decision making. In this report, we present a case of late intra-uterine fetal demise with fetal hydrops, whom was admitted on her 35 weeks age gestation. We performed elective Caesarean Section in order to deliver the stillborn fetus, with no significant post-operative complication. Unfortunately, this condition was actually diagnosed earlier during 20th weeks of gestation, hence advised to continue the pregnancy without further evaluation and information to the mother regarding the hydrops condition.

Introduction

Intra-Uterine Fetal Demise/Death (IUFD) or Stillbirth is a generally defined by World Health Organization (WHO) and American College of Obstetrics and Gynecology (ACOG) as death of human conception/fetus at age of 20 weeks' gestation or older or with a minimum 500-g birthweight, which occurs before complete delivery/expulsion/extraction from the mother and not considered as an induced termination of pregnancy. The term is further classified into different periods as: early/intermediate IUFD, if completed 20-27 weeks of gestation; and late IUFD, if completed 28 weeks of gestation and more.[1] Based on the data acquired by United Nation International Children's Emergency Fund (UNICEF) in 2015, Indonesia has contributed a neonatal mortality rate of 14 out of 1,000 total births

with a stillbirth rate of 13 out of 1,000 total births; the main causes of neonatal deaths in 2015 were prematurity (35,5%), birth asphyxia and trauma (21,6%), and congenital anomalies (17,1%).[2]

One condition of congenital anomalies associated with high fetal mortality is fetal hydrops. Fetal Hydrops or *Hydrops Fetalis* is described as a pathological condition in which there is an accumulation of fluid in fetal soft tissues (generalized skin edema) and serous cavities (commonly in peritoneal, pleural and pericardial cavities); This condition is often associated with placental thickening (placentomegaly) and polyhydramnios.[1,4,5] Currently, fetal hydrops is further divided into two etiological groups: (1) Immune Fetal Hydrops (IFH), associated with red cell alloimmunization; and (2) Non-Immune Fetal Hydrops (NIFH), mostly associated with abnormalities of: cardiovascular (20%), chromosomal (13%) and hematologic (12% cases, with alpha thalassemia accounts for 28-55% of case in Southeast Asia).[6]

Cause	Cases	Mechanism
Cardiovascular	17-35%	Increased central venous pressure
Chromosomal	7-16%	Cardiac anomalies, lymphatic dysplasia, abnormal myelopoiesis
Hematologic	4-12%	Anemia, high output cardiac failure; hypoxia (alpha thalassemia)
Infectious	5-7%	Anemia, anoxia, endothelial cell damage, and increased capillary permeability
Thoracic	6%	Vena caval obstruction or increased intrathoracic pressure with impaired venous return
Twin-twin transfusion	3-10%	Hypervolemia and increased central venous pressure
Urinary tract abnormalities	2-3%	Urinary ascites; nephrotic syndrome with hypoproteinemia
Gastrointestinal	0.5-4%	Obstruction of venous return; gastrointestinal obstruction and infarction with protein loss and decreased colloid osmotic pressure
Lymphatic dysplasia	5-6%	Impaired venous return
Tumors, including chorioangiomas	2-3%	Anemia, high output cardiac failure, hypoproteinemia
Skeletal dysplasias	3-4%	Hepatomegaly, hypoproteinemia, impaired venous return
Syndromic	3-4%	Various
Inborn errors of metabolism	1-2%	Visceromegaly and obstruction of venous return, decreased erythropoiesis and anemia, and/or hypoproteinemia
Miscellaneous	3-15%	
Unknown	15-25%	
SMFM. Nonimmune hydrops fetalis. Am J Obstet Gynecol 2015.		

Table 1.
Etiologies of Non-Immune Fetal Hydrops (Society of Maternal-Fetal Medicine Clinical Guideline, 2015)

Many studies have proven that fetal hydrops is a serious life-threatening condition for both fetal and maternal health. A retrospective study conducted by Yeom W et al (2005-2013) in Samsung Medical Center South Korea found 42 cases of fetal hydrops were identified out of 17,217 deliveries (24.4 per 10,000 deliveries); 23 of those fetal hydrops case died (4 IUFDs and 19 Neonatal Deaths, overall neonatal mortality rate 54.0%); 3 of those cases were electively terminated, with only 16 cases survived. [3] A similar study shows high fetal mortality rate (60% in NIHF) and low survival rate of less than 50% (almost two-thirds do not survive) with only 25%

survived without major morbidities. [7] One maternal complication most often

associated with fetal hydrops is mirror syndrome with overall rate of intrauterine death was 56%, and maternal morbidity risk of pulmonary edema in 21.4% cases with symptoms disappeared 4.8-13.5 days after delivery. Based on these studies, early diagnosis and giving proper management for fetal hydrops is fundamental and significant.

Identification of fetal hydrops has become uncomplicated with the advancements of sonographic technology throughout the past four decades. However, what remains a challenge is to investigate etiology and determine appropriate management for the pregnancy. Proper management, which ranges from referral for sub-specialty treatments to termination of pregnancy can only be decided upon knowing the prognostic predictor of fetal hydrops (gestational age and etiology); this makes determining etiology a mandatory first process prior to management planning. In Indonesia however, clinical considerations are made complicated due to: (1) limited availability of facilities and experts capable of evaluating etiology and executing proper management for fetal hydrops; (2) complex referral procedure to those facilities; and (3) Eastern norms and religious views toward controversial procedures that they deemed as a taboo (e.g. termination). These complicated matters of consideration have made it difficult for patients and physicians to decide what's best for the pregnancy.

Case Summary

A 21-year old (gravida 1, para 0, abortus 0) on her 35th week of gestation came for the first time to our outpatient department in Siloam Public Hospital Lippo Village for prenatal check-up. The patient had done several prenatal check-ups, once in each first, second and third trimester in another hospital by an obstetric and gynecologic specialist. She recalled that during previous 2D-ultrasound examinations done in another hospital; no major anatomic abnormalities were discovered during the first trimester; anatomical abnormalities became significantly visible during the second and third trimesters. The obstetrics and gynecology specialist advised the patient to return every month for follow-up prenatal examinations regarding the abnormal anatomical condition. The patient had previously done laboratory blood hemoglobin (Hb) examination during her sixth week of gestation to which her Hb was 10,1 g/dL which was considerably low; previous urine dipstick, Hepatitis B Surface Antigen (HbsAg), and anti-HIV showed no significant abnormalities. She denied having previously tested for TORCH (Toxoplasma, Rubella, Cytomegalovirus and Herpes). The patient admitted that she consumes routine folic acid and ferrous sulfate medication. Throughout the recent two-weeks before she came to our outpatient department, the patient complaint that her stomach felt distended and no fetal movements were felt.

2D-Ultrasound imaging was performed in our clinic, revealed a single intrauterine pregnancy in transverse lie position, with absent fetal heartbeat and fetal movement suggestive of intrauterine fetal demise, biometry was appropriate to 35 weeks of gestation (according to Head Circumference in Hadlock Standard). Scalp edema [Figure 1], pericardial effusion [Figure 2], pleural effusion/hydrothorax [Figure 2 and 3] and ascites [Figure 4] were noted suggestive of fetal hydrops. Polyhydramnios was highlighted with Maximum Vertical Pocket (MVP) measured 122,8 mm (normal 20 - 80 mm) [Figure 5]. 4D-Real Time Rendering was done, severe scalp and facial edema; facial cleft; and no fetal movement was observed [Figure 6].

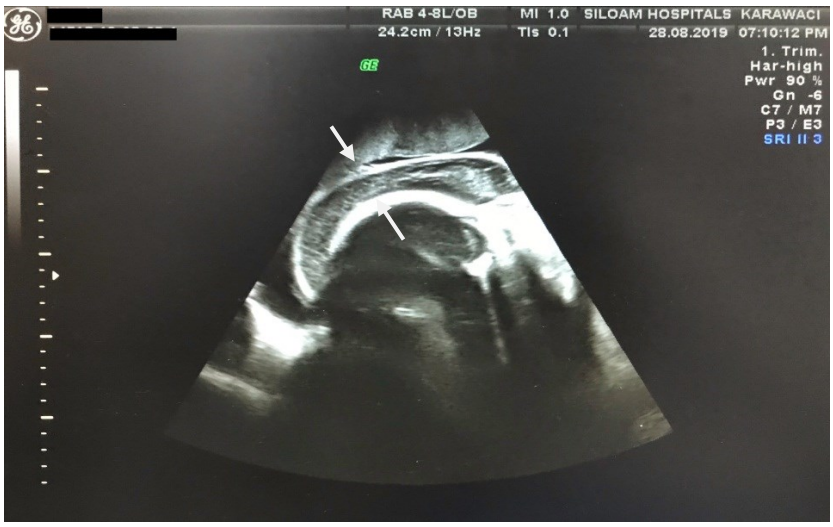

Figure 1.
2D Transabdominal Ultrasound showed extracranial scalp edema (between arrows) of the fetal head at 35 weeks' gestation. (the patient has consented for usage in this case report)

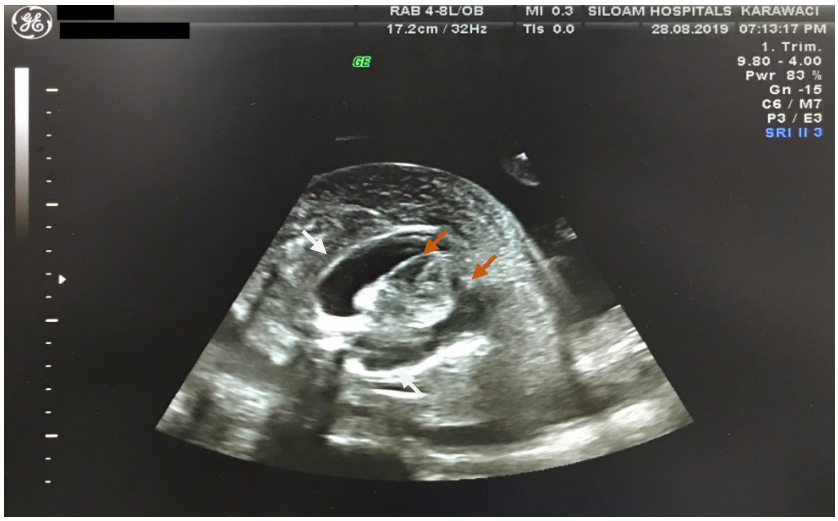

Figure 2.
2D Transabdominal Ultrasound cross-sectional view of the fetal thoracic cavity at 35 weeks' gestation. Note slight pericardial effusion (brown arrows) and bilateral pleural effusion (white arrows).(the patient has consented for usage in this case report)

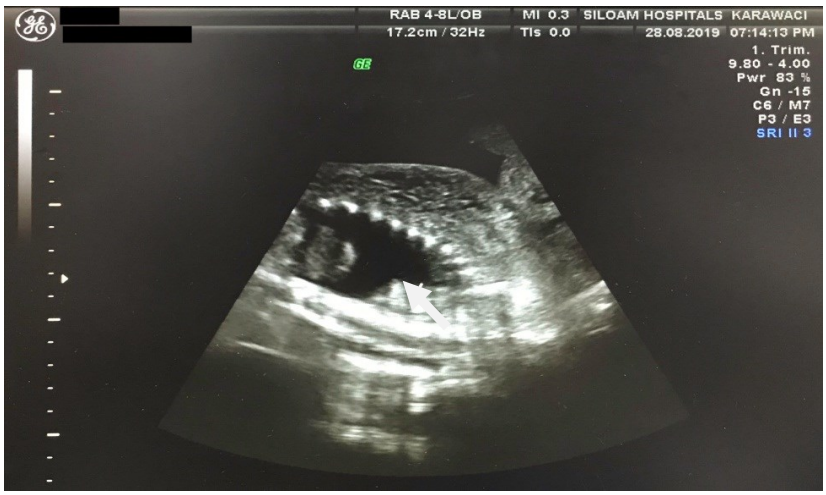

Figure 3.
2D Transabdominal Ultrasound longitudinal view of fetal thoracic cavity at 35 weeks' gestation. Note pleural effusion and hydrothorax (white arrow). (the patient has consented for usage in this case report)

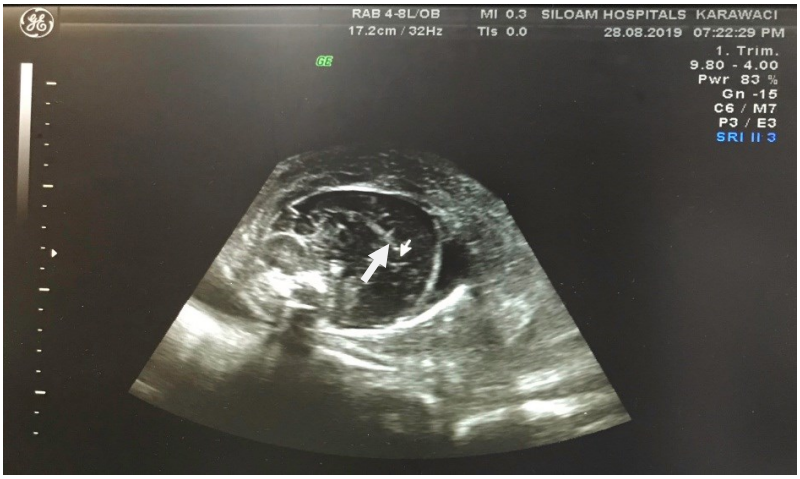

Figure 4.
2D Transabdominal Ultrasound cross-sectional view of fetal abdominal cavity at 35 weeks' gestation. Note ascites (white arrow). (the patient has consented for usage in this case report)

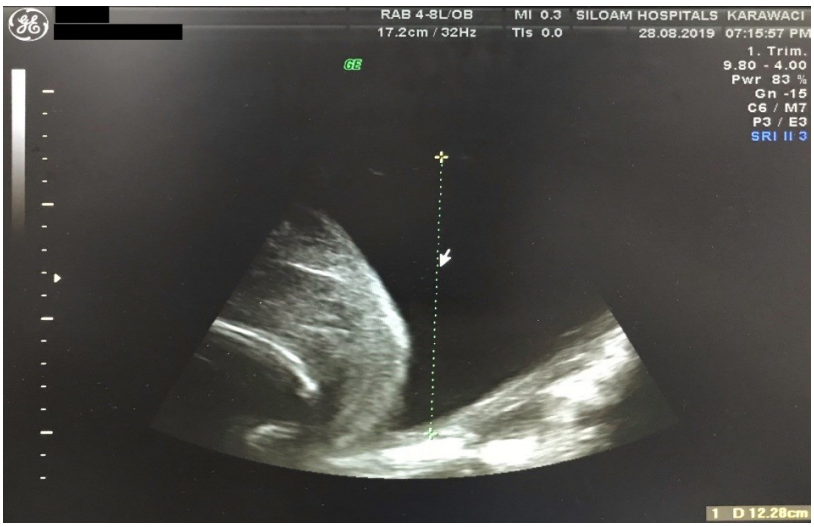

Figure 5.
2D Transabdominal Ultrasound longitudinal view of the patient's intrauterine cavity. Maximum Vertical Pocket (MVP) measured 122,8 mm (normal 20 - 80 mm) signified polyhydramnios. (the patient has consented for usage in this case report)

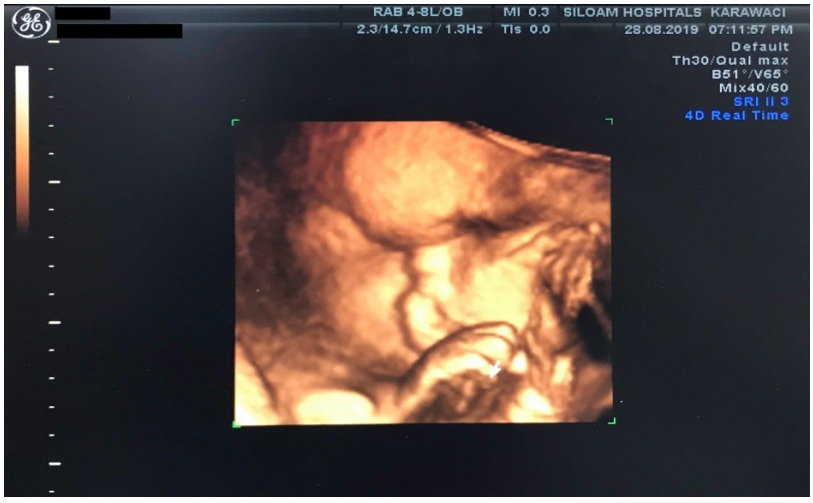

Figure 6.
4D Real Time Rendering Ultrasound of the fetal face at 35 weeks' gestation. Note severe scalp and facial edema with facial cleft. No fetal movement was observed. (the patient has consented for usage in this case report

Given the severity of the clinical picture, the patient was convinced to undergo elective caesarean section with the indication of transverse fetal lie based on ultrasonography imaging. Maternal pre-operative complete blood count was performed in which the patient has low hemoglobin (Hb) of 10.20 g/dL (normal 11.70 - 15.50 g/dL), hematocrit (Ht) of 31.10 % (normal 35.00 - 47.00 %), Erythrocyte (RBC) of 4.99 millions/uL, mean corpuscular volume (MCV) of 62.32 fL (normal 80.00 - 100.00 fL), mean corpuscular hemoglobin (MCH) of 20.44 pq (normal 26.00 - 34.00 pq), and mean corpuscular hemoglobin concentration (MCHC) of 32,7 g/dL suggestive of microcytic hypochromic anemia. The Mentzer index which is a ratio equivalent to MCV (fL) divided by RBC (millions/uL) for this patient is 12,70 suggestive of possible thalassemia trait (Mentzer Index <14 suggestive of thalassemia, >14 suggestive of iron deficiency anemia). At birth, the macerated late stillborn at 35 weeks' gestation with fetal weight of 3175 grams and head circumference of 40 cm presented with severe hydrops, cyanotic, apneic with no movement observed [Figure 7]. The placenta was edematous and large. Further post-mortem fetal laboratory and evaluation was not performed. Post-operative course was uneventful. The patient and her husband was counselled to take complete hematologic, immunologic and if necessary seek for genetic counseling before the next pregnancies to come.

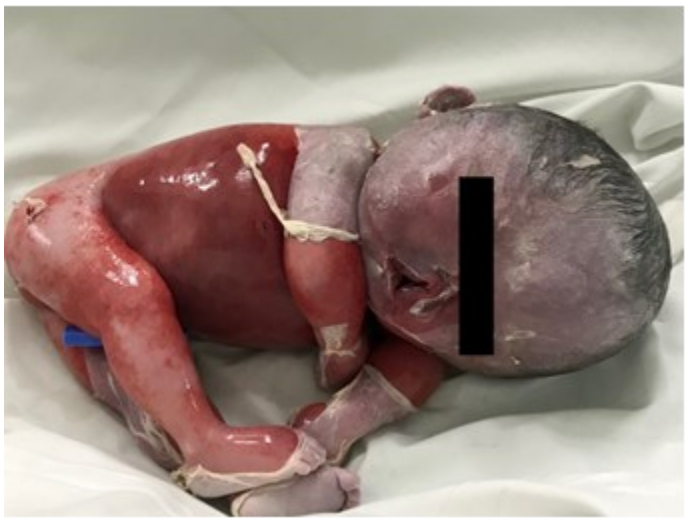

Figure 7.
Post-delivery via Caesarean Section showed macerated late stillborn infant at 35 weeks' gestation presented with severe hydrops, cyanotic, and apneic with no fetal movement observed.(the patient has consented for usage in this case report)

Discussion

The diagnosis of fetal hydrops can be made on the basis of 2D-Transbdominal/gray-scale ultrasonography as showed in Figure 1-5. The diagnosis of fetal hydrops is made if accumulation of fluid can be found in at least two interstitial cavities (pericardial, pleural, or peritoneal) or in one cavity plus generalized edema/anasarca. In order to plan for proper management, The Society of Maternal-Fetal Medicine Clinical Guideline mentioned that decisions will depend on the gestational age and etiology in which the cause is treatable or untreatable, hence determining specific etiology of fetal hydrops is truly necessary.[4] Etiology determination of fetal hydrops require several examinations which includes: hematology (Blood Count, Indirect COOMBS Test, G6PD Test, and Hemoglobin Electrophoresis to rule out any inborn error of metabolism and thalassemia hemoglobinopathy), amniocentesis (Fetal karyotyping for B19 parvovirus, cytomegalovirus, and toxoplasmosis to rule out those infections respectively), and genetic profiling (Chromosome Analysis for fetal anomalies). [1,4]

Proper refferal and early effective management in capable facilities will reduce both maternal (e.g. Mirror Syndrome) and fetal (e.g. intra-uterine fetal death) complications, which will be discussed further. In spite of that, determining specific etiology is still a challenge in Indonesia due to: limited availability of facilities, experts, high costs and complex referral procedure to those facilities. Not all facilities are capable of performing the examinations mentioned above due to lack of technologies and experts (e.g. fetal-maternal subs-specialists for amniocentesis). Referral to ideal facilities with capable technologies and experts (e.g. Harapan Kita Fetal-Maternal Center in Jakarta) can be complicated due to geographical proximity (far distance) from many referring facilities, especially those located outside Jakarta. This makes the patient to consider not to be referred and instead be managed in local or current facilities with limited capabilities. Furthermore, some of the examinations mentioned above are expensive and are not covered by national health insurance; hence, this reality reduced the willingness of a majority of patients with lower socioeconomic class to be referred to ideal facilities. For this patient, we could only perform complete blood count and microcytic hypochromic anemia was noted, other examinations were not performed due to restricted economic condition and limited financial coverage. We asked the patient for any suggestions of referral to fetal-maternal experts offered during her previous prenatal check-ups, in which she didn't remember.

Hematologic disorders contributed as the cause of approximately 7-12% of non-immune fetal hydrops (NIFH) cases. One hematologic disorder known to cause immune fetal hydrops (IFH) is blood group alloimmunization, however it only occurred in less 10% of all fetal hydrops cases. [5] As majority of hematologic disorders more likely to cause non-immune fetal hydrops (NIFH), hemoglobinopathies such as alpha thalassemia accounts for 28-55% of cases in Southeast Asia. [5] Alpha-thalassemia is primarily caused due to reduction in synthesis of alpha-globulin chains located on chromosome 16p13.3. Mutations or deletions that affect one or more alpha globulin genes, most frequently single-gene deletion or inactivation of only one alpha globin chain may cause mild hematologic finding known as alpha thalassemia carrier. Inactivation of two alpha globulin chains results in a mild microcytic hypochromic with normal or altered Hb A2 levels, a condition known as alpha thalassemia trait. [8] The Mentzer index is one predictive indicator of thalassemia trait possibility (Sensitivity/Sn 0.36, Specificity/Sp 0.81, positive predictive value/PPV 0.44 and negative predictive value/NPV 0.75), calculated as a ratio equivalent to MCV (fL)

divided by RBC (millions/uL) (Mentzer Index <14 suggestive of thalassemia, >14 suggestive of iron deficiency anemia). [9] Definite diagnosis of thalassemia cannot be determined only by this predictive indicator, further hematologic examinations such as iron profiling (serum iron, total iron binding capacity and serum ferritin), hemoglobin electrophoresis and if possible cytogenetic evaluation is still necessary to exclude other possibility of mild microcytic hypochromic anemia etiology (iron deficiency anemia/IDA) and to determine hemoglobinopathy types (thalassemia types). [1,4] In this patient, Mentzer Index of 12,70 is obtained, which suggests a possibility of thalassemia trait in the patient. We still cannot determine definite etiology of fetal hydrops in this case, since other examinations couldn't be performed due to restricted economic condition and limited financial coverage as mentioned above. Post mortem detailed anatomic survey of the infant is also necessary as additional information can be gathered to determine specific etiology of fetal hydrops. [1] Unfortunately, in this case, the patient (mother) refused for the infant to undergo further examinations.

Etiology	Therapy	Recommendation
Cardiac tachyarrhythmia, supraventricular tachycardia, atrial flutter, or atrial fibrillation	Maternal transplacental administration of antiarrhythmic medication(s)	Treatment with antiarrhythmic medication unless gestational age is close to term or there is maternal or obstetrical contraindication to therapy
Fetal anemia secondary to parvovirus infection or fetomaternal hemorrhage	Fetal blood sampling followed by intrauterine transfusion	Fetal intrauterine transfusion if anemia is confirmed, unless pregnancy is at an advanced gestational age and risks associated with delivery are considered to be less than those associated with delivery are considered to be less than those associated with procedure
Fetal hydrothorax, chylothorax, or large pleural effusion associated with bronchopulmonary sequestration	Fetal needle drainage or effusion or placement of thoracoamniotic shunt; if gestational age is advanced, needle drainage prior to delivery in selected cases	Consider drainage of large unilateral pleural effusion(s) resulting in NIHF, or, if gestational age is advanced, consideration of needle drainage prior to delivery
Fetal CPAM	Macrocystic type: fetal needle drainage of effusion or placement of thoracoamniotic shunt Microcystic type: maternal administration of corticosteroids, betamethasone 12.5 mg IM q24h x 2 doses or dexamethasone 6.25 mg IM q12h x 4 doses	Consider drainage of large macrocystic CPAM that has resulted in NIHF; if large microcystic CPAM has resulted in NIHF, we suggest that management options include maternal corticosteroid administration
TTTS or TAPS	Laser ablation of placental anastomoses or selective termination	Consideration of fetoscopic laser photocoagulation of placental anastomoses for TTTS or TAPS that has resulted in NIHF < 26 weeks
Twin-reversed arterial perfusion sequence	Percutaneus radiofrequency ablation	Refferal for consideration of percutaneus radiofrequency ablation that has resulted in NIHF
For each of these etiologies, it is recommended that treatment be performed at tertiary care center or center with expertise in relevant therapy. ***CPAM:*** *congenital pulmonary airway malformation;* ***IM:*** *intramuscular; NIHF: nonimmune hydrops fetalis;* ***TAPS:*** *twin-anemia polycythemia sequence;* ***TTTS:*** *twin-twin transfusion sequence.* *SMFM. Nonimmune hydrops fetalis. Am J Obstet Gynecol 2015.*		

Table 2.
Therapy for selected etiologies of nonimmune hydrops
(Society for Maternal-Fetal Medicine Clinical Guideline, 2015)

After specific etiology determined, cases generally classified as: (1) amenable to therapy and urgently treatable cases in which treatment [Table 2] or referral to a specialized center is necessary, (2) lethal prognosis cases (other cases not mentioned in Table 2) in which termination might be offered and (3) idiopathic with uncertain but likely poor prognosis in which termination might also be offered.[4] Note that pregnancy termination should be offered after fetal hydrops is identified and as early as possible before fetus reach viability. Patients amenable to therapy who declines therapy or unable to receive therapy will have poor prognosis. Patients with treatable or non-lethal etiology of fetal hydrops who has reached viable gestational age (28 gestational weeks) is a candidate for antepartum fetal surveillance in order to determine optimal time and mode of delivery. If there is absence in clinical deterioration and complications (e.g. mirror syndrome), delivery by 37-38 weeks should be considered. Mirror syndrome also known as Ballantyne's syndrome is one maternal complication of fetal hydrops in which the mother develops edema that "mirror" that of her hydropic fetus; characterized by edema in approximately 90%, hypertension in 60%, and proteinuria in 40% similar to preeclamsia; with overall rate of intrauterine death was 56%, and maternal risk of pulmonary edema in 21.4% cases; symptoms disappeared 4.8-13.5 days after delivery. [1,4,10] Fetuses with hydrops are at high risk of preterm delivery and hemodynamic compromise, hence corticosteroid treatment is reasonable from gestational age 24-34 weeks if the etiology is deemed non-lethal and if intervention (Table 2) planned.

Management planning for fetal hydrops in Indonesia is also challenging and complicated due to Eastern norms and religious views toward controversial procedures such as termination of pregnancy, which is considered as an act of murder and therefore it cannot be tolerated even with medical indication. The challenges that most physicians face during management planning for fetal hydrops are as follows: (1) if they found out that the etiology of the patient is amenable to treatment, some patient would most likely refuse due to high costs and far distance of referral as mentioned above; (2) In the contrary, if they found out that the etiology of the fetal hydrops has lethal prognosis or idiopathic with uncertain prognosis in which termination could be offered, some physicians hesitate to offer that option due to norms and religious views and some patient would most likely to refuse as well. Hence, the dilemma still persists until now.

We believe that in this complicated and challenging condition, proper counselling to the patient must still be done; since the patient still has the right to know about her condition, and therefore this could prevent misunderstanding, confusion and disappointments. Counselling for pregnancies with fetal hydrops should include potential risk, benefits, and possible alternatives of intervention possible regarding the underlying condition. Hence, the patient in our case has the right to know about the condition. [4]

Optimal mode of delivery depends on findings of antepartum surveillance, drainage of large effusion may improve efficacy of neonatal resuscitation, vaginal delivery is preferred unless otherwise contraindicated. [4] In this patient, caesarean delivery is preferred since the fetus is in transverse lie which is an absolute indication. [1] Delivery in a center with neonatal intensive-care unit must be considered if the fetal hydrops has an idiopathic etiology and potentially require postnatal treatment. [4] For future pregnancies, the patient was advised to do routine prenatal screening, complete hematological screening (complete blood count, red cell index, iron profiling, and Hb electrophoresis), immunological infection screening (TORCH and Parvovirus B19), if possible cytogenetic evaluation and genetic counselling to prevent similar consequences. [1,4,5]

Conclusion

Identification of fetal hydrops has become uncomplicated with the advancements of sonographic technology throughout the past four decades, however what remains a challenge is to investigate etiology and determine appropriate approach for the pregnancy. Since appropriate approach and therapy can only be achievable by first determining the specific etiology, hence etiology evaluation of fetal hydrops is fundamental. In Indonesia however, clinical considerations are made complicated due to: limited availability of facilities and experts capable of evaluating etiology and executing proper management for fetal hydrops; complex referral procedure to those facilities; and Eastern norms and religious views toward controversial procedures that they deemed as a taboo (e.g. termination).

Even with all its difficulties, counselling for pregnancies with fetal hydrops is still necessary; and counselling should include potential risk, benefits, and possible alternatives of intervention possible regarding the underlying condition; since the patient still has the right to know about her pregnancy condition.

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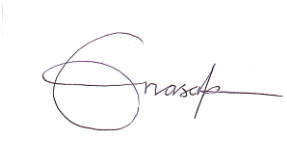

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