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Buku

Winn WC, Allen SD, Janda WM, Koneman EW, Procop GW, Schreckenberger PC, et al. Koneman’s color atlas and textbook of diagnostic microbiology. 5th eds. Philadelphia: A Wolters Kluwer Company; 2006. p.1065-92.

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Original Article

Adverse Events Following Immunization of mRNA and Inactivated Vaccines Against COVID-19 at Universitas Indonesia Hospital: A Cross-Sectional Study

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Abstract

Background: The coronavirus that causes severe acute respiratory syndrome (COVID-19) is coronavirus 2 (SARS-CoV- 2). This virus has caused a global pandemic. The adverse impact of this virus in the past two years has resulted in efforts to build herd immunity through vaccination. This study aimed to identify the side effects after getting the *Pfizer* and *Sinovac* vaccines at the Universitas Indonesia Hospital and the risk factors for Adverse Events Following Immunization (AEFI).

Methods: This observational study used a descriptive, non-experimental method with a cross-sectional design. Google Forms was used to collect data.

Results: The onset of AEFI symptoms ranged from 15 minutes to 24 hours. The common AEFI symptoms were pain at the injection site, fatigue, muscle aches, and joint pain. The AEFI severity was mostly at the mild level, and only a few participants took medication. Female participants, participants with comorbidities and allergies, previous medication histories within the last 6 months, and those with experience of COVID-19 had a higher risk for AEFI with a statistically significant effect (P <0.005).

Conclusion: This study revealed that *Pfizer* and *Sinovac* COVID-19 vaccines were safe to administer as the AEFIs were mostly mild and automatically disappeared and decreased after 1 to 3 days.

Keywords: AEFI, COVID-19, Pfizer, Sinovac, vaccine

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INTRODUCTION

The coronavirus that causes severe acute respiratory syndrome (COVID-19) is coronavirus 2 (SARS-CoV-2). Global pandemic brought on by this virus. There were 27 people with pneumonia in Wuhan, Hubei Province, China, in late 2019. The virus spread quickly across the globe.[1] Indonesia recorded zero cases from December 2019 to February 2020, when China was severely affected by the novel coronavirus/SARS-CoV-2. On March 2, 2020, President Joko Widodo announced Indonesia's initial two COVID-19 infections. Given that Indonesia has the fourth-highest population in the world, more hardship is anticipated there than in other, less crowded nations.[2]

The severe impact of COVID-19 in the past two years has resulted in global efforts to build herd immunity, starting from the individual level and reaching the population level.[3] Referring to national data, a total of 202,623,385 people (97%) have received the first dose of vaccine, while a total of 170,201,649 people (81%) have received the second dose, and a total of 56,829,093 people (24%) have received the third dose (updated on August 4, 2022). At least 70–85% of the population must receive vaccinations in order to acquire herd immunity. Public perceptions change along with the changing condition of the pandemic.[4]

There is currently no licensed coronavirus vaccine for human use. Therefore, the rapid research and development cycle and the scant post-vaccination monitoring raise significant public concerns regarding the safety of the COVID-19 vaccine candidate, particularly for the new platform of RNA vaccines. A common defence for not having the immunization is that there are "concerns regarding the safety of the vaccine in development" and "potential harmful effects". Since the widespread use of vaccination, adverse events following immunization (AEFI), particularly the rare ones, have increased.[5] The AEFI should be monitored for at least

four reasons, according to the Indonesian Society of Internal Medicine (PAPDI). First of all, no vaccine is completely risk-free and safe. Second, it is critical to understand the dangers and how to manage them as they manifest. Third, to preserve public confidence in the immunization program, it is crucial to notify the public about AEFIs appropriately. Lastly, monitoring AEFIs contributes to better service quality.[6]

In consideration of the COVID-19 history, certain unfriendly public impressions surrounding the vaccine's side effects, the low level of AEFI reports, and limited scientific evidence of AEFI in Indonesia, based on the severity of AEFIs at Universitas Indonesia Hospital, researchers were motivated to conduct this study to discover the potential risks that might influence the vaccine's efficacy.

METHODS

This observational study assessed the effectiveness of *Pfizer* and *Sinovac* vaccines using a non-experimental, descriptive, cross-sectional study design. Research participants who received vaccinations at Universitas Indonesia Hospital were directly interviewed to gather data prospectively. Besides, this study used online forms to collect the required information from participants. The information was then categorized, and monitoring was done for 28 days. This research was conducted at the Universitas Indonesia Hospital in August to September 2022.

Data monitoring was carried out successively based on the following timeline. The timeline for monitoring AEFI events was performed in the first 15 minutes of observation at the hospital, 15 minutes to 24 hours, 24 to 48 hours, 48 hours to 7 days and the next 7 to 28 days, respectively. A Google Form in Bahasa was created with a 5-minute completion time for the questionnaire to evaluate AEFI. Therefore, according to the timeframe for the research at the Universitas Indonesia Hospital, the questionnaire covered an AEFI evaluation with five steps.

Participants completed a survey in the Google Form containing information about their personal identity, medical conditions, and perceived AEFI complaints. According to the timeline, the questionnaire data was collected in five stages. Personal data in the questionnaire covered name, gender, telephone number, date of birth, weight and height, blood type, occupation, the previous dose of vaccine, and the dose received during vaccination at the Universitas Indonesia Hospital during recruitment. The questionnaire's medical information also included comorbidities, allergy and COVID-19 histories, hospitalizations in the last three months, and drug use in the previous six months. The questionnaire had closed-ended inquiries concerning AEFI matters. The questionnaire sheet used in the survey is shown in the Supplementary Data 3. The information from the questionnaire was entered into a Microsoft Excel sheet and statistically examined using SPSS 25 and Microsoft Excel. The incidence of AEFI was compared with gender, age, BMI, comorbidities, vaccine types, history of allergies, prior COVID-19, history of hospital admission in the previous three months, and history of medication in the last six months using the Chi-square test. The significance level (P=0.05) was applied to perform statistical comparisons.

The Universitas Indonesia Hospital Ethics Committee had accepted this study under approval number S-033/KETLIT/RSUI/VIII/2022 with protocol number 2022-07-165.

RESULTS

In total, 272 participants were surveyed to obtain a minimum sample of 137 participants. However, only 261 subjects agreed to participate in the study by completing the given online form and meeting the inclusion and exclusion criteria. Of the total of 261 participants, the mean age was 29.88±10.86 years (mean±standard deviation (SD)). The participants consisted of 148 females (57%) and 113 males (43%). The average body mass index (BMI) was 22.9±0.86, with the highest BMI category of underweight - normal (<18.5–24.9) with a total of 187 participants (72%).

Two groups were formed from the participants. The first group had 149 people (57%) who received

the *Pfizer* (BNT162b2) vaccination, while the second group had 112 individuals (43%) who received the *Sinovac* vaccine. Only 31 participants (12%) had comorbidities and 54 participants (21%) took medication in the last 6 months. A total of 13 participants (5%) experienced a hospitalization within the past three months. Meanwhile, participants who had a history of allergies and COVID-19 were 31 participants (12%) and 81 participants (31%), respectively. Table 1 describes the specific participant characteristics in detail.

Overall, the AEFI was divided into 4 monitoring period, namely the initial 15 minutes during hospital observation, 15 minutes to 24 hours, 24 hours to 48 hours, and 48 hours to 7 days. In the initial 15 minutes, a total of 197 participants (75%) experienced AEFI.

Table 1. Characteristics of the Participants

Variable	Category	Frequency	Percentage
Age	Mean±SD	29.88±10.86	
	Adolescence aged ≤25 years	116	44%
	Adulthood aged 26-45 years	109	42%
	Elderly aged >45 years	36	14%
Gender	Female	148	57%
	Male	113	43%
Body Mass Index (BMI)	Mean±SD	22.9±0.86	
	Underweight - Normal (<18.5 to 24.9)	187	72%
	Overweight - Obese (25 to ≥27)	74	28%
Vaccine types	BNT162b2 (*Pfizer)*	149	57%
	Sinovac	112	43%
Vaccine variation	*Pfizer*	8	3%
	Pfizer + *Pfizer*	14	5%
	Sinovac + *Sinovac*	11	4%
	Sinovac + *Sinovac* + *Sinovac*	91	35%
	Sinovac + *Sinovac* + *Pfizer*	23	9%
	Pfizer + *Pfizer* + *Pfizer*	23	9%
	Astrazeneca + *Astrazeneca* + *Pfizer*	19	7%
	Moderna + *Moderna* + *Pfizer*	8	3%
	Sinovac + *Sinovac* + *Sinovac* + *Sinovac*	10	4%
	Sinovac + *Sinovac* + *Pfizer* + *Pfizer*	14	5%
	Sinovac + *Sinovac* + *Moderna* + *Pfizer*	34	13%
	Astrazeneca + *Astrazeneca* + *Pfizer* + *Pfizer*	6	2%
Dose	1st dose *Pfizer*	8	3%
	2nd dose *Pfizer*	14	43%
	3rd dose *Pfizer*	73	28%
	4th dose *Pfizer*	54	43%
	2nd dose *Sinovac*	11	43%
	3rd dose *Sinovac*	91	35%
	4th dose *Sinovac*	10	43%
Comorbidity	No	230	88%
	Yes	31	12%
History of allergy	No	229	88%
	Food allergy	28	11%
	Drug allergy	4	2%
Hospitalization in the last 3 months	No	248	95%
	Yes	13	5%
History of medication in the last 6 months	No	207	79%
	Yes	54	21%
History of COVID-19	No	180	69%
	Yes	81	31%

Table 2. AEFIs and the severity levels in the initial 15 minutes observation at the hospital and in 15 minutes to 24 hours

AEFI	15 minutes				15 minutes – 24 hours			
	Mild	Moderate	Severe	PLT	Mild	Moderate	Severe	PLT
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Local Adverse Events								
Pain at the injection site	103 (39.5)	24 (9.2)	0 (0.0)	0 (0.0)	134 (51.3)	25 (10.0)	0 (0.0)	0 (0.0)
Redness/erythema	4 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	17 (6.5)	2 (1.0)	0 (0.0)	0 (0.0)
Swelling/induration	19 (7.3)	2 (0.8)	1 (0.4)	0 (0.0)	24 (9.2)	6 (2.0)	1 (0.4)	0 (0.0)
Itching/pruritus associated with injection	6 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)	17 (6.5)	1 (0.4)	0 (0.0)	0 (0.0)
Systemic Adverse Events								
Pain in the legs	24 (9.2)	4 (1.5)	0 (0.0)	0 (0.0)	34 (13.0)	5 (1.9)	0 (0.0)	0 (0.0)
Fever	36 (13.8)	0 (0.0)	0 (0.0)	0 (0.0)	43 (16.5)	2 (0.8)	0 (0.0)	0 (0.0)
Nausea/vomiting	4 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	9 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)
Headache	31 (11.9)	8 (3.1)	1 (0.4)	0 (0.0)	37 (14.2)	8 (3.1)	1 (0.4)	0 (0.0)
Fatigue	70 (26.8)	27 (10.3)	1 (0.4)	0 (0.0)	91 (34.9)	28 (10.7)	1 (0.4)	0 (0.0)
Myalgia	44 (16.9)	15 (5.7)	0 (0.0)	0 (0.0)	54 (20.7)	18 (6.9)	0 (0.0)	0 (0.0)
Acute allergic reaction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rash	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Joint pain	34 (13.0)	14 (5.4)	1 (0.4)	0 (0.0)	54 (20.7)	17 (6.5)	3 (1.1)	0 (0.0)
Other adverse event	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Note: PLT=*Potentially Life-Threatening*

Table 3. AEFIs and the severity levels at 24 to 48 hours and 48 hours to 7 days

AEFI	24 to 48 hours				48 hours to 7 days			
	Mild	Moderate	Severe	PLT	Mild	Moderate	Severe	PLT
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Local Adverse Events								
Pain at the injection site	72 (27.6)	3 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Redness/erythema	7 (2.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Swelling/induration	13 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Itching/pruritus associated with injection	9 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Systemic Adverse Events								(0.0)
Pain in the legs	16 (6.1)	1 (0.4)	0 (0.0)	0 (0.0)	7 (2.7)	0 (0.0)	0 (0.0)	0 (0.0)
Fever	26 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	9 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea/vomiting	4 (1.5)	1 (0.4)	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Headache	32 (12.3)	5 (1.9)	0 (0.0)	0 (0.0)	16 (6.1)	4 (1.5)	0 (0.0)	0 (0.0)
Fatigue	49 (18.8)	10 (3.8)	1 (0.4)	0 (0.0)	16 (6.1)	2 (0.8)	1 (0.4)	0 (0.0)
Myalgia	36 (13.8)	3 (1.1)	0 (0.0)	0 (0.0)	15 (5.7)	0 (0.0)	0 (0.0)	0 (0.0)
Acute allergic reaction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rash	0 (0.0)	0 (0.0)	0 (0.0)	0 90.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Joint pain	31 (11.9)	4 (1.5)	0 (0.0)	0 (0.0)	16 (6.1)	1 (0.4)	0 (0.0)	0 (0.0)
Other adverse event	3 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)

Note: PLT=*Potentially Life-Threatening*

Then, in the 15 minutes to 24 hours of monitoring, a total of 215 participants (82%) experienced an increase in AEFI from the previous monitoring. In the 24 to 48 hours monitoring and 48 hours to 7 days monitoring, the incidence of AEFI decreased to 133 participants (50%) and 57 participants (21%).

Table 2 shows that in the initial 15 minutes after vaccination, participants reported 3 main complaints: 130 participants (39.5%) experienced pain at the injection site, 70 (26.8%) experienced fatigue, and 44 (16.9%) participants experienced myalgia with mild severity based on the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials issued by the Food and Drug Administration.

At moderate severity in the initial 15 minutes, the main complaint felt by participants was fatigue in 27 participants (10.3%), followed by pain at the injection site and myalgia. At severe severity in the initial 15 minutes, there was 1 participant in each AEFI category, namely swelling/induration, headache, fatigue and joint pain. At 15 minutes to 24 hours of monitoring (Table 2), there was an increase

in the incidence of AEFI with mild severity, where 134 participants (51.3%) experienced pain at the injection site, 91 participants (34.9%) experienced fatigue, and 20.7% of the participants experiencing myalgia and joint pain.

Table 3 shows the incidence of AEFI at 24 hours to 48 hours and 48 hours to 7 days of monitoring. In 24 to 48 hours of monitoring, there was a decrease in the incidence of AEFI from 134 participants (51.3%) to 72 participants (27.6%) experiencing pain at the injection site. Then, the number of participants experiencing fatigue of mild severity decreased from 91 participants (34.9%) to 49 participants (18.8%). At moderate severity, there was also a decrease from 28 participants (10.7%) to 10 participants (3.8%). On monitoring for 48 hours to 7 days (Table 3), there was no longer any AEFI at the injection site. The most common complaints during 48 hours to 7 days monitoring were headache, fatigue and joint pain. The detailed information is presented in the following table.

Table 4 shows that, with a $P<0.05$, the incidence of AEFI in the first 15 minutes was affected by gender, BMI, vaccine types, comorbidities, history of allergic reactions, taking medication during the previous 6 months, and a prior COVID-19 infection. Meanwhile, monitoring from 15 minutes to 24 hours revealed that the risk factors of gender, vaccine types, comorbidities, history of allergic reactions, taking medication in the previous 6 months, and prior COVID-19 infection all had a $P<0.05$ on the incidence of AEFI.

The incidence of AEFI was affected by gender, age, vaccine types, history of allergic reactions, and previous COVID-19 infection in the 24 to 48 hours monitoring ($P<0.05$), as shown in Table 5.

Table 4. Risk factors affecting AEFI in the initial 15 minutes and 15 minutes to 24 hours

Risk factor	AEFI in 15 minutes				AEFI in 15 minutes to 24 hours			
	No AEFI n (%)	AEFI n (%)	*P*	OR (95% CI)	No AEFI n (%)	AEFI n (%)	*P*	OR (95% CI)
Gender								
Female	27 (18.2)	121 (81.8)	0.009	0.458 (0.258-0.813)	16 (10.8)	132 (89.2)	0.002	0.335 (0.172-0.653)
Male	37 (32.7)	76 (67.3)			30 (26.5)	83 (73.5)		
Age								
≤25 years	27 (23.3)	89 (76.7)	0.215	-	20 (17.2)	96 (82.8)	0.071	-
26–45 years	24 (22.0)	85 (78.0)			15 (13.8)	94 (86.2)		
>45 years	13 (36.1)	23 (63.9)			11 (30.6)	25 (69.4)		
Body Mass index (BMI)								
Underweight-normal (<18.5 to 24.9)	35 (18.7)	152 (81.3)	0.001	0.357 (0.197-0.647)	29 (15.5)	158 (85.5)	0.155	0.615 (0.315-1.204)
Overweight - obese (25 to ≥27)	29 (39.2)	45 (60.8)			17 (23.0)	57 (77.0)		
Vaccine type								
Pfizer	24 (16.1)	125 (83.9)	<0.001	2.894 (1.615-5.185)	15 (10.1)	134 (89.9)	<0.001	3.419 (1.74-6.717)
Sinovac	40 (35.7)	72 (64.3)			31 (27.7)	81 (72.3)		
Comorbidities								
No	62 (27)	168 (73)	0.013	5.351 (1.24-23.093)	45 (19.6)	185 (80.4)	0.023	7.297 (0.969-54.945)
Yes	2 (6.5)	29 (93.5)			1 (3.2)	30 (96.8)		
History of allergic reactions								
No	62 (27.1)	167 (72.9)	0.008	5.569 (1.292-23.997)	45 (19.7)	184 (80.3)	0.023	7.582 (1.008-57.028)
Yes	2 (6.3)	30 (93.8)			1 (3.1)	31 (96.9)		
Acute infection/hospitalization in the last 3 months								
No	62 (25)	186 (75)	0.741	1.833 (0.395-8.499)	45 (18.1)	203 (81.9)	0.476	2.66 (0.337-20.984)
Yes	2 (15.4)	11 (84.6)			1 (7.7)	12 (92.3)		
History of medication in the last 6 months								
No	58 (28)	149 (72)	0.012	3.114 (1.264-7.669)	43 (20.8)	164 (79.2)	0.008	4.457 (1.327-14.975)
Yes	6 (11.1)	48 (88.9)			3 (5.6)	51 (94.4)		
History of COVID-19								
No	54 (30)	126 (70)	0.002	3.043 (1.459-6.344)	38 (21.1)	142 (78.9)	0.034	2.442 (1.083-5.506)
Yes	10 (12.3)	71 (87.7)			8 (9.9)	73 (90.1)		

Note: $P<0.05$

Table 5. Risk factors affecting AEFI in 24 to 48 hours and in 48 hours to 7 days

Risk factor	AEFI in 24 to 48 hours				AEFI in 48 hours to 7 days			
	No AEFI n (%)	AEFI n (%)	*P*	OR (95% CI)	No AEFI n (%)	AEFI n (%)	*P*	OR (95% CI)
Gender								
Female	57 (38.5)	91 (61.5)	<0.001	0.371 (0.224-0.614)	109 (73.6)	39 (26.4)	0.05	0.53 (0.284-0.987)
Male	71 (62.8)	42 (37.2)			95 (84.1)	18 (15.9)		
Age								
≤25 years	56 (48.3)	60 (51.7)			101 (87.1)	15 (12.9)		
26–45 years	47 (43.1)	62 (56.9)	0.023	-	76 (69.7)	33 (30.3)	0.006	-
>45 years	25 (69.4)	11 (30.6)			27 (75.0)	9 (25.0)		
Body Mass index (BMI)								
Underweight - Normal (<18.5 to 24.9)	87 (46.5)	100 (53.5)	0.218	0.7 (0.408-1.203)	143 (76.5)	44 (23.5)	0.323	0.693 (0.348-1.377)
Overweight - Obese (25 to ≥27)	41 (55.4)	33 (44.6)			61 (82.4)	13 (17.6)		
Vaccine type								
Pfizer	67 (59.8)	45 (40.2)	0.003	2.148 (1.304-3.539)	107 (71.8)	42 (28.2)	0.004	2.538 (1.325-4.864)
Sinovac	61 (40.9)	88 (59.1)			97 (86.6)	15 (13.4)		
Comorbidities								
No	118 (51.3)	112 (48.7)	0.056	2.213 (0.998-4.905)	187 (81.3)	43 (18.7)	0.002	3.581 (1.64-7.822)
Yes	10 (32.3)	21 (67.7)			17 (54.8)	14 (45.2)		
History of allergic reactions								
No	118 (51.5)	111 (48.5)	0.038	2.339 (1.06-5.159)	184 (80.3)	45 (19.7)	0.037	2.453 (1.117-5.386)
Yes	10 (31.3)	22 (68.8)			20 (62.5)	12 (37.5)		
Acute infection/hospitalization in the last 3 months								
No	125 (50.4)	123 (49.6)	0.085	3.388 (0.91-12.605)	197 (79.4)	51 (20.6)	0.041	3.311 (1.066-10.281)
Yes	3 (23.1)	10 (76.9)			7 (53.8)	6 (46.2)		
History of medication in the last 6 months								
No	106 (51.2)	101 (48.8)	0.221	1.527 (0.832-2.802)	166 (80.2)	41 (19.8)	0.139	1.705 (0.866-3.354)
Yes	22 (40.7)	32 (59.3)			38 (70.4)	16 (29.6)		
History of COVID-19								
No	96 (53.3)	84 (46.7)	0.045	1.75 (1.027-2.982)	142 (78.9)	38 (21.1)	0.746	1.145 (0.612-2.142)
Yes	32 (39.5)	49 (60.5)			62 (76.5)	19 (23.5)		

Note: *P*<0.05

Monitoring of AEFIs at 48 hours to 7 days (Tabel 5) pointed out that the incidence of AEFI was affected by age, vaccine types, comorbidities, history of allergic reactions, and hospitalization in the previous 3 months with a *P*<0.050.

Table 6 shows the relationship between the vaccine combination variations received by participants and the level of AEFIs. In the first 15 minutes, the combinations with the highest percentage of AEFIs were *Moderna* + *Moderna* + *Pfizer*, *Sinovac* + *Sinovac* + *Pfizer* + *Pfizer*, and *Astrazeneca* + *Astrazeneca* + *Pfizer* + *Pfizer*, in which 100% of participants experienced at least 1 type of AEFIs in the 15 minutes of monitoring. Meanwhile, at 15 minutes to 24 hours monitoring, the highest incidence of AEFI was observed in the combination of the *Astrazeneca* + *Astrazeneca* + *Pfizer* + *Pfizer* vaccines, in which 100% of the participants experienced AEFIs, followed by the combination of *Sinovac* + *Sinovac* + *Moderna* + *Pfizer*, where the AEFI percentage increased from 82% to 94%, and the combination of *Sinovac* + *Sinovac* + *Pfizer* + *Pfizer*, which decreased from 100% to 93% participants with at least 1 type of AEFI.

The combination of *Sinovac* + *Sinovac* vaccine had the highest AEFI incidence in 24 to 48 hours of monitoring, with 91% of participants experiencing AEFIs. This combination of *Sinovac* + *Sinovac* vaccine was higher than other combinations, followed by *Moderna* + *Moderna* + *Pfizer* and *Sinovac* + *Sinovac* + *Pfizer*, with 75% and 74% participants, respectively. In 48 hours to 7 days of monitoring, all vaccine combinations had decreased AEFIs. Of all combinations, only *Moderna* + *Moderna* + *Pfizer* had an AEFI level higher than 50%, with 75% of participants experiencing at least one type of AEFI.

Table 6. Vaccine combination variations on the incidence of AEFI

Vaccine combination variations	AEFI in 15 minutes		AEFI in 15 minutes to 24 hours		AEFI in 24 to 48 hours		AEFI in 48 hours to 7 days	
	No	Yes	No	Yes	No	Yes	No	Yes
Pfizer	25%	75%	13%	88%	63%	38%	75%	25%
Pfizer + Pfizer	7%	93%	14%	86%	43%	57%	79%	21%
Sinovac + Sinovac	18%	82%	9%	91%	9%	91%	73%	27%
Sinovac + Sinovac + Sinovac	38%	62%	31%	69%	68%	32%	89%	11%
Sinovac + Sinovac + Pfizer	30%	70%	13%	87%	26%	74%	78%	22%
Pfizer + Pfizer + Pfizer	22%	78%	13%	87%	35%	65%	65%	35%
Astrazeneca + Astrazeneca + Pfizer	16%	84%	11%	89%	42%	58%	74%	26%
Moderna + Moderna + Pfizer	0%	100%	13%	88%	25%	75%	25%	75%
Sinovac + Sinovac + Sinovac + Sinovac	30%	70%	20%	80%	40%	60%	80%	20%
Sinovac + Sinovac + Pfizer + Pfizer	0%	100%	7%	93%	36%	64%	57%	43%
Sinovac + Sinovac + Moderna + Pfizer	18%	82%	6%	94%	50%	50%	79%	21%
Astrazeneca + Astrazeneca + Pfizer + Pfizer	0%	100%	0%	100%	67%	33%	100%	0%

In dealing with AEFI events, some participants used at least one type of therapy. In the 15 minutes of monitoring, 25 participants used therapy to relieve AEFI. The number of participants who used therapy increased in 4 participants in the 15 minutes to 24 hours monitoring. Meanwhile, at 24 to 48 hours of monitoring and 48 hours to 7 days of monitoring, the participants who used therapy decreased by 3 at each monitoring time.

DISCUSSION

In this study, the highest level of AEFI was found in 15 minutes to 24 hours of monitoring, in which 215 participants (82%) experienced AEFI. This number increased from the previous monitoring, with 197 (75%) participants experiencing AEFI. Then, with 133 participants (50%), it decreased within 24 to 48 hours of monitoring. In the 48 hours to 7 days of monitoring, the decline in AEFI was very large, with 57 participants (21%) experiencing AEFI. This incident is in line with Mohsin et al, who reported an average of only 1–3 days of adverse events, and the study did not identify any examples of serious effects or hospitalizations.[7] Moreover, Lai et al compared AEFI in *CoronaVac* and *Comirnaty* vaccines and stated that the proportion of AEFI reached its peak on the first day after vaccination and gradually decreased.[8]

In this study, 130 participants (39.5%) reported discomfort at the injection site, the highest prevalence of AEFI symptoms in the first 15 minutes after immunization. Then, 44 individuals (16.9%) and 70 people (26.8%) reported having myalgia. Phase 3 study from the United States revealed that following the first and second doses of the mRNA-1273 vaccination, systemic and injection site-related adverse events occurred more frequently in the mRNA-1273 vaccine group than in the placebo group. Additionally, soreness at the injection site is the most prevalent adverse event connected to the site of injection, which is similar with previous research by Bostan et al, in which a local injection site response was the most often observed side effect.[9]

In this study, the perceived severity of AEFI was dominated by mild severity, while moderate, severe, and potentially life-threatening events occurred in a few cases only. This is consistent with the findings of Bostan et al. They found that the modest, self-limiting responses to the *Sinovac-CoronaVac* and *Pfizer-BioNTech* COVID-19 vaccines were both systemic and local. No study participants had severe or life-threatening systemic or local side effects that would have stopped them from getting subsequent vaccines.[9]

The findings of this study are also in line with those of Aryal et al, who found that the most common local reaction was pain at the injection site and rarely swelling, while the most common systemic reactions were lethargy, headache, and muscle pain. These results align with preliminary safety data analyses carried out in China, Bahrain, Egypt, Jordan, and the United Arab Emirates, which found that injection site pain, rash, swelling, induration, and itching were the most frequently reported local reactions. At the same

time, headache, fever, myalgia, fatigue, arthralgia, cough, dyspnea, nausea, and diarrhea were the most frequently reported systemic reactions.[10] Global side effects following COVID-19 vaccination varied by vaccine type, according to study by Anjorin et al. However, the most frequently reported symptoms were fatigue, headache, muscle and joint pain, allergic skin reactions, and chills. The most common symptoms that appeared several days after vaccination were light fever, fever, and pain or redness at the injection site.[11]

Different demographic profiles had been investigated in this study and were associated with existing AEFIs.The age category was divided into three groups in this study. The level of AEFI complaints was dominated by the age group of 17-35 years, followed by 45 years and over. According to Le et al, participants between the ages of 18 and 55 were more likely than participants over 55 to suffer AEFI. Persons between 18 and 55 years old were 1.9 times more likely than participants over 55 to develop AEFIs.[12]

Moreover, this study is also in line with Parida et al, who obtained that the majority of AEFIs were mild. The most frequent AEFI was pain at the injection site, followed by fever and myalgia. Younger people reported AEFIs more frequently than elders. Participants aged 18–29 years (younger) reached 34.6%, while in South India, it was 48.4%, and most AEFIs were reported among the younger age group.[13] In comparison to the elder demographic, Ripabelli noted that 70% of young persons aged 55 experienced adverse effects. In addition to having a stronger immune system than older people, older people have a reduced capacity to respond effectively to vaccination, as evidenced by a lower frequency of neutralizing antibodies following the *Comirnaty* vaccination.[14]

In this study, the percentage of AEFI incidence was higher in female participants than in male participants. In the 15 minutes of monitoring, the AEFI in female participants was significantly higher (P=0.009) compared to that in males. It also occured in the 15 minutes to 24-hours of monitoring (P=0.002), 24to 48 hours of monitoring, and 48 hours to 7 days of monitoring, which significantly differed (P<0.001 and P=0.050, respectively). This is in line with findings from Ripabelli et al, which stated that most female vaccine recipients reported adverse events, with a twofold increase in the likelihood of reporting reactions compared to men. There might be gender-specific variations in vaccine side effects. Studies on different vaccines showed that the cellular immune response in men was generally suppressed compared to women. The significant biological link between sex and immunological response and its implications on disease susceptibility, transmission, and vaccination outcome can be used to explain this discrepancy. The primary sex hormones appear to oppose the innate and adaptive immune systems; for example, rising estradiol and testosterone levels reduce the antibody responses elicited by vaccination.[15]

Additionally, behavioural attitudes toward reporting side effects and autoimmune illnesses were recorded more commonly in women than men. Finally, women are more likely to have side effects due to their higher body fat percentage, which influences the drug's volume of distribution and clearance rate.[14] Chakraborty et al found that the number of women with AEFI was higher than that of men for both local and systemic reactions.[15] Parida et al also demonstrated that, with statistically significant differences (P=0.010), AEFI was 1.30 times more common in women than in men.[13]

Body Mass Index (BMI) does not significantly affected the level of AEFI in this study. Only in the 15 minutes of monitoring, the AEFI in Underweight - Normal (<18,5 to 24,9) participants was significantly higher (P=0.001) compared to that in Overweight - Obese (25 to ≥27), but the percentage of participants in the normal weight category (≥18.5 to <24.9) was higher than those in the overweight and obese categories. This supports the finding by Hidayat et al that those with BMIs below 25 kg/m^2 (underweight or normoweight) were more likely to have AEFIs than those with BMIs above 25 kg/m^2 (overweight).[16] Iguacel et al discovered that people in the underweight and normal weight groups had a higher likelihood of experiencing COVID-19 adverse effects

(fever, vomiting, diarrhea, and chills) than people who were overweight (including obese).[17]

In this study, the *Pfizer* vaccine had a higher AEFI percentage than the *Sinovac* vaccine. In the first 15 minutes and in 15 minutes to 24 hours, the AEFI percentage of *Pfizer* was significantly (*P*<0.001) higher than the *Sinovac* vaccine. In 24 to 48 hours of monitoring, *Pfizer* showed significantly higher AEFIs than *Sinovac* (*P*=0.003), and so did *Pfizer* in 48 hours to 7 days of monitoring (*P*=0.004). This is similar with Bostan et al who noted that the *Pfizer-BioNTech* vaccine in the first and second doses had a statistically higher rate of systemic and local side effects than the *Sinovac-CoronaVac* vaccine.[9]

Additionally, Chen et al noticed that the incidence of AEFI was 23.0% (95% CI=20.0-26.0%; I^2= 55.71%), 48.0% (95% CI=28.0-84.0%; I^2=99.99%), and 76.0% (95% CI=69.0-84.0%; I^2=84.46%), respectively, among inactivated vaccines, mRNA-based vaccines, and viral vector vaccines.[18] *Pfizer-BioNTech* recipients demonstrated a 5.37-fold (95% CI=2.57-11.22) higher likelihood of side effects than *Sinopharm* recipients, according to Mohsin et al.[7] The related claim that *CoronaVac* had less reactogenicity than *Comirnaty* was supported by Lai et al They also stated that those who received *CoronaVac* as opposed to *Comirnaty* had a considerably decreased probability of adverse reactions (global, local, and systemic) two weeks after immunization.[8]

Comorbidity had a big impact on AEFI level in this study. According to Parida et al, people with comorbidities were 2.08 times more likely than healthy individuals to suffer AEFI (*P*<0.001).[13] A history of COVID-19 infection and allergies greatly impacts AEFI levels. This is consistent with the findings by Parida et al, who revealed that AEFI symptoms and a history of allergies were strongly correlated.[13]

Based on studies by Juliane et al, multivariate analysis in this study identified co-morbidities, including chronic lung disease, chronic kidney disease, and cardiovascular disease, that had a substantial association with a high risk of mortality. According to multiple research studies, COVID-19 patients with chronic comorbidities had an increased risk of COVID-19 events, including death. Similar to the relationship with AEFI events, comorbidities increase the incidence of AEFI in patients.[19] Significant predictors of AEFI, in addition to gender, were comorbidities, a history of using corticosteroids, a history of allergies, a history of using drugs within the previous six months, and a history of being hospitalized within the previous three months.[13] Additionally, the history of medication use over the previous six months greatly impacts AEFIs.

The level of AEFI is greatly impacted by COVID-19 history. This is consistent with Ossato et al, who found that previously immunized individuals with COVID-19 infection had a considerably greater antibody response following a single vaccination döşe.[20] All 18 COVID-19 patients who had previously been diagnosed had mild reactions, and nine of them reported moderate reactions, which were connected to a history of SARS-CoV-2 infection, according to Ripabelli et al. This correlation may be explained by increased immunogenicity in those who have had an infection and have antibodies against healthy individuals, as well as heightened concern about side effects, even in those who only have minor symptoms.[14]

Based on the different combinations, the *Pfizer* vaccine combination had a higher AEFI than the *Sinovac* vaccine. During the initial 15 minutes of monitoring and the next 24 to 48 hours of monitoring, the second dosage of the *Pfizer* vaccine in this trial showed a larger AEFI than the first dose. This is consistent with the FDA analysis, which found that after the second dosage of the vaccine, local adverse effects were slightly more common than they were after the first dose.[21]

This is in line with finding by Ripabelli, which obtained that about 80% of people who participated in active surveillance disclosed at least one AEFI after the first or second dose. Additionally, it is consistent with earlier national studies for mRNA-based vaccinations, highlighting the lack of a significant difference between the two dosages. However, as seen elsewhere, some reactions commonly happened after the second dose.[14] The

investigation by Maruyama et al into the *Pfizer* vaccine related to AEFI discovered that the incidence of systemic reactions increased following the second dose, which was consistent with the results of the earlier study.[22] In contrast, it could not further examine which vaccination combination substantially impacted the occurrence of AEFI due to the less widespread distribution of the vaccine variety.

In this research, some participants who experienced AEFIs took medication independently. The most commonly consumed drug by participants to relieve AEFI symptoms was Paracetamol. This is consistent with Ripabelli et al, who reported that 141 participants (50.2%) had adverse effects after receiving *Pfizer*'s second dose (n=281). These participants were treated for their symptoms mostly with paracetamol (n=101; 71.6%), followed by NSAIDs (n=21; 14.9%).[14] According to Mohsin et al, more than 70% of responders who had *Pfizer* and *Moderna* vaccine adverse effects took medicine. On the other hand, only 9.87% of individuals took medication and had side effects after getting *Sinopharm* vaccinations.[7]

LIMITATION

This study has some limitations. Following the vaccination, we only conducted a one-week follow-up. To evaluate late symptoms of immunization, long-term follow-up is required. Despite the fact that a high quality of data was acquired due to the target population's degree of knowledge and skills about health concerns and their ability to recognize post-vaccination symptoms, the use of self-reported data might potentially create misclassification bias. Additionally, we did not conduct immunological testing to demonstrate the respondents' immune responses.

CONCLUSION

This study revealed that *Pfizer* and *Sinovac* COVID-19 vaccines were safe to administer as AEFIs were mostly mild and automatically disappeared and decreased after 1 to 3 days. This research offered a thorough analysis of the variables influencing AEFIs in immunization participants at the Universitas Indonesia Hospital. The findings of this study demonstrated that female participants with comorbidities, prior allergy history, history of medication use during the past six months, and history of COVID-19 had a higher risk of AEFI and a statistically significant effect (P <0.005). Furthermore, people receiving mRNA immunization should be monitored more closely than those receiving inactivated vaccines because the *Pfizer* vaccine significantly worsened side effects compared to the *Sinovac* vaccine.

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CONFLICT OF INTEREST

The authors affirm that no material competing interests—financial, professional, or personal—might have impacted how the work described in this publication was performed or presented.

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Case Report

Pulmonary Tuberculosis Coinfected with COVID-19 Compounded by Bacterial Superinfection: A Case Report and Critical Appraisal of The Evidence Regarding Its Mortality

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Abstract

Background: The WHO has declared COVID-19 as a global pandemic. However, Indonesia is also challenged by high burden of tuberculosis (TB). In this study, reported an active pulmonary TB case coinciding with COVID-19 but deceased due to bacterial infection. There is a need to further explore this new problem in developing countries to determine the prognosis of COVID-19 patients with tuberculosis infection.

Methods: A comprehensive literature search was conducted by using databases such as The Cochrane Library, PubMed, Google Scholar, EBSCO-Host, and Scopus, including systematic reviews of cohort studies, cohorts, and case controls. As many as 309 studies were identified, after screening for duplicates and against the inclusion and exclusion criteria, three studies were included for critical appraisal.

Results: The meta-analysis by Gao et al included two studies with an odds ratio (OR) of 1.4 [95% CI=0.1-18.93], the cohort study by Sy et al reported a relative risk (RR) of 2.17 [95% CI=1.4-3.37], and Motta et al showed that COVID-19 patients with tuberculosis had a mortality rate of 11.8% [95% CI=7.75-15.45].

Conclusion: TB has yet to be an identified as a major predictor of increased mortality in COVID-19 patients but can be considered a predictor of increased severity in COVID-19 patients. Studies with a bigger sample size and better study design are suggested to obtain new evidence.

Keywords: COVID-19, mortality, *Mycobacterium tuberculosis*, SARS-CoV-2, tuberculosis

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INTRODUCTION

The World Health Organization (WHO) has declared COVID-19 as a global pandemic in 2020. In Indonesia, the prevalence of COVID-19 cases and mortality continue to increase until the end of 2020. COVID-19 is known for several comorbidities that may increase the risk of severity and mortality, including hypertension, diabetes, and tuberculosis. Both tuberculosis and COVID-19 are infectious diseases that affect human respiratory system with similar symptoms, such as cough, fever, and breathing difficulty.[1]

It is suggested that tuberculosis causes a higher risk of mortality in COVID-19 patients. Pulmonary tuberculosis (pulmonary TB) can damage the lung parenchyma and increase the susceptibility of the hosts' immune system. Meanwhile, COVID-19 can also destroy the lungs and impair the patient's immunity by causing a cytokine storm, increasing the possibility of acute distress syndrome and subsequently causing death.[2,3] A meta-analysis exploring the relationship between tuberculosis and the severity and mortality of COVID-19 patients suggested that coinfection with tuberculosis doubled the risk of severity, despite no statistical difference.[2,3] A case of pulmonary TB co-infected with COVID-19 but passed away due to bacterial infection was reported. This study aimed to explore the possible relationship between pulmonary tuberculosis and COVID-19, especially regarding the mortality of patients with COVID-19 and active TB infection.

CASE

A 42-year-old male was admitted to the

hospital due to high-grade fever, productive cough and difficult breathing for the past five days. The patient was under routine insulin injection for type 2 diabetes mellitus. Physical examination showed lethargic, with a respiratory rate of 36 X/minute, heart rate of 110x/minute, blood pressure 160/90 mmHg, a temperature of 40^0C, oxygen saturation of 92% with 6 liters nasal cannula, and BMI of 20. Rales were identified following lung auscultation, mostly on the upper right hemithorax. Six weeks earlier, he was diagnosed as bacteriologically confirmed pulmonary tuberculosis and has been treated with 4FDC (fixed dose combination anti tuberculosis agents) from primary health center.

Laboratory findings showed a normal hemoglobin level with mild leukocytosis and a high neutrophil-to-lymphocyte ratio (NLR). Marker of inflammation was high (high C-Reactive Protein and high Ferritin) with low procalcitonin and signs of coagulopathy with high D-dimer and fibrinogen and low albumin level. The latest HbA1C level was still high (Table 1). Chest X ray showed infiltration in both side of the lung and cavity on the right lung consistent with pneumonia and tuberculosis (Figure 1A).

Table 1. Laboratory finding of the case

Laboratory finding	Day 1	Day 8	Day 16	Normal values	Unit
Haemoglobin	13.1	10.6	12.6	13.0-16.0	g/dL
Hematocrite	37.5	31.4	33.4	40.0-48.0	%
Erytrocyte	4.50	3.60	4.10	4.50-5.50	10^6/uL
Platelets	590.000	236.000	360.000	150-400	10^3/uL
Leukocyte	11.82	9.24	19.24	5.00-10.00	10^3/uL
Diff count					
Basophile	0.2	0.8	0.4	0-1	%
Eosinophile	1.9	0.0	0.0	1-3	%
Neutrophiles	80.1	85.6	90.6	52.0-76.0	%
Lymphocyte	12.0	6.8	4.9	20-40	%
Monocyte	5.8	6.8	4.8	2-8	%
Neutrophile to Lymphocyte Ratio	6.68	12.59	14.19	-	-
Haemostasis					
APTT	36.4	35	49.3	31.0-47.0	second
Control	34.8	34	34.8		second
Fibrinogen	696	320	433	136-384	mg/dL
D dimer	4360	1050	1200	0-500	ug/L
CK	539	-	-	30-200	U/L
CK MB	26.6	-	-	<25	U/L
hsTroponin I	19.2	-	24	<26	Pg/mL
HbA1C	10.5	-	-	< 5.8	%
Blood glucose	135	-	200	70-200	mg/dL
Immunoserology					
CRP	207.50	160.80	343.90	<=5.0	mg/L
Ferritin	1400.1	-	1700	20.0-250.0	ng/mL
Procalcitonin	0.17	-	3.5	<0.05	ng/mL
HIV	Negative	-	-	<1.0: Non reaktif	
IGG SARS-CoV-2	Positive	-	-	MRR	S/CO
Blood gas analysis					
pH	7.465	7.388	7.255	7.350-7.450	-
pCO_2	34.60	45.20	64.40	35.00-45.00	mm Hg
pO_2	67.70	90.50	77.20	75.00-100.00	mm Hg
HCO_3	25.10	27.40	29.30	21.00-25.00	mmol/L
O_2 saturation	94.50	28.80	92.40	95.00-98.00	%
Standard HCO_3	26.4	26.9	25.8	22.0-24.00	mmol/L
Lactate	4.2	-	-	-	mmol/L
Blood calcium	4.1	7.4	7.6	8.4-10	mg/dL
Blood magnesium	4.0	2.2	1.5	1.6-2.6	mg/dL
Others					
Albumin	2.80	2.40	2.20	g/dL	3.5-5.2
SGOT/SGPT	27/26	14/40	25/25	U/L	5-34/0-55
Ureum/Creatinie	66/1.3	68	177/2.6	mg/dL	19-44

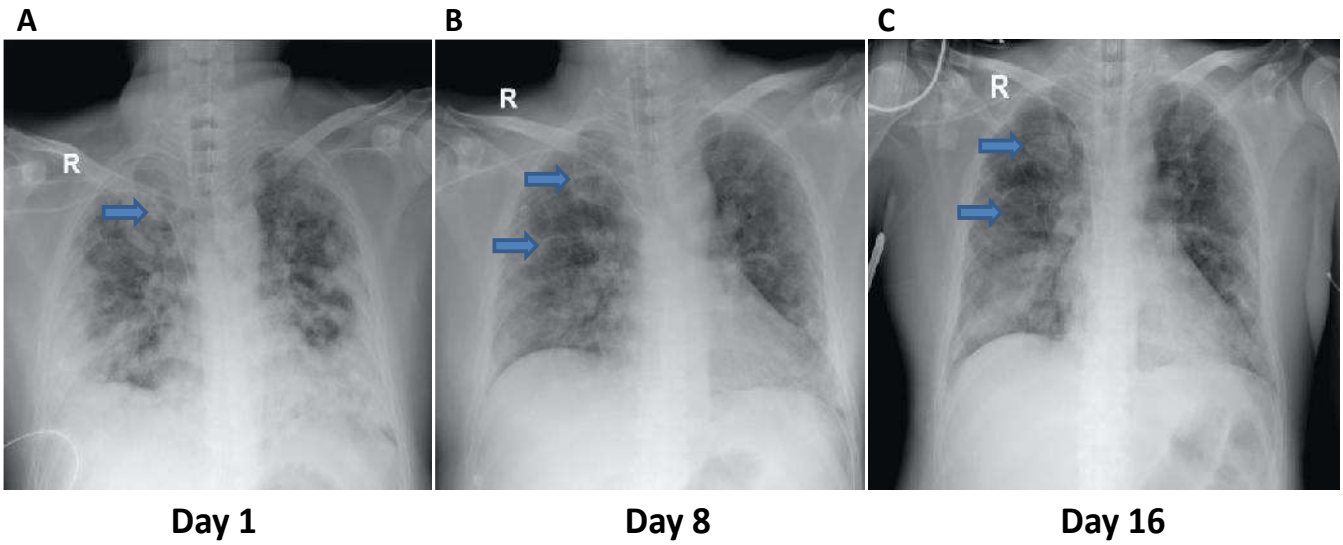

Figure 1. Serial Chest X rays; A) CXR taken on the day 1 showed both fibroinfiltrate, cavity (arrow) and bilateral infiltrate; B) CXR taken on day 8 showed infiltrate improvement but cavities were clearly visible; C) CXR taken on day 16 showed increase infiltrate compare with (B) compatible with pneumonia

Positive result from morning AFB confirmed active TB diagnosis, and repeated SARS-CoV-2 RT-PCR from nasopharyngeal also showed positive result with Ct value of 21. The patient was treated with standard COVID-19 care according to Indonesian National COVID-19 Guideline ie. oxygen therapy with HFNC 70 liter/m, FiO_2=80%); heparin as an anticoagulant; intravenous corticosteroid, intravenous remdesivir and standard treatment for diabetes mellitus with insulin and antituberculosis drugs in addition to symptomatic treatment and multivitamins.

The patient deteriorated after 12 hour and intubation/mechanical ventilator support was applied and levofloxacin as antibiotic was added. He was clinically and radiologically improved after 7 days in the ICU (Figure 1B) but could not wean from ventilator. SARS-CoV-2 RT-PCR testing on day 7 was still positive, but viral load showed improvement with Ct value >30.

On day 16, his condition deteriorated with fever, and maximum ventilator setting. Bacterial pneumonia was suspected. Laboratory findings consistent with bacterial infection with increased procalcitonin and high C-reactive protein (Table 1), CXR showed new infiltrate compared to previous CXR on day 8 (Figure 1B and 1C). Culture from endotracheal aspirate and blood showed multidrug resistance Acinetobacter baumanii (Table 2). SARSCOV2 RT PCR testing on day 15 was still positive, but viral load showed improvement with Ct value >30. Despite appropriate antibiotic and supportive care with mechanical ventilation, the patient passed away on day 20 of hospitalization due to bacterial sepsis.

Table 2. Culture of laboratory finding of the case

Culture	ETT aspirate	Blood
Acinetobacter baumanii	Positive	Positive
Ampicillin /sulbactam	R	R
Pipperacillin tazobactam	R	R
Cefazolin	R	R
Ceftazidime	R	R
Ceftriaxone	R	R
Cefepime	R	R
Meropenem	R	R
Amikacin	R	S
Gentamycin	R	R
Ciprofloxacin	R	R
Tigecycline	S	I
Trim+Sulfamethoxazol	S	R

DISCUSSION

Based on the Indonesian Ministry of Health data in 2013–2014, the prevalence of positive smear TB in Indonesia was 257 per 100000 population aged >15 years old. In 2017, 420994 new tuberculosis cases occurred in Indonesia.[4] New data from the WHO estimated that total TB incidence was 845000, equivalent to 312/100000 Indonesian population, and with increasing MDR-TB cases, an estimated incidence of 24000 in 2019 in Indonesia.[5]

Indonesia suffered COVID-19 pandemic since its first case was reported in March 2020. By the end of January 2021, more than 1 million COVID-19 cases were reported, with a mortality of more than 30000 deaths. Both tuberculosis and COVID-19 could pose a double burden of infectious diseases, especially in high burden countries such as Indonesia. Observational studies in countries with a high number of BCG vaccines as TB prevention showed fewer COVID-19 cases.[2] Earlier research also showed BCG vaccinations provided immunity and could reduce COVID-19 infection and its progression; however, more evidence is needed to confirm the finding.

A case of pulmonary TB co-infected with COVID-19 but passed away due to bacterial infection was reported. A fourty two-years-old male with confirmed pulmonary TB and type 2 diabetes mellitus was admitted to the hospital with acute high-grade fever and dyspnea with severe clinical presentation suggesting COVID-19. CXR showed a cavity and fibro infiltrate consistent with tuberculosis. TB diagnostic standard test or AFB was positive, and SARS-CoV-2 RT-PCR was also positive from nasopharyngeal swabs. The patient slowly recovered after 7 days supported by mechanical ventilation in the ICU. Unfortunately, the patient infected with Gram Negative bacteria and sepsis was inevitable despite maximal therapy. The patient passed away after 20 days in the ICU.

In high-tuberculosis burden countries, tuberculosis diagnosis should not be overlooked during the COVID-19 pandemic. Recently, Singapore reported four cases of foreign workers presenting with TB and COVID-19 from countries with a high number of tuberculosis cases. Clinical manifestations and atypical radiographic features of COVID-19, such as pleural effusion and cavity, led to the diagnosis of TB through positive interferon-gamma release assay and culture results. All of 4 cases were recovered and continue antituberculosis drugs in outpatient clinic.[6]

Favorable outcome of TB-COVID-19 coinfection was also seen in a referral hospital in Italy of which only 1 patient died among 20 TB-COVID-19 (5% mortality rate).[7] On the contrary, 27.3% mortality rate was reported in India among active/treated TB and COVID-19.[8] The clinical case was a confirmed TB on antituberculosis treatment, coinfected with COVID-19 but died after severe bacterial infection.[9–11]

Table 3. Critical appraisal of selected studies.

Assessment Indicator	Gao Y et al (2020)	Sy KTL et al (2020)	Mottal I et al (2020)
Validity Assessment of Meta-Analysis Study			
Does the systematic review address a focused question (PICO)?	+	N/A	N/A
…. And use it to direct the search and select articles for inclusion?	+	N/A	N/A
Did the search find all the relevant evidence?	-	N/A	N/A
Have the studies been critically appraised?	+	N/A	N/A
Did they only include high quality studies?	+	N/A	N/A
Have the results been totaled up with appropriate summary tables and plots?	+	N/A	N/A
.... And heterogeneity between studies assessed and explained?	+	N/A	N/A
Validity Assessment of Cohort Study			
Was a defined, representative sample of patients assembled at a standard (usually early) point in the course of their disease?	N/A	+	+
Was patient follow-up sufficiently long and complete	N/A	+	+
Were objective outcome criteria applied in a "blind" fashion?	N/A	-	-
If subgroups with different prognoses are identified, was there adjustment for important prognostic factors?	N/A	-	+
Was there validation in an independent group ("test-set") of patients?	N/A	-	-
Importance Assessment			
How likely are outcomes over time?	OR=1.4	RR=2.17	Risk=11.6%
How precise are the prognostic estimates?	CI=0.1-9.93	CI=1.4-3.37	Unclear

Note: OR=odds ratio; RR=relative risk; CI=confidence interval; + clearly stated (Yes); - not stated (No); ? states unclearly

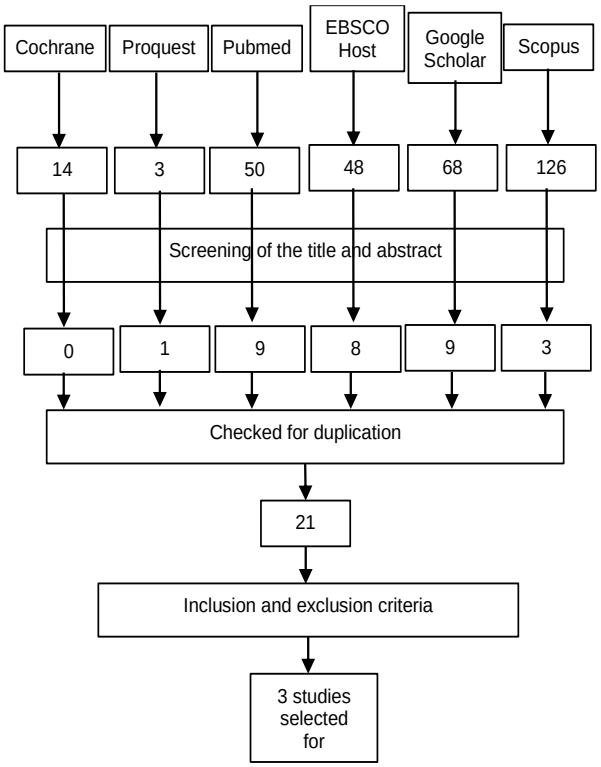

Figure 2. Search strategy regarding mortality among Tuberculosis and COVID-19 coinfections

Note Searching Terminology:

a. Pubmed: Search: (("severe acute respiratory syndrome coronavirus 2"[All Fields] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019-nCoV"[All Fields] OR "COVID-19"[All Fields] OR "SARS-CoV-2"[All Fields]) AND ("tuberculosis"[MeSH Terms] OR tuberculosis[Text Word])) AND ("severity" OR "mortality" OR "prognosis")
b. Cochrane: "COVID-19" OR "SARS-COV 2" OR "SARS-COV-2 Virus" OR "Novel coronavirus") AND ("tuberculosis" OR "mycobacterium tuberculosis infection" OR "mycobacterium tuberculosis" OR "MTB infection") AND ("prognosis" OR "severity" OR "progression" OR "mortality"))
c. Scopus: (TITLE-ABS-KEY ("COVID-19" OR "SARS-COV 2" OR "SARS-COV-2 Virus" OR "Novel coronavirus") AND TITLE-ABS-KEY ("tuberculosis" OR "mycobacterium tuberculosis infection" OR "mycobacterium tuberculosis" OR "MTB infection") AND TITLE-ABS-KEY ("prognosis" OR "severity" OR "progression" OR "mortality"))
d. Proquest: ti("COVID-19" OR "SARS-COV 2" OR "SARS-COV-2 Virus" OR "Novel coronavirus") AND ti("tuberculosis") AND ti("prognosis" OR "severity" OR "progression" OR "mortality")
e. EbscoHost: (“Covid-19) AND (“Tuberculosis”) AND (“Severity) or (“Death”) or (Mortality)
f. GoogleScholar: allintitle: COVID 19 and TUBERCULOSIS

Based on the clinical case, an evidence-based appraisal regarding the mortality among tuberculosis patients coinfected with COVID-19 was conducted. A systematic search of evidence was performed on April 6, 2021, involving six databases, namely Pubmed, The Cochrane Library, Google Scholar, Proquest, Scopus, and EBSCO, by using appropriate keywords that included "SARS-CoV-2" and "Tuberculosis." The search strategy results were then screened for proper titles and abstracts, followed by the removal of duplicates, which yielded 21 articles. Further screening based on the inclusion and exclusion criteria yielded three selected articles compatible with the clinical questions (Figure 2). One study was a meta-analysis study, and the other two studies were cohort studies.[9–11] The Oxford Centre for Evidence-Based Medicine Levels of Evidence tools were used to appraise these articles, as shown in Table 3.

The meta-analysis by Gao et al has a good validity where the study fulfilled almost all the assessment points.[9] However, the study did not include the keywords with MeSH terms and searched for unpublished studies. In the study, there was a clear PICO following the clinical case, and there were also clearly defined eligibility criteria. The literature search was carried out on more than two databases, such as EMBASE, PubMed, Web of Science, CENTRAL, CBM, CNKI. This study was also assessed by two independent reviewers utilizing the Newcastle-Ottawa Quality Assessment Scale (NOS) to determine the quality of the included literature with a score of 6 by Chen et al and a value of 8 by Du et al. The total number of subjects was 382. This study included a summary table and forest plots in the data presented. The heterogeneity test in this study was also performed well.[9] In terms of importance, the pooled Odds Ratio was 1.40 (95% CI=0.10–18.93), which reported no significant association between tuberculosis and increased risk of mortality.

It is suspected that the inconsistent results may be due to differences in follow-up time (41 days for Chen et al and 45 days for Du et al), differences in the treatment regiment, and the small number of samples analyzed in the studies. The wide confidence interval indicated imprecision of the results, which might be due to the small sample size. The study patients were similar to the patients presented in this case report, where the study was conducted on COVID-19 patients with active tuberculosis infection. This study was considered clinically significant. Overall, the level of evidence in this study classified as 2A.

The study by Motta et al has good validity.[10] The study aimed to describe the characteristics of a cohort of deceased COVID-19 patients with active tuberculosis infection. The Global Tuberculosis Network (GTN) database of large observational projects monitoring adverse reactions to anti-TB drugs in 27 centers in 8 countries identified 69 cases of TB and COVID-19. All consecutive cases with TB diagnosis at present or in the past, besides TB sequelae, were included. All patients had the same zero point, with adjusted inclusion and exclusion criteria to have similar characteristics. Patients were also followed for an appropriate length of time until an outcome was achieved. The highlight of the study was that 8 out of 69 patients (11,6%) died. The study concluded that TB might not be a major determinant of mortality, and mortality was likely to occur in elderly patients with comorbidities such as diabetes and cardiovascular disease.[10] Overall, the level of evidence in this study classified as 2B.

The critical appraisal results for the study of Sy et al showed sufficient validity for the cohort study.[11] However, it should be used with caution. Sy et al analyzed the risk of mortality and recovery time in COVID-19 patients with previous and active tuberculosis based on national COVID-19 surveillance in the Philippines. As many as 106 subjects had previous or active tuberculosis with COVID-19 were propensity score-matched with a 4:1 ratio of COVID-19 confirmed subjects to create a comparable population and reduce confounding factors. All subjects were also followed within the appropriate time frame and analyzed accordingly. In the study, blinding was not carried out or did not have a test-set because the outcome evaluated was only mortality, which must be assessed objectively.[11]

The importance assessment in this study was carried out by comparing the risk of recovery time and mortality of COVID-19 patients who were currently infected or previously infected with tuberculosis against those without any tuberculosis. The calculated relative risk was 2.17 (95% CI=1.4–3.37) from this assessment. That study's limitation was the TB definition, in which previous TB diagnosis and current TB disease were considered confirmed TB, therefore was unable to distinguish between the independent effects of these two groups separately. That study was conducted in the Philippines which share similar characteristics to Indonesians, such as demographics, socioeconomics, and the suitability of the high number of COVID-19 and tuberculosis diseases.[11] Overall, the level of evidence in this study classified as 2B.

Gao et al also assessed the association between tuberculosis and the severity of COVID-19, which reported an OR value of 2.10 (95% CI=0.61-7.18). Although not statistically significant, tuberculosis was shown to increase the severity of COVID-19. Severe COVID-19 was defined as having acute respiratory distress syndrome (ARDS), requiring mechanical ventilation and admission to the intensive care unit (ICU), or required basic life support. Patients suffering from respiratory diseases, such as pulmonary TB, can cause pulmonary dysfunction, resulting in lower defense against the virus and more likely to develop ARDS.[9]

The Center for Disease Control and Prevention (CDC) warned that tuberculosis patients with a minimum age of 65 and had compromised respiratory systems are at a greater risk of suffering from COVID-19 with severe symptoms.[12,13] Chen et al assessed the impact of active and latent tuberculosis on the severity of COVID-19. A study was conducted on 36 positive SARS-CoV-2 patients (based on RT-PCR results) assigned into groups based on the severity of symptoms to mild/moderate and severe/critical cases. Of the 36 patients, 30 patients had IGRA +ve results, three of which were active TB with severe/critical COVID-19. They indicated that the severe/critical group had a significantly higher percentage of TB coinfection in the mild/moderate group (78% vs. 22%; P=0.0049). These data suggested that *Mycobacterium tuberculosis* and SARS-CoV-2 coinfection possibly led to increased severity of COVID-19.[12] That case showed that patient with confirmed tuberculosis could also be infected with SARS-CoV-2 and sepsis with severe clinical symptoms.

The person with tuberculosis with slow response with antituberculosis should be evaluated

further. Immunocompetent patient without comorbidities usually response very well with oral antituberculosis drugs and could be evaluated clinically, bacteriologically and radiologically after 2 weeks treatment.[14] This case showed slow recovery during 6 weeks antituberculosis agents despite good adherence and regular treatment. Factor that may delay treatment response could be impaired immune response.[13,14]

The patient had negative HIV test result, but suffered from diabetes mellitus more than 5 years with uncontrolled status most of the time despite treatment with regular insulin. Diabetes has potential impact since it impairs immune response which leads to higher vulnerability to develop active tuberculosis and also slow response to treatment. Immune impairment might also contribute to high susceptibility to severe COVID-19. The patient was further infected with bacteria that resist to most antibiotics available. Bacterial sepsis is well known for bad prognosis especially in those with comorbidities. The severe systemic infection and sepsis was the main reason of deterioration and death in this case.

The hypothesis of impaired immune response ideally should be validated by using surrogate markers, for example CD4/CD8 T cells. However, due to clinical setting and feasibility, the assays could not be performed.

Patient's uncontrolled diabetes mellitus might be the underlying factor which aggravates his overall condition and consistent with a study in Italy by Motta et al[10] and study in India by Gupta et al that claimed that those who died with COVID-19 and tuberculosis had Diabetes Mellitus as comorbid.[8] Secondary bacterial infection might further impair the disease and unfortunate grave prognosis in this case report. Based on metanalysis by Langford et al, secondary bacterial infection was found in 14.3 % of hospitalized COVID-19 patients, and more common in critically ill patient. Most of them had poor prognosis.[15]

Given the increasing number of COVID-19 cases in developing countries, tuberculosis and pneumonia remains a significant health problem in Indonesia. Effective prevention strategies for tuberculosis and bacterial infection are imperative. Early screening for COVID-19 and bacterial infection in tuberculosis patients with comorbidities, education and monitoring of high-risk patients, and proper comorbid management could help prevent patients' deterioration with a coinfection of tuberculosis, COVID-19 and sepsis.

LIMITATION

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CONCLUSION

This case report highlights the possible multi organism infection due to Mycobacterium tuberculosis, SARS-CoV-2 virus and aggravated by severe secondary pan-resistant bacterial infection in an individual with comorbid that further worsened the prognosis. Based on this case report, tuberculosis patients are not immune to COVID-19 coinfection. Other comorbidities might play a role in COVID-19 coinfection susceptibilities and disease progression. Based on the current critical appraisal of evidence, tuberculosis is not a major predictor of mortality in patients with COVID-19. However, it can be considered a risk factor for increased severity in COVID-19 patients. There is no enough evidence to answer this question, and better research methodologies such as more suitable study designs and large numbers of subjects are suggested.

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CONFLICT OF INTEREST

None.

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Case Report

Late-Onset Pneumothorax and Bullous Disease in Post-COVID-19 Pneumonia with Severe ARDS

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Abstract

Background: Patients with COVID-19 pneumonia may develop bullae that can rupture into spontaneous pneumothorax (SP) during the diagnosis and treatment, which can be a predictor of a poor prognosis. However, late-onset bullous disease and SP after recovering from COVID-19 are unusual.

Case: A 48-year-old male presented with sudden shortness of breath accompanied by chest pain. Three weeks earlier, the patient had finished treatment in the COVID-19 isolation room for 20 days with a diagnosis of COVID-19 pneumonia with severe ARDS. Physical examination demonstrates tachypnea, desaturation, decreased vesicular breath sounds, and hyperresonance percussion on the right hemithorax; without rhonchi or wheezing. Chest X-ray and CT scan showed a right pneumothorax with infected subpleural giant bullae in right perihilar, right lung collapse, minimal right-to-left lung herniation and post-covid pulmonary fibrosis. Culture and sensitivity examination of the pleural fluid showed the growth of Providencia stuartile. A chest tube was placed for the management of the pneumothorax. Subsequently, according to the results of culture and antibiotic sensitivity test, the patient was treated using piperacilin/tazobactam and amikacin. The patient showed clinical and radiological improvement following 41 days of treatment and could be managed as an outpatient.

Conclusion: Our patient had infected giant bullae and pneumothorax post COVID-19 pneumonia and severe ARDS. The patient did not undergo a bullectomy in consideration of the post-COVID-19 condition and was managed conservatively using adequate chest tube and antibiotics. Patient responded well to therapy, showed clinical improvement and could be discharged.

Keywords: ARDS, COVID-19, late-onset, pneumothorax, pulmonary bullous disease

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INTRODUCTION

During the diagnosis and treatment of COVID-19 pneumonia, patients may have a number of complications. Complications arise as a result of cell damage, a strong innate immune response with the release of inflammatory cytokines, and the pro-coagulant condition induced by SARS-CoV-2 infection.[1,2]

Fibrosis and pulmonary bullae are two COVID-19 problems that might occur. In the instance of COVID-19 pneumonia, ground glass opacity (GGO) and consolidation findings occurred early on the CT scan, increased in quantity and density, and were eventually absorbed, leaving fibrous alterations in their original site. Pulmonary bullae are air-filled pockets in the lung that develop as a result of emphysematous deterioration of the lung parenchyma.[3]

Bullae development is caused by inflammatory injury to the bronchioles, which results in air entrapment. Bullae may form as a result of mechanical forces interacting with weakened tissue.[3] Pulmonary bulla can rupture into spontaneous pneumothorax (SP), which can indicate a poor prognosis.[4]

There has been no specific report on the prevalence of SP in COVID-19 to date. Several prior studies reported SP during diagnosis and therapy of COVID-19.[3,5–7] Although SP due to pulmonary bullae rupture is relatively common in COVID-19 patients, however, late-onset bullous disease and SP after recovering from COVID-19 are unusual. In order to improve clinicians' understanding and treatment of the disease, we summarized the clinical characteristics of our patient with late-onset bullous disease and SP after recovering from COVID-19.

CASE

Our patient, a 48-year-old male, presented with sudden shortness of breath accompanied by chest pain that occured when coughing or changing positions. Three weeks earlier, the patient had finished treatment in the COVID-19 isolation room for 20 days with a diagnosis of COVID-19 pneumonia and severe ARDS, and he still complained of non-productive cough when leaving the isolation room. The patient had no known history of pulmonary bullae, pneumothorax, or any other lung conditions prior to the COVID-19 infection. On physical examination, his blood pressure was 130/80 mmHg, his heart rate was 105 bpm, his respiratory rate was 26 times/minute, his temperature was 36.7^{o}C, and oxygen saturation was 87% on room air; he appeared comfortable on an oxygen flow of 15 L/min via a non-rebreathing mask (oxygen saturation increased to 98%).

On the right hemithorax, there was decreased tactile fremitus, decreased vesicular breath sounds, and hyperresonance to percussion. No rhonchi or wheezing were found. Chest X-ray (CXR) showed right lung pneumothorax, and the CT scan showed a right pneumothorax with infected subpleural giant bullae in the right perihilar, right lung collapse, minimal right-to-left lung herniation and post-covid pulmonary fibrosis (Figure 1 and Figure 2).

On admission, a complete blood count (CBC) showed increased white blood cells of 14.900/ul (normal reference: 4.000-10.500/ul) with a decreased lymphocyte count of 7.4% (normal reference: 20–40%), and NLR and ALC were 11.2 and 1.4 x 10^{9}/L, respectively. The metabolic blood panel was normal. Arterial blood gas was taken with oxygen supplementation of 15 L/m and showed pH 7.37, $PaCO_2$ 53.9, PaO_2 115 mmHg, HCO_3 31.4, BE 6, SaO_2 98%, and PaO_2/FiO_2 ratio of 141.9 with the interpretation of respiratory acidosis compensated with metabolic alkalosis.

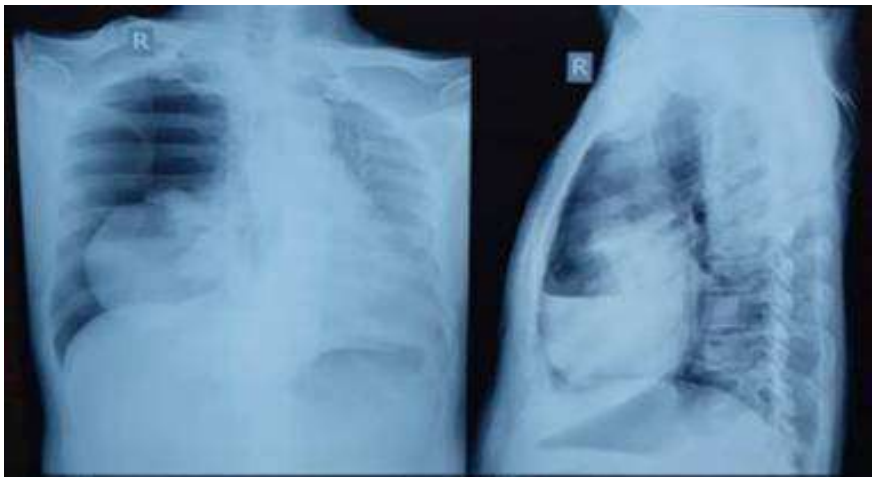

Figure 1. CXR on admission revealed a right pneumothorax, pneumonia, and bullae in the right hemithorax.

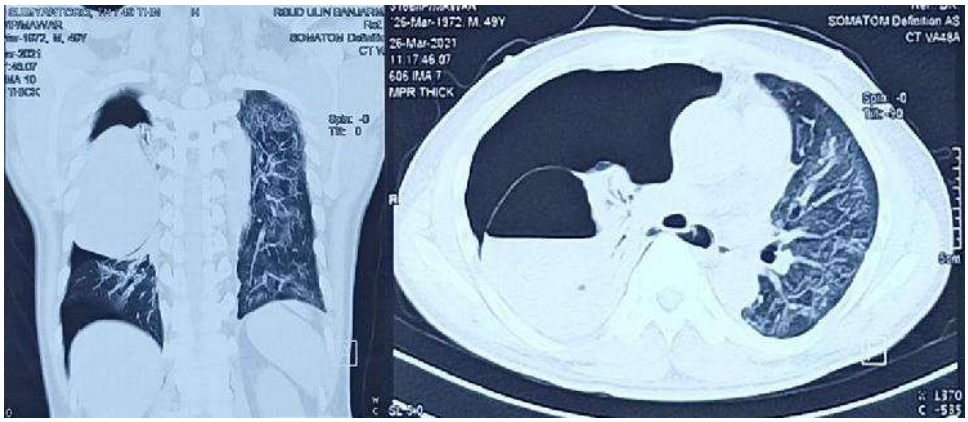

Figure 2. Chest CT scan showed right pneumothorax, post covid pulmonary fibrosis, infected giant bullae subpleural right perihilar, accompanied by right lung collapse and minimal right to left lung herniation. No left intrapulmonary bullae seen

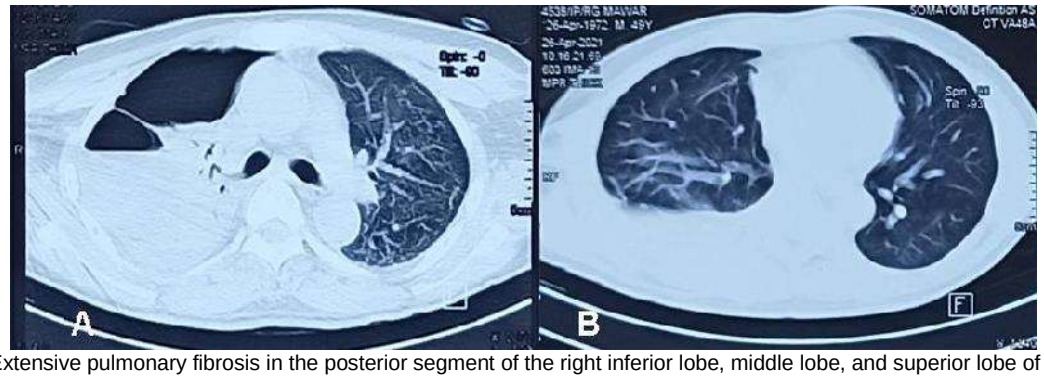

Figure 3. A) Extensive pulmonary fibrosis in the posterior segment of the right inferior lobe, middle lobe, and superior lobe of the right lung. Infected giant bullae in the superior lobe of the right lung which was smaller in size than the previous chest CT scan. Right pneumonia which was reduced in size compared to the previous imaging; B) Post-COVID fibrosis of both lungs with traction bronchiectasis. No bullae and pneumonia were seen. The right lung expansion appeared better than previous CT scan results.

Culture and antibiotics sensitivity examination of the pleural fluid showed the growth of *Providencia stuartile* bacteria. The patient then received high flow oxygenation therapy and a chest tube was placed for the management of pneumothorax. Subsequently, the patient was treated with piperacilin/tazobactam and amikacin according to the results of culture and antibiotic sensitivity. The patient did not undergo a bullectomy in consideration of the post-COVID-19 condition.

On the 15th day of treatment, the CT scan evaluation still showed infected giant bullae in the superior lobe of the right lung, but they were slightly smaller in size compared to the previous chest CT scan (Figure 3A). The CT scan on the 36th day of treatment finally revealed no bullae and right lung expansion compared to the previous CT scan (Figure 3B). The patient showed clinical and radiological improvement following 41 days of treatment and could be managed as an outpatient.

DISCUSSION

In severe COVID-19 cases, SARS-CoV-2 infection triggers a cytokine storm, which is an overactive immune response. A cytokine storm is a possibly lethal immunological condition characterized by high-level immune cell activation and excessive synthesis of inflammatory cytokines and chemical mediators. This condition causes an increase of immune cell infiltration from the circulation, such as neutrophils, macrophages, and T cells, into the site of infection, causing destructive effects on human tissue due to destabilization of endothelial cell to cell interactions, vascular barrier injury, extensive alveolar damage, capillary damage, multiorgan failure, and death. Cytokine storms will eventually cause lung injury, which can progress to acute lung injury or its more severe version: acute respiratory distress syndrome (ARDS).[8–10]

A pulmonary bulla is a well-defined air-space in the lung parenchyme that measures more than 1 cm in diameter when swollen and has a wall thickness of less than 1 mm. A bullae is classified as a giant pulmonary bullae (GPB) if it takes up at least 30% of one hemithorax.[11] Risk factors known to be associated with the development of bullae include smoking history, alpha-1 antitrypsin deficiency, alpha-1 anti-chymotrypsin deficiency, pulmonary sarcoidosis, Marfan syndrome, Ehlers–Danlos syndrome, marijuana smoking, and inhaled fiberglass exposure.[12]

COVID-19 ARDS is hypothesized to be linked to the development of bullous pulmonary disease. The underlying pathophysiology for bullae production is inflammatory injury to the bronchiole, which causes structural changes that contribute to air entrapment and the formation of GPB. The interaction of mechanical forces on the weaker tissue, such as high-flow oxygen support, may also result in the formation of bullae.[2,13,14]

Edema, vascular congestion, and microthrombi each have the potential to cause the rupture of preexisting bullae.[12] Spontaneous pneumothorax can result from the rupture of these bullae. Despite being a male, the patient never smoked. He also did not have any chronic lung

diseases, which was a risk factor for bullae development or pneumothorax. As a conclusion, it may be hypothesized that the formation of GPB and SP in this patient was associated with his history of COVID-19 condition with severe ARDS.

The surgical intervention of a bullectomy is the standard method of treatment for GPB. The indications for bullectomy are progression of symptoms with disability, obstructive spirometry, and a single or dominant bullae with radiological evidence of compression of surrounding preserved lung parenchyma.[11,15] However, adhesions between lung tissues and mediastinal structures may occur in post-COVID-19 patients, causing complications during surgical intervention. In addition, risk factors such as length of hospitalization, morbidity, and mortality may increase.[16] Therefore, due to the difficulties of the process and the increased risk to the patient following surgery, we could only perform chest tube insertion on the patient.

As shown in the CT scan results, this patient had infected bullae, specifically a right pneumothorax with infected giant bullae subpleura right perihilar. Furthermore, the presence of leukocytosis and an examination of pleural fluid culture and sensitivity showed growth of *Providencia stuartile* which was sensitive to several antibiotics such as piperacillin/tazobactam, amikacin, gentamicin, and trimethoprim-sulfamethoxazole. The patient was then treated with piperacilin/tazobactam and amikacin based on culture and antibiotic sensitivity.

Despite only being treated conservatively with a chest tube and antibiotics, the patient showed clinical improvement. Chest tube insertion had been found to improve the condition of the pneumothorax and to expand the initially compressed lung. The lung expansion increased with time, and the bulla reduced until it was no longer visible on the 36th day of therapy. The GPB resolution without surgery has already been reported and is known as an "autobullectomy." The exact mechanism of the natural resolution of the giant bullae is yet unknown. Reduced pneumothorax, which leads to lung expansion, and healing of inflammatory lung conditions with antibiotics and anti-inflammatory therapy may contribute in the resolution of giant bullae.[11,17]

LIMITATIONS

This case report has some limitations, one of which is that the patient was not tested for alpha-1 antitrypsin to rule out emphysema caused by a deficiency in alpha-1 antitrypsin. Furthermore, there was no data on chest CT scan performed prior to COVID-19 infection, so the exact risk of bullae in these patients cannot be determined.

CONCLUSION

Our patient was diagnosed with infected giant bullae and pneumothorax post COVID-19 pneumonia and severe ARDS. The patient did not undergo a bullectomy in consideration of the post-COVID-19 condition and was managed conservatively with an adequate chest tube and antibiotics. Patients responded well to therapy, showed clinical improvement and could be managed as an outpatient.

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CONFLICT OF INTEREST

None.

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Case Report

Candida Glabrata Pneumonia in Post COVID-19 Patient: A Rare Case Report

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Abstract

Background: One of the issues in post COVID-19 is secondary infection and fungal infection is one of the complications that must be detected at early stage to prevent. Early detection to prevent underdiagnosed and undertreatment. *Candida glabrata*, one of the pathogens in fungal infection is rare and can acts as infectious agent with immunocompromised patients.

Case: A 69-year-old man came to hospital with major complaints of cough and shortness of breath for five days. He was diagnosed COVID-19, After completed treatment the nasopharyngeal PCR swab show negative result for COVID-19. After being discharged, he did several chest X-ray examinations with progressively worsening cough. Chest CT-Scan revealed consolidations and cavity. Sputum culture was positive for *Candida glabrata* and negative for BTA. He received echinocandins as anti-fungal treatment, which inhibits enzymes that is necessary for fungi's cell wall synthesis, shows clinical and radiological improvement.

Discussion: COVID-19 affect immune system which resulting higher risk for secondary infection. The use of broad-spectrum antibiotics, immune-suppression of the host, and use of medical devices are major risk factors for *Candida* infections. Meanwhile *C. Albicans* is still the most common cause of fungal pneumonia by *Candida*, we should consider *C. glabrata* as one of its pathogens.

Conclusion: COVID-19 affects many aspects in our life, even after we treat the main problem, some patients manifest symptoms later. Diagnosing fungal infection especially invasive candidiasis is quite challenging with higher mortality rate. Not only *C. glabrata* more uncommon than *C. albicans*, but also it was one of difficult to treat pathogens.

Keywords: *candida*, glabrata, pneumonia, post COVID-19

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INTRODUCTION

Since March 2020, World health organization (WHO) has been declared severe acute respiratory syndrome (SARS-CoV2) as global pandemic and it affects many aspects in civilization.[1] It can develop into long COVID-19 syndrome, which means people suffering from symptoms after SARS-CoV2 infection, and it had been an issue we all have to face.[2]

Secondary infection in post COVID-19 is a problem with high mortality (56.7%) and often underdiagnosed especially fungal infection.[3] COVID-19 carries a risk of developing secondary infection and health practitioner should recognise and treat it properly. *Candida* species rarely cause pneumonia with the most common pathogen among the *Candida* species is *C. albicans*. C. *glabrat*a is known as non-pathogen *Candida* species and rarely acts as infectious agent but it can present in immunocompromised patients.[4] In this study, we present a case study regarding post COVID-19 patient with *Candida glabrata* pneumonia.

CASE

A 69 years old male came to our hospital with main complaints progressively worsened purulent cough in the last 4 days. He also Suffered with shortness of breath, fever, and myalgia.

A month before, he had prior infection of COVID-19 (confirmed by PCR swab) 1 month before admission and hospitalized for 9 days. Figure 1 showed first chest X-ray when diagnosed with COVID-19. One day after being discharged, he suffered with another episode of cough, fever, and desaturation (90–91%) with worsening lung infiltrates

and hospitalized for 8 days. Later on, he was confirmed negative for COVID-19. Figure 2 is serial chest x-ray upon admission in our hospital showed worsening infiltrate followed by cavitary lesion. Past medical history is diabetes mellitus without prior infection of tuberculosis. From physical examination showed fever (37.8^{o}C) with slightly increased respiratory rate 26/minute, and decreased peripheral saturation (92%).

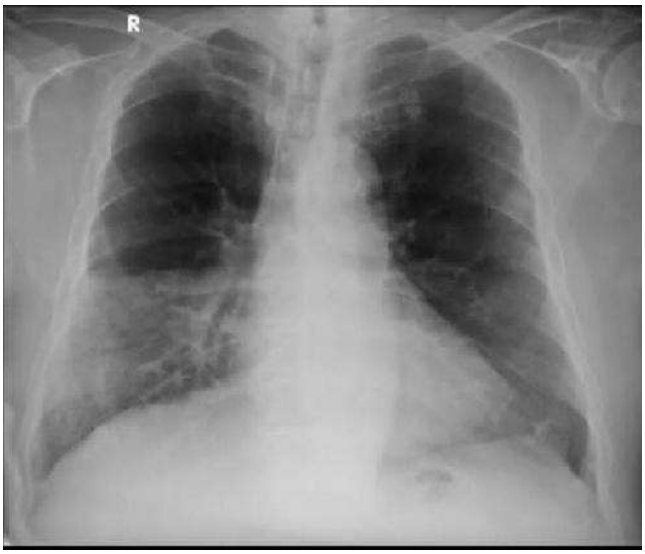

Figure 1. Chest X-Ray when he first admitted for being positive for COVID-19

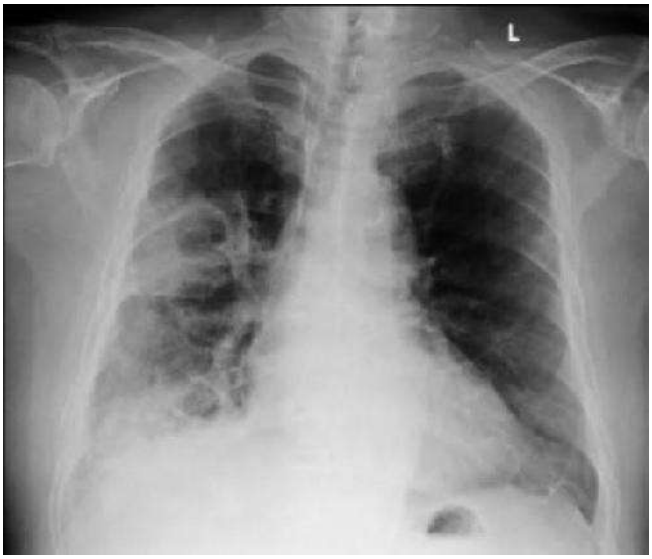

Figure 2. Chest X-Ray on current state, showed areas of consolidation with cavitation in right mid and lower lobes

Rales were present on auscultation on mid and lower zones of right lung. He showed no oral candida and showed no respond on antibiotics (based on his previous prescription). Laboratory investigation showed leucocytosis with WBC count of 11.8/mm^3 and negative swab PCR test for COVID-19. On third day of admission, he had chest CT-scan (Figure 3a) showed consolidations, nodule with irregular wall thickening and cavitation (doughnut sign) on upper and mid right lung with suggestive fungi infection with differential diagnosis lung tuberculosis. He was confirmed negative infection of tuberculosis from rapid molecular sputum testing and Ziehl-Nielseen sputum smear. Microbiology finding showed *Candida Sp*. (Figure 3b) and sputum culture was positive for *Candida galbrata* (*C. galbrata*). He started anidulafungin, an anti-fungal agent which belong to echinocandins group. Echinocandins inhibit beta-(1,3)-D-glucan synthase, an enzyme that is necessary for the synthesis of fungi's cell wall. There is gradual improvement within clinical and radiological findings, while patients being discharged.

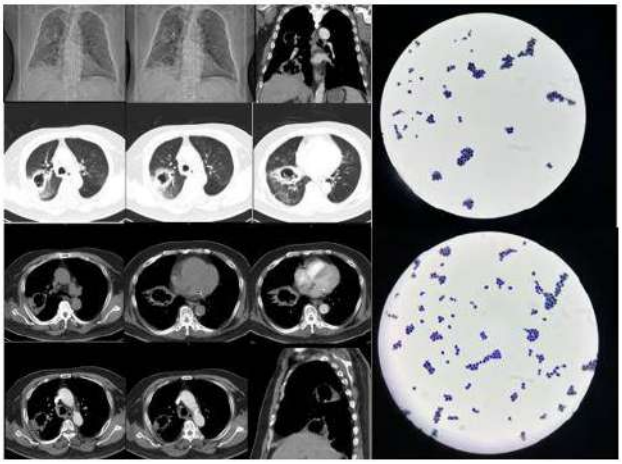

Figure 3. (a) CT-scan showed consolidation with nodule with irregular wall thickening and cavitation; (b) microbiology findings showed *Candida Sp.* and continued with sputum culture showed *Candida galbrata*.

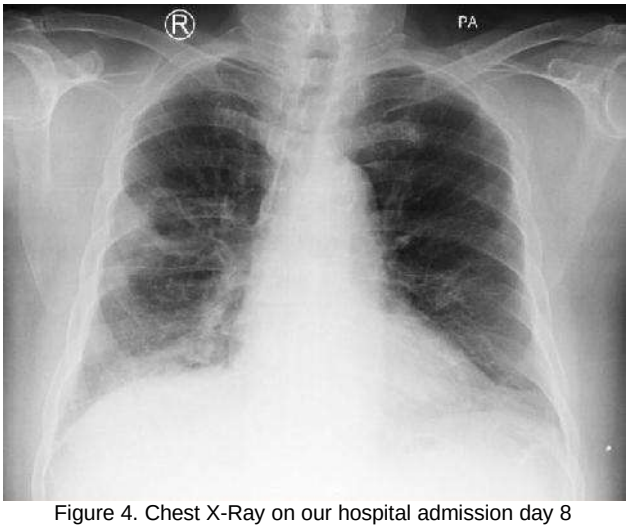

Figure 4. Chest X-Ray on our hospital admission day 8

Figure 4 showed a decreased of infiltrates within the cavitary lesion 4 days after starting antifungal treatment. Figure 5 showed faded cavitary lesion within 1 week after discharged. He was allowed to discharge from hospital and did some follow up treatments.

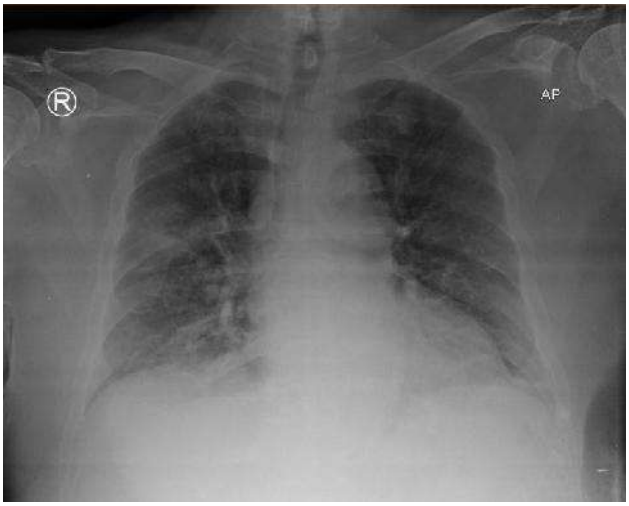

Figure 5. Chest X-Ray Followed up on clinic, one week after discharged

DISCUSSION

Severe Acute Respiratory Syndrome (SARS-CoV-2) affects many aspects in life. Even after being treated, it still affected part of human population. Researchers and several studies have reported the long-term complications of COVID-19 has variety of symptoms and organ-related injuries, which referred as “long COVID” or “post-acute COVID-19 syndrome”.[5]

Post COVID-19 is condition to describe health issues that persists more than four months after first being infected with the virus. Most people with COVID-19 infection recovered within weeks to months of illness, but some do not.[6] Even after the infection being properly treated, the massive number of people who have been infected with SARS-CoV-2 suggests that this will represent a public health issue leading to a major consumption of healthcare resources. Long COVID has been identified as a clear priority of the utmost importance for the World Health Organization.[7]

Secondary infection and fungal infection are major issue in post COVID-19 patients. COVID-19 patients especially with comorbid like diabetes mellitus, are severely immunocompromised thus could be easily infected with fungal infection. It is often underdiagnosed and undertreatment which can leads to mortality.

Fungi Is a normal colonization in body without harming the host. The true pathogens will generating variety of syndromes. Fungal pneumonia is an infectious process in the lungs caused by one or more endemic or opportunistic fungi. From studies, the main fungal pathogens for fungal coinfections in severe COVID-19 are *Aspergillus* and *Candida*. Other infrequent opportunistic pathogenic fungus caused lung infections also need to be considered, such as *Mucormycosis* and *Cryptococcus*. Opportunistic fungal organisms like we mentioned before, tend to cause pneumonia in patients with congenital or acquired defects in the host immune defences such as COVID-19 patients.[8,9]

The recent global pandemic of COVID-19 has predisposed a relatively high number of patients to acute respiratory distress syndrome (ARDS). This carry risk to develop super-infections and dysregulation in immune system. *Candida* species are major constituents of the human mycobiome and non-pathogen if the host immune is normal and it is inhabiting various mucosal surfaces. Although being commensal within the human host, *Candida* species are equipped with virulence attributes, enabling them to invade when opportunities arise and cause various infections in humans, especially when the immune system is impaired.

The most prevalent *Candida* species as per the recent studies COVID-19 patients, is *Candida albicans* (44.1%); followed by *C. auris* (23.2%); *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, and *S. cerevisiae* (4.6% each); and *C. krusei* and *Rhodotorula spp*. (2.3% each). *Candida* infection is rare, meanwhile the estimated mortality attributed to invasive candidiasis is 19–40%.[10,11]

The use of broad-spectrum antibiotics, Immunosuppresants agents, and the use of medical devices are major risk factors for *Candida* infections. Meanwhile *C. Albicans* is still the most common cause of fungal pneumonia by *Candida*, non-*C. albicans* species has increased over the years and

need more attention. *C. glabrata* is the second or third most frequently isolated *Candida* species. This high incidence can be partially explained by the inherent low susceptibility of *C. glabrata* to the most used class of antifungal drugs, the azoles, and consequently *C. glabrata* are associated with high mortality rates.

Invasion of the pulmonary parenchyma by *Candida* is rare, due to its presence in respiratory specimens is usually regarded as contamination. However, with the increased use of immunosuppressive agents, mucosal and systemic infections caused by *C. glabrata* have increased significantly, especially in the HIV-infected population.[12,13]

The wide usage of antibiotics, steroids, along with insult by SARS CoV-2 infection, causes commensal *Candida* to invade internal organs. When *Candida* enters the blood and spreads to other body sites, there occurs invasive candidiasis. The various predisposing factors include immunosuppression, surgical procedures, renal failure, prolonged placement of central venous catheter, malignancy, prolonged antibiotic usage, late sepsis. Fear of missed secondary infection and lack of specific therapy for COVID-19 leads to over-prescription of antibiotics.

Sending appropriate cultures, use of biomarkers like procalcitonin and galactomannan and antibiotic time-out at 48 hours of prescription can help in reducing unnecessary antibiotic prescriptions.[1,3] Awareness of the possibility of fungal co-infection is essential to reduce delays in diagnosis and treatment in order to help prevent severe illness and death from these infections.[14]

In this patient, COVID-19 carries its own risk as major risk factor for Candida infection along with his diabetes mellitus as his comorbid. It made host immune system became impermeable. One of risk factor for fungal infection is prior used of AB. This is due to bacterial infection is the most common secondary infection in COVID-19. Cavitary pneumonia presentation of pulmonary candidiasis is rare but was seen in the present case and chest X-Ray.

This patient was diagnosed as invasive candidiasis by clinical features, positive sputum cultures, Chest X-Ray and chest CT-Scan. Although differential diagnosis arise such as tuberculosis infection that has similar manifestation but the acid fast bacilli (AFB) stain and rapid molecular testing (RMT) was negative MTB.

After given anidulafungin, an anti-fungal treatment which belongs to echinocandins group, The patient's condition was getting better and showed less infiltrates and cavitation in his follow-up chest X-Ray. The echinocandins have a unique mechanism of action, inhibiting beta-(1,3)-D-glucan synthase, an enzyme that is necessary for the synthesis of an essential component of the cell wall of several fungi. Echinocandins show as effective treatment against most *Candida spp.*, including strains that are fluconazole-resistant.[15]

Health practitioner should be aware that COVID-19 can develop secondary infection even after we treat the main COVID-19. When it is developing into secondary infection, it is hard to diagnose the etiologic and relies on a combination of clinical, radiologic, and microbiological factors.[9] COVID-19 itself is a risk factor, furthermore there are other risk factors besides immunosuppression condition made by COVID-19 like the use of broad-spectrum antibiotics and host immune status and patients comorbid. Antibiotics should be given wisely and think about the benefits and the risks. Diagnosis and prompt treatment should be delivered quickly, especially when the patient gets candidiasis as secondary infection because it has high mortality.

LIMITATION

Specific tests or biomarkers to diagnose candidiasis in this case like the Galactomannan test were not performed due to lack of facility.

CONCLUSION

COVID-19 affects many aspects in our life, even after we treat the main problem, some patients can occur symptoms after it. Fungal infection especially invasive candidiasis is difficult to diagnose

and have high mortality rate. Health practitioner should consider host immune status, comorbid such diabetes mellitus, to diagnosed it thoroughly and treated it properly. Although *C. glabrata* is rarer than *C. albicans,* it has its own problem and hard to treat too.

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Case Report

Clinical Response and Safety of Alternating Daily Dosage of Crizotinib due to Side Effects in Advanced NSCLC patient harboring ROS1-rearrangement: A Case Report

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Abstract

Background: Advanced lung cancer has the lowest overall survival than other stage and tyrosine kinase inhibitor (TKI) are promising to prolong life and prevent disease progression. ROS1 rearrangement was very rare and constitute around 1.4 % of all NSCLC. Previous preclinical and clinical trial have reported the efficacy and safety of crizotinib against advanced NSCLC with ROS1 rearrangement, but little is known about its efficacy with nonstandard dosage.

Case: A female, 58 years old, with no history of cancer nor smoking, came with persistent chest pain and cough for three months. The patient was then diagnosed with advanced lung cancer by FDG-PET CT Scan. The biopsy confirmed adenocarcinoma with genotyped ROS1-rearrangement. After receive standar dose of 200 mg bid, the patient intolerated and treatment plan was adjusted with 200 mg of alternated daily dosage (one-day on-off drug administration). Fortunately, the intolerance symptoms were alleviated and showed positive response during 3-years therapy.

Discussion: Pulmonary tuberculosis has been linked to pneumothorax in HIV-associated TB patients. This study is done to better our understanding of the link between the two. The patient had active pulmonary tuberculosis as well as HIV and a rare case of bilateral pneumothorax in the ER.

Conclusion: This case showed that advanced NSCLC with ROS1 rearrangement has positive response to crizotinib despite using alternating daily dose, with good response during 3 years and on.

Keywords: Crizotinib, NSCLC, ROS1 rearrangement

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INTRODUCTION

Advanced lung cancer has the lowest overall survival than other stage, thus pose great challenge to the physician.[1] By far, current available treatment could not optimize the survival rate. However, immunotherapy and targeted therapy, i.e. tyrosine kinase inhibitors are promising to prolong life and prevent disease progression, especially for non-small cell lung cancer (NSCLC).[2] The decision of prescribing small molecules kinase inhibitor is based on the present of molecular profile of lung cancer, for example, C-ros oncogene 1 (ROS1) and anaplastic lymphomakinase (ALK).[3]

Lung cancer detected positive for both markers are proven to be sensitive to multiple receptor protein kinases inhibitors, for instance crizotinib (first generation), ceritinib (second generation), and lorlatinib (third generation).[4–6] Previous preclinical and clinical trial have reported the efficacy and safety of crizotinib against NSCLC, especially in late stage.[4,7–13] However, since the cost for the treatment was high, small molecule kinase inhibitor is not the first line treatment in lung cancer with ROS1-positive especially in developing countries. Here, we report our case of naïve-advanced NSCLC with ROS1-positive treated with the first generation of small molecule inhibitor of multiple receptor tyrosine kinases, crizotinib, as first-line therapy. The patient showed both clinical and radiological remission and long-term progression free-survival (PFS).

CASE

A 58 years old housewife with no history of cancer and smoking, came with persistent chest pain

and cough for three months. The patient later diagnosed advanced lung cancer with liver nodule (metastasis) through CT Scan and FDG-PET Scan (figure 1A). Biopsy confirmed adenocarcinoma with genotyped ROS1-rearrangement, EGFR wild type, ALK-negative, and PD-L1 0% through next-generation sequencing (NGS).

As the diagnosis confirmed with ROS-1 positive, the patient was then initiated with crizotinib 250 mg bid per day without starting other therapy regimens. The patient experienced diarrhea 8–10 times/days, nausea and vomiting with mild dehydration with limited daily activities after 1 week administration. Common terminology criteria for adverse events (CTCAE) grade 3–4. Patient was hospitalized and treated with loperamide, proton pump inhibitor and rehydration while crizotinib was stopped. No evidence of gastrointestinal infection based on stool evaluation. The treatment was started again after 1 week recovery with lowering dose 200 mg ones a day. But after 1 week therapy, the patient remain intolerant.

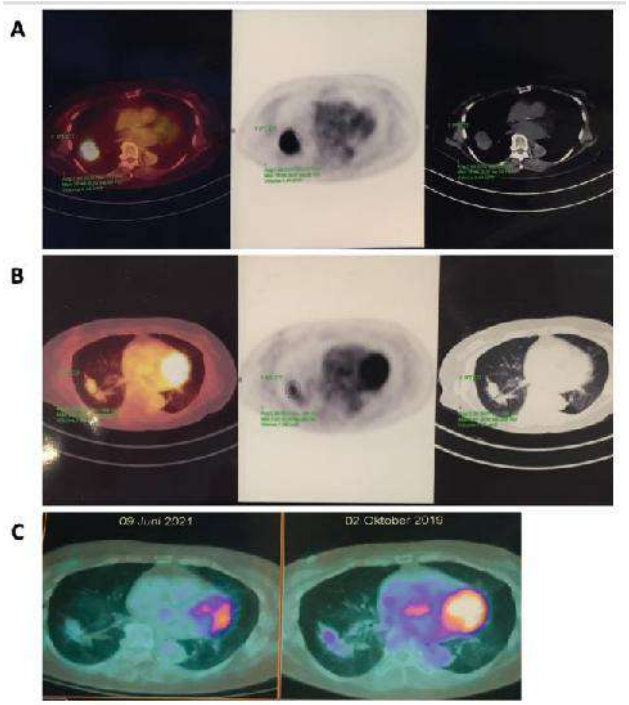

Figure 1. A) ^{FDG}-PET-CT scan in 2018 showed pulmonary mass with enhanced uptake; B) PET-CT scan taken 1 year later show stable disease; and C) PET-CT scan after 3-years therapy showed decreased mass with fibrotic loci and no metabolic activity.

The diarrhea and nausea reappeared in milder symptoms (<4 times) despite loperamide and symptomatic medication. The patient decided to stop the treatment due to side effects again but started again the crizotinib with adjusted dose of 200 mg alternate-day dosing. Fortunately, increased. But when the dosage was increasing 200 mg twice daily, the symptoms reappeared and inconvenient for the patients. The alternate-day dosing was then continued since the patient has minimal side effect and significant improvement in respiratory symptoms after 2 weeks.

The patient maintains symptoms' improvement during evaluation in the first 3- and 6-months treatment with partial response based on thoracic CT scan. The tumor reduced in size from 4 cm in diameter to 1 cm. In the first year of therapy, the patient feels better subjectively. The patient also had achieved radiological partial response (Figure 1B) according to Response Evaluation Criteria in Solid Tumor Version 1.1 (RECISTv1.1). The tumor decreases in sized but still with metabolic activities and fibrotic foci. The patient continued her treatment. Thoracic CT scan were checked every 3–4 months during therapy.

After the third year of therapy, the patient continued showing partial response. FDG-PET scan (figure 1C) showed lung fibrosis without contrast enhancement, with tumor diameter <1 cm. The laboratory examination, including complete blood count, C-Reactive Protein (CRP), D-dimer, liver, and renal function, and (carcinoembryonic antigen) CEA, also remains stable, which was maintained until publication. At last, our patients showed an overall survival rate of 3 years and still on going.

DISCUSSION

ROS1 is the gene that encodes the tyrosine kinase receptor, located on chromosome 6q22 and ROS1-positive lung cancer is a type of lung cancer harboring a ROS1 gene rearrangement that is thought to be the driver mutations. The exact mechanism of mutation is translocation mutations which affect cell growth and division. ROS1-positive lung cancer is rare, approximately account 1–2% of

adenocarcinoma and 1.4% of the entire NSCLC.[14,15] Furthermore, ROS1-positive lung cancer is prevalent in middle-aged women who are never smoking.[16] Consistent with the study, our case also presents as a middle-aged female.

ROS1-positive lung cancer exhibits a phenotype of aberrant tyrosine kinase receptor and has been too active, which help the cancer cells to grow uncontrollable. Crizotinib, known as small molecule inhibitor of multiple receptor tyrosine kinases, has posed a benefit in ROS1 and ALK-positive lung cancer and developed to inhibit ligand binding and receptor oligomerization. In vitro data suggested the potent activity of crizotinib to downstream effector functions and inhibit apoptosis.[11]

Based on available clinical trials, crizotinib is administered perorally and with a daily dose of 250 mg bid and personally adjusted based on the occurrences of the side effect, such as visual disturbance, nausea, dizziness, fatigue, and decreased appetite.[4,9–13] EUCROSS clinical trial has also suggested reducing dose up to 200 mg twice daily and 250 mg of daily dosage for patients with intolerance symptoms.[11]

Rothenstein and Letarte did a review of ALK inhibitors side effects including crizotinib.[17] It is recommended to withhold crizotinib if grade 3 or grade 4 appear in the patient. In patients with diarrhea, infectious causes should be rule out. Loperamide could be used followed with dietary modification and adequate hydration are strongly recommended. If the adverse events were recovered, it is recommended to reduce the dose at 200 mg twice daily.[17]

Alternative way to introduced crizotinib after side effect is desentization procedure in cases with skin adverse events.[18] Crizotinib is given orally starting with 10 mg and increase to 25, 50 and 100 with interval of 30 minutes each. During desensitization protocol, the skin lesion will be observed carefully. This desensitization protocol could be used in skin rash or rapid onset skin hypersensitivity due to crizotinib. Unfortunately, no recommendation for crizotinib desensitization protocol other than for rapid onset skin hypersensitivity.[18]

Our patient experienced gastrointestinal intolerance symptoms with 250 mg po. For that reason, the dose was reduced to acceptable dose up to 200 mg with alternating daily dosage. To our knowledge, there is no report of efficacy and safety reducing the crizotinib with alternating dosage.

There is evidence that crizotinib is superior than chemotherapy (platinum-pemetrexed based) as the first-line and maintenance of therapy in advanced ROS1-positive lung.[19] Our case was unique in that she had prolonged PFS and OS longer with lower dose than reported in previous trial. Our finding infers the need for randomized controlled trials to confirm crizotinib alternating daily dose superiority over regular dosage in the purpose for both achieving maximum response rate and avoiding detrimental adverse effects.

LIMITATION

There are limitations in this case report. Despite the favorable response with alternating dose of crizotinib, there was no data regarding serum concentration of crizotinib in this case whether it was still within therapeutic dose and factors that affect its concentration in serum i.e., changes in crizotinib metabolism. We do not have data regarding details molecular characteristic/mutations of the tumor that might effect the treatment responses. Since this is only one case and the treatment protocol is not mention in the guideline, generalization into all NSCLC patients should be used with cautious.

CONCLUSION

Our case report showed that advanced NSCLC with ROS1 rearragement showed positive response to crizotinib alternating day as first line therapy and remain stable after 3 years, respectively, with acceptable side effects.

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Case Report

Simultaneous Bilateral Spontaneous Pneumothorax in an HIV Positive Tuberculosis Patient

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Abstract

Background: Even though tuberculosis has been linked to pneumothorax for a long time and has caused significant morbidity and mortality in some patients, it has been the topic of few publications and analyses, thus very little study has been done to evaluate and review on this matter.

Case: In this article, we reported a 39-year-old male, presented to the ER with breathlessness for the last 3 days accompanied by increased sputum productivity. The patient had an active pulmonary tuberculosis taht was under treatment, as well as HIV. Physical examination showed low chest expansion, weakened breathing sounds on both lungs, and the use of accessory breathing muscles. The chest X-ray showed bilateral pneumothorax. The patient underwent emergency chest decompression with a 16-gauge needle on both sides, followed by the insertion of an IPC and chest tube. The patient's breathlessness got significantly better, and after 35 days, the IPC was removed.

Discussion: Pneumothorax is a frequent complication in Tuberculosis with HIV, with a prevalence of 6.8% compared to 0.95-1.4% in Tuberculosis without HIV. The progression of breathlessness in bilateral pneumothorax on HIV positive Tuberculosis patient is slower, up to 3 days since onset, compared to pneumothorax occured in other etiologies. Secondary pneumothorax usually occurs after extensive destruction of the lungs, leaving a little functionality and lower cardiopulmonary reserve, thus requiring prompt evaluation and more aggresive lifesaving treatment.

Conclusion: Based on this case, bilateral pneumothorax found in HIV-associated TB patients comes with an insidious onset but warrants immediate evaluation and aggressive treatment or surgery if necessary.

Keywords: HIV-associated tuberculosis, pneumothorax, pulmonary tuberculosis

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INTRODUCTION

Secondary spontaneous pneumothorax in HIV-associated tuberculosis (TB) patients is more prevalent compared to immunocompetent TB patients (6.8% versus 0.95–1.4%). In immunocompromised patients, many blebs form on the lungs, and pneumothoraxes can happen when they rupture.[1–5]

While most secondary spontaneous pneumothoraxes are found with a sudden onset of breathlessness, secondary spontaneous pneumothoraxes found in HIV-infected TB patients have an insidious symptom; many have days of breathlessness before presenting to the hospital, even if they had bilateral pneumothoraxes. Such distinct characteristics need to be known and anticipated when tending to patients with HIV-associated TB.[1–5]

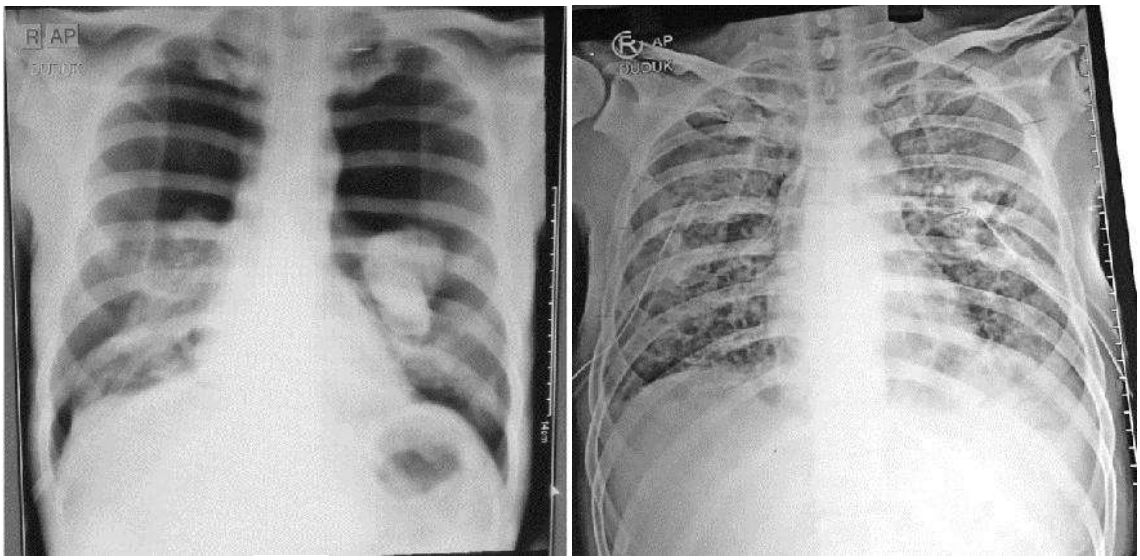
Tuberculosis has been linked to pneumothorax for a long time, but very few publications and analyses are performed on this subject. This case report discussed pneumothorax on TB, especially on people living with HIV.[1]

CASE

A 39-year-old male was presented to the ER with the chief complaint of breathlessness that started for the last 3 days and got worsened. The patient and his family said that he had never suffered from such a condition before. The patient had a productive cough for the last one month, which increased in production for the last 3 days. The patient had a history of having active pulmonary TB and had been undergoing treatment for the last 2 weeks with a fixed drug combination consisting of rifampicin, isoniazid, pyrazinamide, and ethambutol;

as well as being HIV positive, but had not received any treatment yet. No fever, difficulty swallowing, vomiting, nor any other symptom that was currently experienced.

Initial physical examination showed the patient was fully alert with GCS E4-V5-M6, blood pressure of 122/87 mmHg, heart rate of 105 bpm, body temperature of 36.5^{o}C, respiratory rate of 28/minute, and SpO_2 of 86% on room air. His chest was symmetrical, with low chest expansion, weakened breathing sounds on both lungs, and the usage of accessory breathing muscles. No other physical abnormalities were found.



(a) (b)

Figure 1. Chest X-Ray taken on (a) admission, radiological examination at the first time the patient went to the referral hospital, and (b) the fifth day, evaluation after IPC chest tube insertion and continuous suctions

The patient received oxygen supplementation, underwent emergency chest X-ray and blood laboratory examination. Chest X-ray showed bilateral pneumothorax (figure 1.a); no COVID-related laboratory abnormalities were found. The patient underwent emergency chest decompression with 16-gauge needle on the 2nd intercostal space midclavicular line on both side of his chest, followed by IPC insertion but no change in dyspnea. The IPC was changed to a chest tube with active suction for 15 minutes every 12 hours. The patient's breathlessness got significantly better, and the patient was admitted for further observation. Following 5 days of chest tube insertion, the patient felt better, and after confirming bilateral lung expansion (figure 1.b) on the 6th day, the chest tube was switched to IPC with occasional drainage whenever the patient had breathing difficulty. The patient was then discharged with stable hemodynamic and breathing.

On an outpatient visit after 35 days of IPC insertion, the patient had no breathing complaints, and the cough has subsided. The IPC was then removed, and since then the patient has been regularly treated and has not had a pneumothorax incident.

DISCUSSION

Tuberculosis is an infectious disease caused by *Mycobacterium tuberculosis*. Depending on the infected organ, it is grouped into pulmonary TB, which is tuberculosis occurring in the lung parenchyma (constituting 80% of all cases), and extrapulmonary TB, which affects organs other than lungs, and is most common in the pleura, lymph nodes, spine, joints, genitourinary tract, central nervous system, abdomen, and other organs.[6]

Not everyone gets sick after becoming infected. Some people can get sick years after the infection; others whose immune systems got weakened by

other means may get sick just weeks after infection; while others may even never get sick. Only about 5–10% of all infected people get sick from *Mycobacterium tuberculosis* infection. Weakened immune systems strongly correlate with rate of TB disease development.[7]

There are two groups of people with higher rates of TB disease development. The first is people who have been recently infected, such as healthcare workers, people who have just traveled from high-risk areas, TB patient caregivers, and those who live in a high-TB transmission area. The second is those with lowered immunity, such as babies, children, or the elderly; an HIV-positive patient; drug abusers; people with diabetes mellitus, chronic kidney disease, low body weight; organ transplants; or head and neck cancer.[7]

People with TB most often come to their physician with a chief complaint of a chronic productive cough, sometimes with blood in their sputum. This symptom often comes with systemic symptoms, such as fever, night sweats, weight loss, and anorexia, while lymphadenopathy is a feature almost exclusively found in people with HIV infection.[8]

Cavitation is a major manifestation of human TB and closely related to poor prognosis, including delayed sputum conversion, infection relapse, and, arguably most avoided of all, the development of drug-resistant bacteria. If the cavity persists after 6 months of anti-tuberculosis therapy, the risk of relapse is doubled. Cavitation also increases transmission between humans since cavitation is attributable to a high bacterial burden and extensive disease. Relapse and the development of drug resistance are thought to be a result of poor drug penetration into the poorly vascularized cavity.[9]

Cavitation is found in 29% to 87% of all TB upon diagnosis. This could be higher than it actually is because cavitary TB has a higher bacterial load on its sputum, thus increasing the sensitivity of laboratory test. Lower immunity has a different effect on cavitation. Cavitation is found more often in people with diabetes mellitus but is significantly lower in people with untreated HIV, organ transplant recipients, and the elderly, although increased cavitation is seen after 6 months of ARV therapy.[9]

Cavitation most often occurs in the apices of the upper or lower lobes; once this happens, an exponential growth of bacteria in the lungs occurs, causing a higher bacterial burden and more bacteria being expectorated into the air through coughing. There are two ways the *Mycobacterium tuberculosis* can reach the apex of the lungs: first, through initial deposition in the apex; the other way is through the bloodborne phase in TB. This bloodborne phase is consistent with the way TB disseminates throughout the lungs in miliary TB and in positive TB blood culture in some HIV positive patients.[9]

Human lung parenchyma mainly consists of collagen fibers, specifically Type I, III, and IV. These collagens are very resistant to destruction and can only be degraded by specific enzymes. The aforementioned enzymes are found in leukocytes, which are recruited and activated by *Mycobacterium tuberculosis* to the lungs, consequently causing the destruction of lung parenchymal collagens. This release of protease enzymes activates particular matrix metalloproteinases (MMPs).[10]

MMP concentration correlates with the extent of lung tissue destruction. TB patients with more extensive tissue destruction have a significantly higher MMP yield in their sputum. Similarly, people with HIV and TB co-infection are more likely to have a lower MMP yield in their sputum, consistent with their anatomical finding that people with HIV and TB co-infection who have a lower CD4 count have lesser lung tissue destruction. This implies that in people with HIV and TB co-infection, the immune system is so weakened that it is insufficient to cause major lung destruction.[11]

Pneumothorax is a frequent complication found in TB patients with HIV infection. While TB alone is a frequent underlying cause of secondary spontaneous pneumothorax, consisting around 44.7–78% of pneumothorax patients, this seemingly high number consists only of about 0.95–1.4% of all active TB. Compared to pneumothorax in immunocompromised patients, the prevalence of pneumothorax in these patients goes up to 6.8%, which means around 20%

of all pneumothoraxes in immunocompromised patients are linked to the presence of TB.[1,2]

According to the WHO, in 2018, about 862,000 people living with HIV had tuberculosis co-infection, causing a third of AIDS deaths or about 251,000 deaths in 2018. Based on these numbers calculated with the pneumothorax incidents in HIV-infected TB patients, around 58,616 pneumothoraxes occurred in these patients, but many might not be documented due to the fact that up to 44% of all people with HIV-associated TB did not achieve medical care. [2,12]

Mechanism of pneumothorax in immunocompromised TB patients is still unclear, however, it is suspected that *Mycobacterium tuberculosis* induced a chronic inflammation through macrophage activation, causing obstruction, hyperinflation, and alveolar rupture. Other possible mechanisms are where a subpleural miliary nodule undergoes caseation and necrosis, followed by rupture, causing pneumothorax; and the formation of bullae or an emphysematous lesion, which then rupture.[2,3]

In the article published by Liu et al., several blebs were found on the lung surface during video assisted thoracoscopy (VAT), which supports the proposed mechanism where rupture of an emphysematous lesion causes pneumothorax, possibly even a bilateral pneumothorax in our case when a patient had multiple lesions on both lungs, which then rupture following a heavy cough induced by the first pneumothorax. The existence of multiple blebs also explains why patients with miliary TB often had recurrent pneumothoraxes, although this phenomenon was absent in our patient.[4]

Most secondary pneumothorax cases, such as secondary to COPD, TB, necrotizing pneumonia, *Pneumocystis carinii*, lung cancer, cystic fibrosis, acute severe asthma, and many others, had sudden onset of severe breathlessness as a primary symptom, accompanied with chest pain, hypoxemia, and hypercapnia. In contrast to other causes, pneumothorax secondary to TB in HIV patients has a different symptom: the onset of breathlessness is slower, even took 3 days in both our patient and the two patients mentioned in articles from Dhamgaye et al. and Liu et al., even though these 3 patients had bilateral pneumothorax, which arguably should present with more acute and severe breathlessness.[3–5]

Compared to primary spontaneous pneumothorax, secondary spontaneous pneumothorax bears a more severe complication to the patient; this is because of the underlying disease, be it TB, COPD, or HIV which compromises the patients' cardiopulmonary reserve, thus lowering their chance of survival. Added to this is the fact that most pneumothorax usually occurs after extensive destruction of the lungs, leaving only a little lung functionality. These premises warrant and prompt diagnosis from a precise and accurate history taking, physical diagnostic, chest radiography, and/or ultrasound which was found to be superior. Followed with aggressive lifesaving treatment such as chest tube, oxygen supplementation, or even a thoracotomy.[11,13]

In order to prevent the occurrence of recurrent secondary spontaneous pneumothorax, pleurodesis in form of thoracotomy surgery or Video Assisted Thoracoscopic Surgery (VATS) is considered the best solution, where identification and stapling of lesions are followed by pleurectomy and pleural abrasion to obliterate the pleural space. Although the recurrence of spontaneous pneumothorax following pleurodesis procedures is approximately 1%, pleurodesis in the form of VATS for secondary spontaneous pneumothorax is associated with higher morbidity compared to VATS for primary spontaneous pneumothorax, possibly due to the lower cardiopulmonary reserve observed in these patients; therefore, selective and strict patient evaluation before such procedure is essential to ensure patient safety and procedure benefit.[4,5]

LIMITATION

This study has potential limitations. The low number of patients currently documented with bilateral pneumothorax in Tuberculosis with HIV positive caused lack of generalizability and low level evidence. In this particular patient, late of treatment,

lack of medication history information may cause incomplete data and discussion.

CONCLUSION

This case report highlights insidious breathlessness onset in the case of bilateral pneumothorax in HIV positive patient, but due to more extensive pulmonary destruction that occured before pneumothorax and lower cardiorespiratory reserve, that requires more aggresive lifesaving treatment.

ACKNOWLEDGMENTS

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CONFLICT OF INTEREST

None

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Literature Review

Effectiveness of Vitamin C Administration on Outcome in COVID-19 Patients: A Systematic Review and Meta-Analysis

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Abstract

Background: Numerous studies on the effectiveness of vitamin C against the COVID-19 infection have been widely carried out recently. However, the differences in dosage ranges and therapeutic efficacy in previous studies have prompted a systematic literature review on the effectiveness of vitamin C on outcomes in COVID-19 patients. In addition, this study aimed to determine the appropriate therapeutic dose of vitamin C for COVID-19 patients, either alone or in combination with other supplements, and to determine the side effects.

Methods: Gleaned from the search on Pubmed, Science Direct, and Google Scholar databases up to April 25, 2022, fourteen studies were relevant, namely five studies using vitamin C orally and nine studies administered intravenously. We assessed multiple outcomes, including mortality, hospitalization, and symptoms. The quality and risk of bias analyses were performed using JBI critical appraisal tools.

Results: The oral administration of vitamin C resulted in a significant difference in the mortality of COVID-19 patients (OR=0.66; 95% CI=0.45–0.97; *P*=0.04; I^2=0%) and a non-significant difference in the outcome. Duration of hospitalization (OR = -0.21; 95% CI = -2.70-2.28; *P*=0.87; I^2=94%). Regarding the cost-effectiveness and side effects manifested in digestive disorders such as nausea, diarrhea, stomach cramps, and vomiting, vitamin C with a dose of 500-1000 mg could be given orally.

Conclusion: Oral administration of vitamin C showed a reduction in the mortality of asymptomatic COVID-19 patients with moderate symptoms.

Keywords: ascorbic acid, mortality, SARS-CoV-2, supplements

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a disease characterized by severe acute respiratory syndrome.[1] It spread rapidly around the world and led to an increase in confirmed cases of COVID-19. Hence, the World Health Organization (WHO) declared a pandemic in 2020 due to this disease. The prevalence of COVID-19 in the world as of March 18, 2022, reached 480,170,572 confirmed cases with a death toll of 6,124,396. In Indonesia, the incidence of COVID-19 was 6,001,751 confirmed cases, with a death toll of 154,774. [2]

Since its first appearance, the high rate of confirmed COVID-19 by reverse transcription-quantitative polymerase chain reaction (RT-qPCR) and the death rate in COVID-19 patients have led to continued research on this subject, one of which is research on supplements for COVID-19 patients.[3] Additional supplementation in COVID-19 patients is necessary because the pathophysiological involvement is very complex and involves a decrease in the immune system. This additional supplement can act as an immunomodulator, anti-oxidant, and anti-inflammatory. [4]

The supplement for COVID-19 that has been widely studied is vitamin C. [5] Ascorbic acid, or vitamin C, is an anti-oxidant that can fight reactive oxygen species (ROS). In COVID-19 patients, there is excessive ROS production due to an impaired body defense system resulting in an increase in oxidative stress that contributes to tissue damage. [6] Apart from being an anti-oxidant, vitamin C also acts as an immunomodulator.[7,8] In the case of influenza, the administration of vitamin C has a symptom-

ameliorating effect, reduces hospitalization duration, and significantly reduces the risk of death.[9]

Several studies on the effectiveness of vitamin C in COVID-19 patients have been conducted, both in RCTs and cohort studies. The results show differences in the effectiveness of therapy and variations in the dose used. Therefore, further research studies are required to provide up-to-date information on the effectiveness, therapeutic dose, and side effects of vitamin C administration on outcomes in COVID-19 patients.

METHODS

We collected the data from articles published in Google Scholar, Pubmed, and Science Direct until April 25, 2022, using Coronavirus Disease, COVID-19, SARS-CoV-2, vitamin C, and ascorbic acid as the keywords. A critical analysis of the selected studies was performed using The Joanna Briggs Institute (JBI) Critical Appraisal Tools for risk assessment of bias by the researcher and three reviewers. The meta-analysis was generated in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

The inclusion criteria used were: (1) randomized control trial (RCT) and cohort studies, from 2019 to 2022; (2) studies related to the administration of vitamin C to COVID-19 patients (primary or reinfection COVID-19 patients). The exclusion criteria were: (1) treatment of COVID-19 in the pregnant female population; (2) samples of less than 50; (3) incomplete information or full texts unavailable.

We used Review Manager Software version 5.3 to perform our meta-analysis to estimate the pooled odds ratio (OR), mean difference (MD), and 95% confidence interval (95% CI). The value of *P* less than 0.05 was considered to be statistically significant. The statistical heterogeneity was evaluated using the I^2 statistics. We performed a subgroup analysis among subjects who received vitamin C orally or intravenously, with mortality as the outcome of efficacious therapy, to minimize the impact of heterogeneity on the outcome of our results.

RESULTS

Based on the search of three databases, we found 1,222 studies. Subsequently, an eligibility assessment was conducted, and we excluded 1,208 studies, resulting in fourteen studies for further review. The study selection process is laid out in Figure 1.

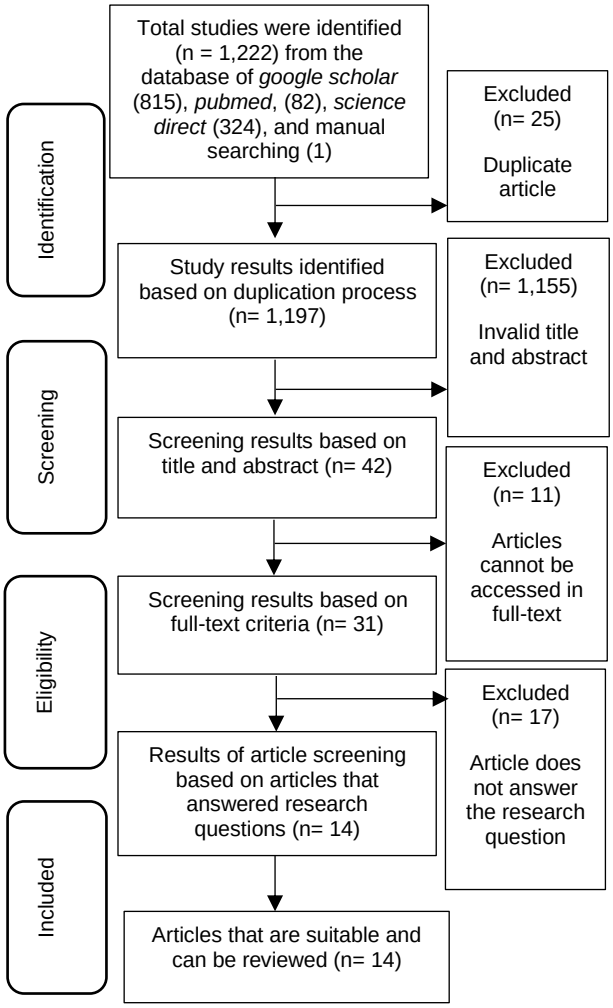

Figure 1. PRISMA flowchart of article selection

From the 14 studies reviewed, ten articles discussed the administration of vitamin C as a single supplement[10–19], and four studies examined the administration of a combination of vitamin C.[20–23] We analyzed the articles by extracting and synthesizing data. Outcomes obtained from this study were grouped into three types: mortality, hospitalization, and symptoms (duration of illness, fever, and anosmia). The results of data extraction and synthesis are shown in Table 1.

Table 1. Results of data extraction and synthesis

No	Author, Year of Publication, Country	Study Design	Study Setting	Subject Characteristics					Results	
				Type of Intervention	Mode of administration	Dose	Duration of Study	Infection (Primary/ Reinfection)	Effectiveness	Side Effect
1	Jamali Moghadam, Saeidreza, et al., 2020, Iran	RCT	Administration of vitamin C to 60 severe COVID-19 patients at Ziaeian Hospital, Iran from April - May 2020 was divided into two groups	Group I: vitamin C lovinapir/ritonavir and HCQ Group II: only lovinapir/ritonavir and HCQ	IV	6 grams vitamin C per day	5 days	Primary	There was an improvement in temperature in both groups, can reduce fever (*P*=0.001)	Unknown
2	Kumari, Poona, et al., 2020, Pakistan	RCT	Administration of vitamin C to 150 COVID-19 patients at Karachi Hospital from March – to July 2020 which was divided into two groups	Group I: vitamin C and standard therapy Group II: only standard therapy	IV	50 mg/kg BW/day	4 weeks	Primary	Symptoms improved (fever, dry cough, anosmia, and diarrhea) more quickly (5-9 days) (*P*=0.001) and hospitalization time (7-9 days) (*P*= 0.001) compared to the control group.	Unknown
3	Zhang, Jing, et al., 2020, China	RCT	Administration of vitamin C to 56 patients with severe COVID-19 in the ICU of three hospitals in China from February to March 2020 which was divided into two groups	Group I: vitamin C Group II: bacteriostatic infusion	IV	12 grams 2 times a day	7 days	Primary	Did not affect the use of mechanical ventilation (*P*=0.57)	Unknown
4	Li, Matthew, et al., 2021, United States of America	*Cohort Retrospective*	Administration of vitamin C to 56 COVID-19 patients from April – to May 2020	Group I: vitamin C, hydrocortisone, and thiamine Group II: only standard therapy	IV	1.3 grams 4 times a day	4 days	Primary	Did not affect mortality (*P*=0.05) and hospitalization duration (*P*=0.71)	Unknown
5	Gao, Dengfeng et al., 2021, China	*Cohort Retrospective*	Administration of vitamin C to 76 COVID-19 patients in the ICU of the China Hospital which was divided into two groups	Group I: vitamin C and standard therapy Group II: only standard therapy	IV	Loading dose of 6 grams of vitamin C IV twice a day on the first day followed by 6 grams a day the next day	28 days	Primary	Reduced mortality (*P*=0.03)	Unknown

No	Author, Year of Publication, Country	Study Design	Study Setting	Subject Characteristics					Results	
				Type of Intervention	Mode of administration	Dose	Duration of Study	Infection (Primary/ Reinfection)	Effectiveness	Side Effect
6	Hakamifard, Atousa, et al., 2021, Iran	RCT	Administration of vitamin C and vitamin E to 72 COVID-19 patients with pneumonia in Iran	Group I: vitamin C, vitamin E, and standard therapy Group II: only standard therapy	Oral	Vitamin C: 1000 mg per day Vitamin E: 400 IU per day	7 days	Primary	Vitamin C and vitamin E did not have a significant effect on COVID-19 patients (*P*=0.380)	Unknown
7	Suna, Kavurgaci, et al., 2021, Turkiye	*Cohort Retrospective*	Administration of vitamin C to 323 COVID-19 patients in Turkiye in September 2020	Group I: vitamin C and standard therapy Group II: only standard therapy	IV	2 grams per day	30 days	Primary	Did not affect hospitalization duration (*P*=0.05) and mortality (*P*=0.52)	Unknown
8	Zheng, Shaoping, et al., 2021, China	*Cohort Retrospective*	Administration of vitamins to 397 severe COVID-19 patients in China in February 2020	Group I: vitamin C and standard therapy Group II: only standard therapy	IV	2 – 4 grams per day	7 days	Primary	Did not affect mortality and symptom improvement (*P*>0.05)	Unknown
9	Liu, Fang, et al., 2020, China	RCT	IV administration of vitamin C to 308 patients in two ICUs in China	Group I: vitamin C and standard therapy Group II: only standard therapy	IV	12 grams 2 times a day	7 days	Primary		Unknown
10	Majidi, Nazanin, et al., 2021, Iran	RCT	Administration of vitamin C to 69 COVID-19 patients in Iran in May-June 2020	Group I: vitamin C and standard therapy Group II: only standard therapy	Oral	500 mg per day	14 days	Primary	Reduced the average duration of hospitalization in COVID-19 patients four days faster than the control group (*P*<0.01)	Unknown
11	Al Sulaiman, Khalid, et al., 2021, Saudi Arabia	*Cohort Retrospective*	Administration of vitamin C to 739 severe COVID-19 patients in Saudi Arabia from March – to December 2020	Group I: were given vitamin C Group II: were not given vitamin C	Oral	1000 mg per day	30 days	Primary	Did not affect mortality (*P*=0.11)	Unknown

No	Author, Year of Publication, Country	Study Design	Study Setting	Subject Characteristics					Results	
				Type of Intervention	Mode of administration	Dose	Duration of Study	Infection (Primary/ Reinfection)	Effectiveness	Side Effect
12	Thomas, Suma, et al., 2021, United States of America	RCT	214 COVID-19 patients were divided into four groups	Group I: Standard therapy (anti-viral) Group II: Vitamin C Group III: Zinc gluconate Group IV: Vitamin C and Zinc gluconate	Oral	50 mg zinc per day 8000 mg vitamin C (2-3 times a day)	10 days	Primary	There was no significant difference (*P*=0.45) in the treated group (reduction of symptoms such as fever, shortness of breath, or fatigue)	Nausea, diarrhea, and stomach cramps in the vitamin C group
13	Ried, Karin, et al., 2021, Australia and Turkiye	RCT	237 COVID-19 patients were divided into two groups	Group I: HCQ, AZM, zinc Group II: HCQ, AZM, zinc, and IV C + all groups were given vitamin D3	Oral zinc IV vitamin C	Zinc citrate: 30 mg Vitamin D: 5000 IU Vitamin C: 50 mg/kg (divided by 4 times on the first day); 100 mg/kg (divided 4 times per day on the next 6 days)	14 days	Primary	Significantly faster recovery in the group with IV vitamin C (*P*=0.0069)	Diarrhea, nausea, and vomiting in both groups
14	Margolin, Leon, et al., 2021, United States of America	*Cohort*	113 individuals were given over the counter (OTC) products as treatment and prophylaxis	Group I: were given OTC (zinc, vitamin C, vitamin D, vitamin E, quina, l-lysine, azithromycin, and doxycycline) Group II: were not given OTC drugs	Oral	Zinc: 25 mg Vitamin C: 1000 mg Vitamin D: 1000 IU	5 days	Primary	Effective in treating mild to moderate symptoms (*P*=0.04) at 2 doses/day, with no or only minimal addition to prescription (other standard antibiotics)	Unknown

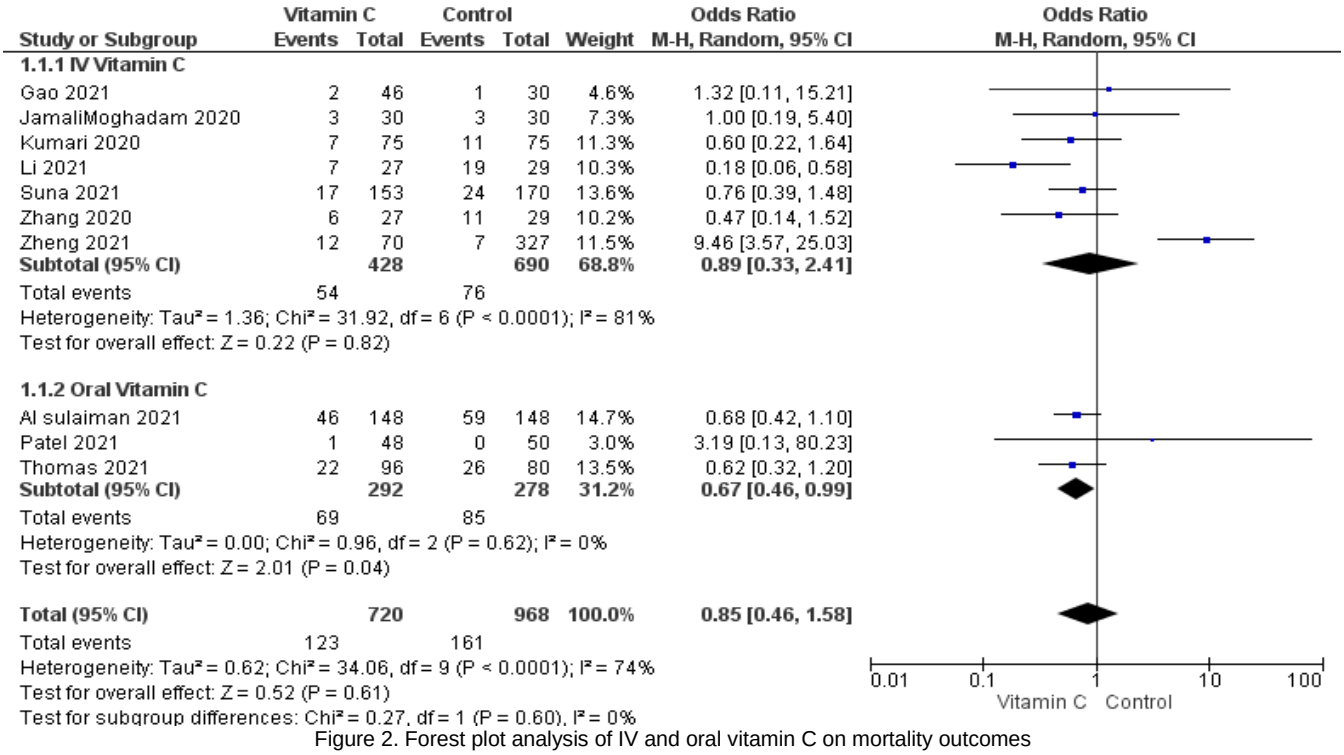

Figure 2. Forest plot analysis of IV and oral vitamin C on mortality outcomes

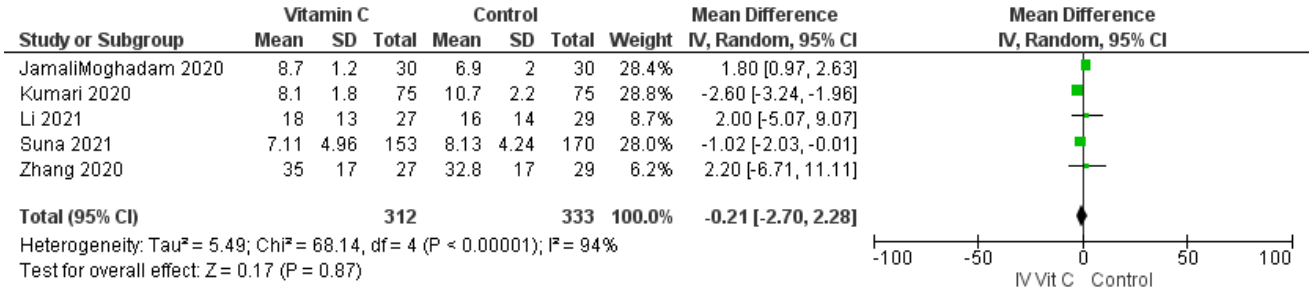

Figure 1. Forest plot analysis of vitamin C IV on inpatient outcomes

The meta-analysis design was performed on eleven articles with oral or IV vitamin C administration based on mortality outcomes and six articles with hospitalization outcomes. Eight articles using an IV vitamin C intervention and three using an oral vitamin C intervention were depicted through forest plot analysis in Figures 2 and 4. When viewed from the articles obtained, the IV vitamin C intervention did not significantly affect the mortality of severe COVID-19 patients (OR=0.80; 95% CI=0.31–2.09; *P*=0.66; I^2=79%). Conversely, oral vitamin C significantly affected the mortality of asymptomatic COVID-19 patients and patients with mild to moderate symptoms of COVID-19 (OR=0.66; 95% CI=0.45–0.97; *P*=0.04; I^2=0%). In this case, oral vitamin C intervention can reduce the mortality rate in COVID-19 patients by 66% compared to the control group.

The results of the second meta-analysis showed that the use of IV vitamin C had no effect (OR = -0.21; 95% CI = -2.70-2.28; *P*=0.87; I^2=94) on the duration of hospitalization for COVID-19 patients.

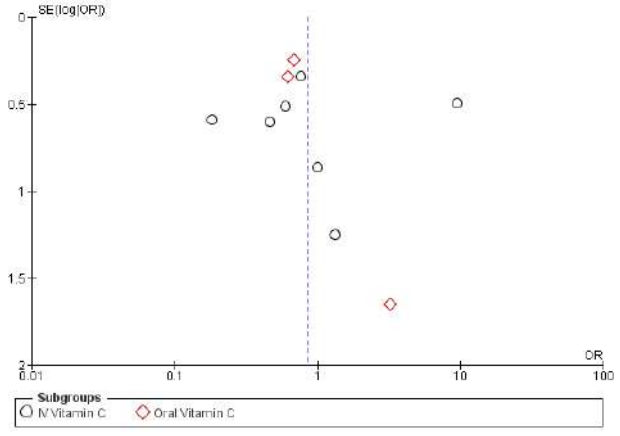

Figure 2. Results of funnel plot analysis of IV and oral vitamin C on mortality outcomes

Based on the funnel plot analysis results obtained in Figures 3 and 5, the asymmetric distribution of the data indicates a high publication bias. These results can be caused by many factors, such as the small number of studies used and the lack of databases used.[24]

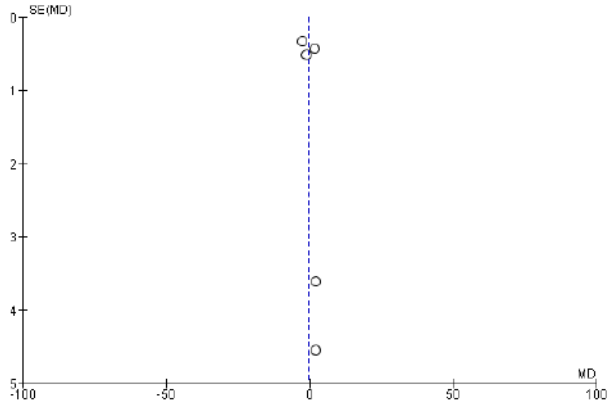

Figure 3. Results of the funnel plot analysis of vitamin C IV on inpatient outcomes

DISCUSSION

This systematic review assessed studies related to the effectiveness, dosage, and side effects of vitamin C administration either alone or in combination up to April 25, 2022. Based on these results, eight of the 14 studies showed notable results according to the significant values obtained from the statistical test.

The first outcome was the duration of hospitalization, and five studies assessed the variable duration of hospitalization as an outcome of the effectiveness of the therapy given. The meta-analysis results showed that the results were insignificant (*P*=0.87). One of the studies[11] discovered that giving IV vitamin C at a dose of 50 mg/kg BW/day significantly (*P*=0.0001) reduced hospitalization duration by six to ten days faster than the control group.

A prior study[22] supported this finding and revealed that administering a combination of oral vitamin C at a dose of 100 mg per day, vitamin D, and zinc showed a significant (*P*=0.00069) reduction in the duration of hospitalization compared to the control group. However, not all measurements of normal levels in the blood are carried out either before or after supplementation. Consequently, it cannot determine whether the levels in the blood are within normal limits.

The second outcome was symptoms, and five studies assessed this variable as an outcome of the effectiveness of the therapy given. The study[10] explained that giving IV vitamin C significantly (*P*=0.001) reduced symptoms in the form of fever. Other studies[11,22,23] revealed that giving IV vitamin C significantly (*P*<0.05) decreased symptoms in the form of fever and the duration of pain was shorter than in the control group.

The third outcome was mortality, and two studies showed a decrease in mortality rates.[12,18] These studies obtained a significantly reduced mortality (*P*=0.03 and *P*=0.05) in the treatment group. The meta-analysis results for mortality outcomes pointed out significant results (*P*=0.04) in the sub-group using oral vitamin C in asymptomatic to moderately symptomatic COVID-19 patients. In contrast to the previous meta-analysis,[25,26] it was explained that vitamin C administration had no effect on COVID-19 patients. The distinction between the findings of previous studies and our study could be due to differences in study design. The prior study only used one study design, an RCT. Other causes were found in the outcomes assessed.[26,27] Both studies looked at the outcome of using mechanical ventilation and duration of stay in the ICU. Because the patient's condition was already severe, the effectiveness of a supplement decreased, yielding insignificant results.[27]

Another reason for the difference in results could be due to many factors, such as the clinical classification of patients, advanced age, and comorbidities, which were groups prone to worsening symptoms and even death. Comorbidities that aggravated the patient's condition included metabolic diseases, for instance, diabetes mellitus and hypertension, a history of smoking, and chronic lung disease (asthma, COPD, and chronic bronchitis).[26]

Oral administration of vitamin C has been described in prior studies[14,19–21,23] that used vitamin C at a dose of 500-1000 mg and 8000 mg per day.

The IV administration of vitamin C in other studies[10,12,16–18,22,28] used doses of 1.3 grams per day, 2-12 grams per day, 50 mg/kg BW/day, and 100 mg/kg BW/day. Oral vitamin C comes in doses of 100 mg, 250 mg, 500 mg, and 1000 mg, while IV solutions are available in 100 mg/ml and 200 mg/ml.[16]

In general, dosing to get maximum results with minimal side effects needs to be considered based on the history of the disease, individual needs, over-the-counter drugs, and the costs involved. Based on cost-effectiveness considerations, oral administration of vitamin C with a dose range of 500-1000 mg was significantly (*P*=0.04) effective for reducing mortality in asymptomatic COVID-19 patients compared to COVID-19 patients with moderate symptoms.

Three of the 14 studies stated that there were side effects. These studies[12,21,22] revealed similar side effects of vitamin C when taken orally and intravenously. Side effects manifested in digestive disorders include nausea, diarrhea, stomach cramps, and vomiting. The IV administration of vitamin C still causes indigestion, even though it is not as common as oral administration.[29]

Digestive disorders in COVID-19 patients often occur because the ACE2 receptor is expressed in numerous body tissues. The digestive organs are receptors for the SARS-CoV-2 virus, which will activate ACE2 receptors in the digestive tract in the early stages of infection and cause digestive disorders. However, in the next phase, the symptoms of indigestion will decrease. On the condition that side effects arise, it is recommended to discontinue vitamin C since gastrointestinal disturbances might induce changes in gut microbes and increase pro-inflammatory cytokines.[30] Other side effects are lymphopenia, leukopenia, ARDS, shock, and sepsis. However, it has been confirmed that these side effects are not related to the administration of vitamin C.[12]

Apart from determining the dose and method of administering the drug, it is essential to consider the side effects due to supplementation. Multiple factors can induce side effects when consuming supplements, including the patient's medical history (such as gastritis), the degree of disease, reactions that may arise from each component, and the synergistic effect of the drug. The physician and other health professionals must ascertain this point to determine from which factor these side effects emerge. Whether it is purely due to supplementation in the absence of other factors, the supplementation administration should be reconsidered.[31]

LIMITATION

This systematic review had some limitations, such as the limited number of similar study designs, thus using a combination of RCT and cohort study designs. Furthermore, not all studies included complete data, such as expected levels of vitamin C in human blood samples, follow-up data for patients after treatment, and strategies for dealing with lost to follow-up patients.

Lastly, there was heterogeneity in the meta-analytical assessment of IV vitamin C due to the heterogeneous population. Despite these limitations, our study engaged a plentiful sample consisting of 2,870 participants from fourteen studies with a low risk of bias across all articles.

CONCLUSION

Based on the meta-analysis conducted in this study, we found that oral administration of vitamin C had a significant effect (*P*=0.04) on the mortality rate of COVID-19 patients, and the use of IV vitamin C showed no significant effect (*P*=0.87) on the duration of hospitalization for COVID-19 patients. Other outcomes, in particular symptoms, could not measure the effectiveness of therapy due to the limitations of the participants involved in the study. In consideration of cost-effectiveness, oral administration of vitamin C with a dosage range of 500-1000 mg demonstrated efficacy in reducing mortality rates in COVID-19 patients. Side effects due to supplementation consumption included digestive disorders such as nausea, diarrhea, stomach cramps, and vomiting.

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CONFLICT OF INTEREST

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Literature Review

Convalescent Plasma Therapy in COVID-19 Patients with Acute Respiratory Distress Syndrome (ARDS)

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Abstract

COVID-19 is caused by SARS-CoV-1, an RNA virus of the betacoronavirus genus, making it the seventh coronavirus infecting humans. Because particular therapies are still in the research stage, no confirmed treatment for this illness has been agreed upon by the World Health Organization (WHO) or other clinical institutes. The reason is that there are many different potential remedies. Antiviral treatments like favipiravir, oseltamivir, and remdesivir have been investigated and tested. On the other hand, the outcomes of the replies of patients who were given these medications are still quite inconsistent. Furthermore, the COVID-19 mortality rate has remained at a level of less than 5.21 percent of cases that have been documented. Patients suffering from COVID-19 may be treated with convalescent plasma, a therapeutic option that utilizes a mix of neutralizing antibodies and other immunological components. Activation of body-dependent cellular cytotoxicity (ADCC) and phagocytic activity against COVID-19 will occur due to this immunological component. This medication also has the potential to reduce the systemic inflammatory response brought on by COVID-19. Clinical improvement was different after 28 days when convalescent plasma was used as a treatment for patients with severe COVID-19 symptoms and emergency conditions compared to patients treated with conventional therapy alone. However, it is not very significant.

Keywords: ARDS, COVID-19, Convalence Plasma Therapy

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INTRODUCTION

In 2019, the Wuhan Province in China was first notified of the sickness known as COVID-19 (coronavirus disease 2019). It soon spread around the planet, and as of the 20th of April 2020, 2.4 million individuals worldwide had been impacted by it. As a direct result of this, the WHO classified it as a pandemic.[1] COVID-19 was infected with SARS-CoV-2, which stands for severe acute respiratory syndrome coronavirus-2. This virus is a species that is a part of the betacoronavirus genus that causes the severe acute respiratory syndrome. This virus is the seventh specimen of a coronavirus that has been identified as being able to infect humans.[2]

Recently, effective therapy for the illness has not yet been developed by WHO or any other clinical institutions have developed one. The research phase of the illness is still in progress since the disease is still in its early stages.[3] Antiviral medications, such as favipiravir, oseltamivir, and remdesivir, have been used in conjunction with one another to treat this condition. However, unfortunately, the medication response was unpredictable. Hence, COVID-19 is still responsible for the deaths of 5.21 percent of all patients.[4]

The use of convalescent plasma (CP) as an antiviral model is one of the neutralizing antibody-containing antiviral models. The therapeutic effects of COVID-19 are thought to arise from three distinct immunological pathways: phagocytosis, complement activation, and antibody-dependent cellular cytotoxicity (ADCC). The therapeutic action against COVID-19 is believed to be mediated via these immunological mechanisms. Defensins, pentraxins, and anti-inflammatory cytokines are thought to reduce severe inflammatory response syndrome (SIRS). SIRS. is the underlying pathophysiology of acute respiratory distress syndrome (ARDS) and

death.[5] The CP treatment was revealed to be effective in treating a variety of viral conditions, for instance Middle East respiratory syndrome (MERS) and Ebola infection, according to the findings of several studies.[6]

In treating COVID-19, CP is beneficial only when used with other therapies. The reduction of viral load, improvement in cytokine response, and reducing mortality are the goals of convalescent plasma treatment. In addition, the CP treatment transfers antibodies from patients who have been successfully in good health caused by a specific agent to patients whom that agent also afflicts. These forms of passive immunity may assist patients in combating their sickness and slowing the rate at which it progresses.[7]

Because it includes antibodies with certain receptor domains, CP attained from COVID-19 patients who have recovered is thought, according to the findings of some research, to have the potential to possess antiviral characteristics.[8] When implementing CP, some elements must be considered, although their exact nature is still unclear. Considerations include the severity of patients who would benefit from CP, the availability of plasma donors, the timing of CP's delivery, and the severity of patients who would not benefit from CP.

The Treatment of CP was reported to generate good consequences in a limited sample of patients suffering from severe COVID-19 symptoms, according to the research conducted by Shen et al. (2020).[9] To determine whether or not this treatment was effective, a task that had become extremely challenging in pandemic conditions before the vaccine's introduction, the research needed to involve a greater number of patients and should have been designed more effectively.[10] This article discusses the studies conducted on CP therapy for ARDS patients carrying the COVID-19 virus.

ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS)

The early onset of pulmonary edema, bilateral pulmonary infiltration, and poor respiratory system compliance are the characteristics of ARDS, which is not caused by a cardiac etiology. ARDS is an abbreviation for acute respiratory distress syndrome.[11] As this description describes it, ARDS is a severe kind of diffuse lung damage that occurs when all of the following criteria are satisfied:[12]

a. A new clinical cause or a worsening of respiratory symptoms within a week of the onset;
b. A bilateral X-ray opacity in the chest that has nothing to do with fluid accumulation, lung collapse, or nodules;
c. Recognizing breathing failure caused by fluid overload or cardiovascular collapse; and
d. Hypoxemia is defined as having a PaO_2/FiO_2 ratio that falls into one of these three categories:
    1. Low ($200<PaO_2/FiO_2<300$ mmHg)
    2. Moderate ($100<PaO_2/FiO_2\leq200$ mmHg)
    3. Severe ($PaO_2/FiO_2\leq100$ mmHg)

A feature of the heterogeneous illness known as ARDS is an intensification in the pulmonary capillary endothelial cell permeability.[13]

ARDS used to be commonly known as non-cardiogenic pulmonary edema. ARDS causes the alveoli to become filled with fluid exudate, increasing the permeability of the alveolar-capillary barrier so that fluid-containing proteins can enter the alveoli. This is in contrast to congestive heart failure, which results in pulmonary edema due to elevated left heart pressure-related hydrostatic pressure.[14]

Congestive heart failure leads to pulmonary edema. Fluid in the alveoli may lead to hypoxemia, shunting from right to left, and a reduction in respiratory compliance. Although arterial PCO_2 levels are usually within normal limits, there is an increase in ventilation dead space, which is reflected in increased minute ventilation. A common complication of ARDS is pulmonary hypertension, which may trigger a variety of factors, including the accumulation of fibrin inside blood vessels and the narrowing of blood vessels in response to low oxygen levels. This condition may be addressed using positive pressure ventilation and vessel compression techniques.[14]

The pathological phases of ARDS are often described using a standard format that includes three

stages that follow one another and overlap. During the initial stage of lung injury, known as the exudative phase, the pathological abnormalities seen were referred to as diffuse alveolar destruction. The alveolar gap is filled with an edematous fluid containing protein, and hyaline membranes line the alveolar walls. In addition, the epithelium is disturbed, and neutrophils enter the interstitial space and alveoli, which results in the accumulation of macrophages and, in some cases, bleeding. This stage, which lasts for between five and seven days, is followed, in some individuals, by the proliferative phase.[14]

Fibrosis and the hyaline membrane organization have occurred at this point in the process. Decreased neutrophil count and the severity of pulmonary edema are diagnostic of the proliferative phase, which is marked by pulmonary capillary occlusion, interstitial collagen buildup, and alveolar collagen deposition. The proliferative stage is characterized by pulmonary capillary obliteration and interstitial and alveolar collagen accumulation. The fibrotic phase may be seen on radiographs of patients with chronic ARDS (which has lasted for more than two weeks) after this phase has passed.[14]

At first, it was thought that either direct or indirect lung damage caused an excess production of inflammatory mediators in the pulmonary microcirculation. As inflammatory mediators like neutrophils activate and migrate across the surfaces of the alveolar epithelium and vascular endothelium, they produce proteases, cytokines, and reactive oxygen species (ROS). Pathological vascular permeability, a breach in the alveolar epithelial cell barrier, and necrosis of type I and type II alveolar cells are the results of the migration and release of these mediators. The result is a fluid buildup in the lungs, known as pulmonary edema. The reduction in lung compliance and increased gas exchange difficulty were caused by hyaline membrane development and surfactant depletion. Collagen deposition, fibrosis, and illness progression are also the outcomes of fibroblast infiltration.[14]

During the recovery phase, some processes coincide. Anti-inflammatory cytokines slow down activated neutrophils. Proliferation and differentiation of type II alveolar cells into type I alveolar cells strengthen the epithelial lining of the alveoli, allowing for the drainage of fluid from the alveoli into the microcirculation and pulmonary lymphatic system through an osmotic gradient. Alveolar cells and macrophages collaborate throughout the healing process to clear the alveoli of protein debris.[14]

DEFINITION THERAPY OF CONVALESCENT PLASMA

Patients who have overcome an illness and gained humoral immunity are used in convalescent plasma treatment. Humoral immunity is a kind of tolerance to the bacteria that cause sickness. In most cases, donors' plasma is obtained after completely recovered, making it suitable for use in the convalescent period. Water, proteins, and inorganic salts comprise the convalescent plasma's bulk. Antibodies and immunoglobulins directed against an infectious pathogen may inhibit viral replication and lower viremia in those who are already infected. These antibodies may kill viruses by doing two things: blocking the attachment of viruses to endosomes and halting the discharge of virions from infected cells. Third, preventing viral protein cleavage through extracellular proteolysis, and fourth, preventing viral protein entrance into human cells.[15]

SEVERE CATEGORY CLINICAL SYMPTOMS IN COVID-19 PATIENTS

Dyspnea distinct as a respiratory rate above 30 breaths per minute, a blood oxygen saturation below 93%, a PaO_2:FiO_2 portion of 300 mmHg or less, and a percentage of air infiltration into the lungs more than 50% is all indicative of severe COVID-19 symptoms.[16]

CYTOKINE STORM MECHANISM IN COVID-19

Similar in appearance to SARS-CoV is SARS-CoV-2, a dissimilar betacoronavirus. In order to infect cells, both viruses rely on a protein known as angiotensin-converting enzyme 2 (ACE2). ACE2 receptors are another name for these receptors. These receptors may be found in cardiovascular

tissue and in hematological cells such as monocytes and macrophages. Lymphopenia is an essential component of a COVID-19 infection and is linked to the clinical severity of the condition. MERS-CoV uses dipeptide peptidase 4 to infect monocytes and T cells, while SARS-CoV uses dipeptide peptidase 4 to infect primary monocytes and dendritic cells. The possibility of dendritic cell infection by SARS-CoV-2 has also been targeted. It is possible that apoptosis of T cells, which happens when dendritic cells do not work right, also contributes to COVID-19's immunopathology.[17]

In SARS and MERS infections, cytokine release syndrome is a leading cause of illness (CRS). After contracting MERS, a person's blood will show elevated levels of cytokines such as interleukin-6 (IL-6) and others involved in inflammation. Clinical symptoms, such as ARDS, respiratory failure, and CAS, are often reported in COVID-19 and are linked to increased serum IL-6. When IL-6 is present, the inflammatory protein C-reactive protein (CRP) rises, serving as a biomarker for severe betacoronavirus infection.[18]

As a result of infection with the betacoronavirus, innate immune cells such as monocytes, macrophages, and dendritic cells mature and release inflammatory cytokines like interleukin 6. (IL-6). Both cis signaling and trans-signaling are considered to be the primary traditional ways via which, In the context of cis communication, IL-6 may serve as a messenger. At a complex containing gp130, IL-6 binds to the membrane-bound IL-6 receptor (MIL-GR); subsequent signals are translated by STAT3 and JAKS (Janus kinases) (signal transducer and activator of transcription 3). While gp130 is widely distributed, mlL-6R is exclusively found on immune cells. CRS is induced by the activation of cis signaling, which has pleiotropic effects, meaning it may influence both the adaptive and innate immune systems (B and T cells, neutrophils, macrophages, and natural killer (NK) cells).[19]

To activate trans-signaling, circulating IL-6 binds to the soluble IL-GR (SIL-BR), creating a complex with 9p130 dimer potential on the cell surface. Signaling involving IL-6, SIL-6R, JAK, and STAT3 activates endothelial cells, although these cells do not express mlL-BR. Along with IL-8 and IL-6, the production of monocyte chemoattractant protein-1 (MCP-1) and vascular endothelial growth factor (VEGF) also occurs as a consequence of this process. On the other hand, the amount of E-cadherin produced by endothelial cells is lower. In ARDS, VEGF plays an integral part in the pathophysiology of vascular permeability and leaky hypo physiology, in addition to pulmonary dysfunction, by lowering E-cadherin expression, which can be shown in Figure 1.[20]

SARS-CoV-2 infection-related acute respiratory distress syndrome (ARDS) was fatally established in the clinical data obtained from COVID-19 patients with severe symptoms. This condition was commonly associated with organ failure and lung alveolar damage. Additional investigation found that the condition was associated with cytokine storm, commonly referred to as CRS, which is an increase in the synthesis of cytokines in the body. Cytokines are a class of tiny proteins that have an essential function in the body's immunological response, both to infections and inflammation. However, excessive cytokine synthesis harms tissue as a counterweight to overactive immune responses.[21]

According to several research findings, the first phases of infection are characterized by a pause in the release of cytokines and chemokines. After this, a limited amount of interferons (IFNs) are created, which is subsequently tracked by a rapid rise in the proinflammatory of immune cell-attracting cytokines and chemokines. Furthermore, the process leads to an excessive infiltration of lung tissue, which in turn causes damage to the lung tissue. Additionally, infected cells produce more chemokines to entice inflammatory mononuclear macrophages after activation of other signals (IMM). That leads to an abnormal increase in proinflammatory cytokine production, which only worsens things. IFN-γ and other proinflammatory cytokines drive T cells to commit suicide during the latter stages of the infection, which prevents the virus from being eliminated.[22]

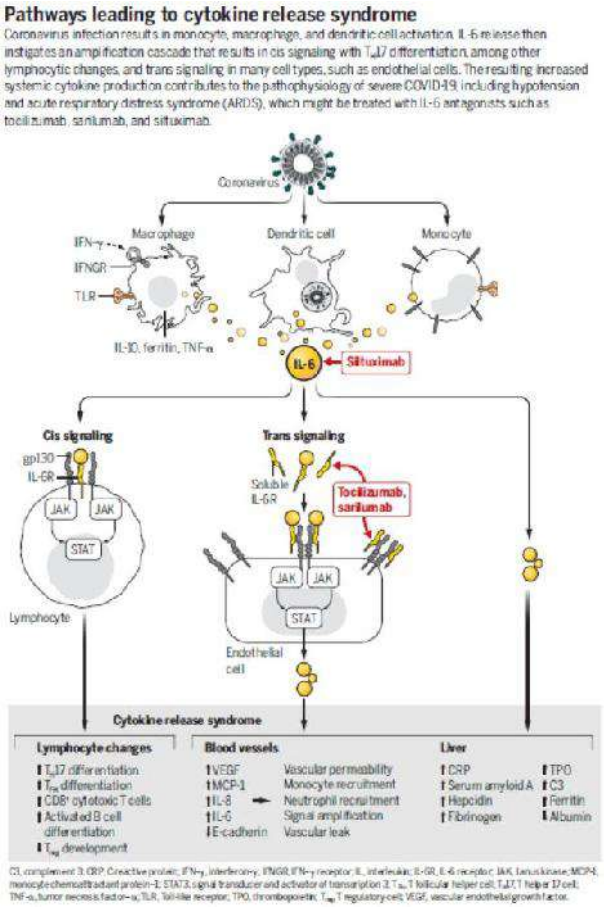

Figure 1. CRS lines on COVID-19[20]

IFN-α and IFN-β, both subtypes of IFN-γ, act as an initial line of guard against viral infections when activated through the JAK-STAT pathway. An infection caused by a coronavirus may induce a strong but delayed response from the immune system's IFNs, which might foster the development of cytokine storms under certain conditions.[23]

One of the proteins produced by the coronavirus, known as the NSP1 protein (non-structural protein 1), inhibits the phosphorylation of STAT1, which stops the production of IFNs in the host cell. STAT1 is the transcription factor responsible for the expression of interferon stimulated genes (ISGs), which are responsible for producing antiviral defensive mechanisms. The composition of M (membrane) and N (nucleocapsid) proteins in coronaviruses allows them to block IFN signaling. One possible approach to getting a target is to disrupt the activity of IRF3, a transcription factor for the IFN gene.[24]

Additionally, irregularities or inhibition of induction IFN brought on by the aging host, and TRAF3's proteolytic degradation may contribute to the pathophysiology of the disease by creating an imbalance between proinflammatory cytokines and responses in aged individuals. These two elements may work together to cause an imbalance in proinflammatory cytokines and reactions in the aged.[24] It is solely for research purposes that leukocyte and cytokine counts are measured in patients with COVID-19.

RISKS OF CONVALESCENT PLASMA THERAPY

Similar to SARS, studies have revealed that viremia peaks during the first week after infection. It is common for patients to develop an immunological response, which may lead to a potentially catastrophic cytokine storm during the second week following the beginning of symptoms. Given that passive immunity via the administration of pathogen-specific antibodies is the basis for CP treatment, there are hidden dangers associated with CP infusion, such as the exacerbation of hyperimmune reactions.[25]

However, one research found that CP treatment could lessen serum cytokine responses depending on when the medication was administered. This conclusion has been corroborated by studies of SARS, lending more credence to the idea that treating CP at an earlier stage is preferable. Therefore, it is crucial to time the administration of CP in COVID-19.[25]

In reality, the titer of the SARS-CoV2 neutralizing antibody (NAT) determines the therapeutic efficacy of CP on COVID-19. A study of people with SARS shows that levels of a certain IgG started to rise in the third week after symptoms began and peaked twelve weeks later. Additional studies have shown that CP with a NAT of 1:160 may reduce mortality from influenza. The CP isolated from patients who are improving 12 weeks after symptom starts with NAT of at least 1:160 is thought to be more potent. The capacity to get CP is limited, however, by factors such as the donor's health, the availability of suitable donors, and the presence of informed permission.[25]

All risks associated with transfusions must be taken into account. Transfusion of CP may lead to various unwanted side effects, including fever, anaphylaxis, chills, hemolysis, circulatory overload, and transfusion-associated acute lung damage. When considering the safety of a CP transfusion, it is essential to remember the risk of transmitting diseases like hepatitis and HIV.[25]

CONVALESCENT PLASMA THERAPY PROCEDURES

The first step was identifying a suitable CP donor from among the COVID-19 patients who had been declared clinically hostile with the PCR test twice in more than a day, indicating that they had fully recovered and been released from the hospital at least two weeks before. Plasmapheresis is used to remove plasma from a patient throughout the healing process. Fresh frozen plasma (FFP) is used to create various plasma products.[26]

Titer IgG antibodies are measured and reported with S-RBD (Spike-Receptor Binding Protein). Only plasma units with IgG titers of at least 1:640 should be used to ensure therapeutic potential, as the Food and Drug Administration (FDA) recommendation.[26]

The CP transfusion dosage for COVID-19 is around 4–13 milliliters per kilogram of the recipient's body weight. It is of the utmost importance that the ABO, the patient blood type, and the ABO type of the dispersed plasma be the same. A convalescent plasma transfusion begins with 10 milliliters given over the first 15 minutes, and the rate of administration is subsequently raised to 100 milliliters per hour while the patient is carefully monitored. When determining an appropriate transfusion rate, it is possible to consider a patient's risk of fluid overload and tolerance.[9]

THE EFFECT MECHANISM OF CONVALESCENT PLASMA THERAPY

Antivirus mechanism

Regarding getting rid of viruses, NAbs are crucial since they can defend against viral infections. Viruses and bacteria may be fought off with the help of passive immunity, which is powered by antibodies. Remember that the plasma concentration of NAbs from the recovered donor influences how well the treatment works. NAbs have been shown to bind to the S1RBD, S1-N, and S2 terminal domains of the SARS and MERS viruses. The entry of these viral proteins is thereby inhibited, and viral multiplication is stymied. Activation of the complement system, antibody-dependent cellular cytotoxicity, and phagocytosis are all antibody-mediated processes that may improve the therapeutic efficiency of CP.[27]

A single SARS-CoV-specific antibody, CA3022, was shown by Tian et al. to bind to the COVID-19 RBD and not compete with ACE-2 for this binding. These results were proved by the SARS-CoV-specific antibody bound to the COVID-19 RBD. Significant differences may be found between COVID-19 RBD and SARS-CoV at the C-terminus residue. Even though COVID-19 cannot form a binding with the ACE-2 receptor, this variation affects the cross-reactivity of NAbs.[27]

Plasma includes NAbs as well as the protective antibodies IgG and IgM. Improved prevention and treatment might be possible using non-NAb antibodies that bind to the virus. IgG antibodies against N are initially seen after the first four days of symptoms in a person with SARS-CoV infection, and seroconversion occurs 14 days after infection. Up to 89% of cured SARS patients showed detectable levels of specific IgG and nabbed two years after infection. IgM levels peaked nine days after sickness onset, while IgG production took over after two weeks.[27]

Donors who had previously been infected with COVID-19 but had recovered showed SARS-CoV-2-specific antibody titers ranging from 1,800 to 16,200 and NAbs titers from 80 to 480, as reported by Shen et al. Infections were reduced in the CP group that had been donated and administered on the same day. After receiving a CP transfusion, the recipient's IgG and IgM titers rose steadily. Defending against viral infection is a crucial function of NAbs. In another study, researchers analyzed the temporal dynamics of the emergence of NAbs that specifically target

SARS-CoV-2. In SARS-CoV2 infect patients, NAbs titers were low before day 10, rose with a peak 10–15 days following the beginning of the disease, and remained constant after that in all patients.[27]

Immunomodulating mechanism

According to F(ab')2's action method, activated complement contributes significantly to inflammation throughout the body, neutrophils moving to the pulmonary, and tissue damage. Some antibodies block complement cascades (C3a and C5a), lending credence to this theory. Additional research has shown that plasma IgG inhibits the effects of cytokines, including IL-1ß and TNF-α that can be seen in Figure 2.[27]

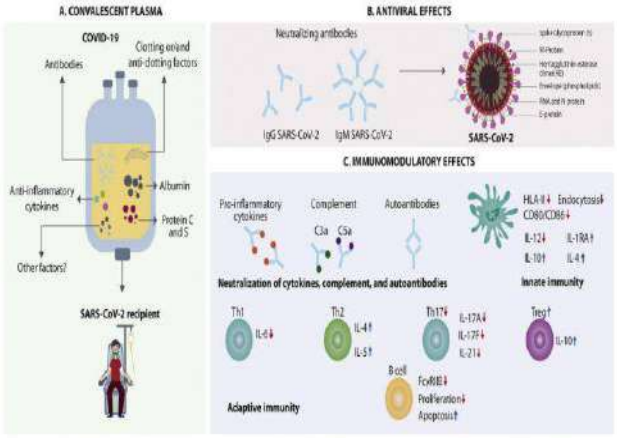

Fig. 1. Schematic representation of convalescent plasma components and its mechanisms of action. A. Main convalescent plasma components. B. Antiviral effects of NAbs. IgG and IgM are the main isotypes, although IgA may be also important, particularly in mucosal viral infections. Other non-NAbs may exert a protective effect. The humoral immune response is mainly directed towards spike (S) protein. C. Anti-inflammatory effects of CP include network of autoantibodies and control of an overactive immune system (i.e., cytokine storm, Th1/Th17 ratio, complement activation and regulation of a hypercoagulable state) (see text for details). N: Nucleoprotein; M: Membrane; E: Envelope.

Figure 2. Convalescent plasma effect mechanism[27]

The interaction of NAbs with Fc and complement receptors is the mechanism behind antibody-dependent enhancement (ADE), whereby infection severity is increased despite the relatively low levels of NAbs in macrophages and other cells that are beneficial for virus reproduction. Given the potential for ADE to have a detrimental impact affecting individuals with latent infections, it is essential to keep this occurrence in mind while treating COVID-19 patients by promptly administering convalescent plasma.[27]

FcRn performs part-time regulation of IgG function. Antibody trafficking within the cell and subsequent excretion on the cell's rear surface are made possible by these receptors by blocking the breakdown and removal of IgG through a pinocytosis process. When FcRn is fully saturated, immunomodulatory pathways may be activated, which might benefit patients receiving convalescent plasma.[27]

Fc-ɣ receptors are found on almost every kind of immune cell. These receptors are essential for regulating and suppressing lymphocyte and other immune cell activities. When IgG activates the Fc receptor, the immune system is inhibited as a consequence of enhanced regulation of FcRIIB.[27]

IgG plays a critical role in reducing inflammation by inhibiting dendritic cell maturation and activating B-catenin. Research suggests that IgG may boost production of Th2 cytokines including IL-4 and IL-10 while reducing the number of Th1 cells, as well as FN- γ and TNF-α synthesis and TNF-α levels. By suppressing dendritic cells, which in turn stops signals to B cells, IgG limits the expansion of Th17 cells and reduces antigen presentation on T cells.[27]

Efficacy of Convalescent Plasma Therapy in COVID-19 Patients with ARDS

Individuals diagnosed with ARDS who also met the criteria for severe pneumonia with rapid viral load progression, mechanical ventilation, and antiviral and methylprednisolone treatment were included in the COVID-19 case series published by Shen et al. (2020). Patients having a neutralization titer of higher than 40 and an antibody specificity (IgG) titer of greater than 1:1000 (final dilution with ELISA) against SARS-CoV-2 are given convalescent plasma transfusions.[9]

Within three days of receiving plasma transfusion, four out of five patients had normalized body temperatures, and in the 12 days that followed, PaO_2/FiO_2 rose (before 172–276, after 284–366). Antibody titers and neutralization levels improve following a transfusion (80–320 before 40–60 days), and virus loads drop and become negative within 12 days.

Table 1. Analyzing Pre and Post Convalescent Plasma Transfusion Viral Load, Clinical Index, and Laboratory Results[9]

Indicators	Patient				
	1	2	3	4	5
Clinical characteristics					
Body temperature, ℃					
Just before transfusion	38.6	39.0	37.6	38.3	39.0
Day 1 posttransfusion	38.5	36.8	37.7	37.9	39.0
Day 3 posttransfusion	38.1	36.6	37.0	36.6	36.8
Day 7 posttransfusion	37.8	37.2	36.5	37.9	36.8
Day 12 posttransfusion	37.0	36.8	36.6	36.8	37.9
SOFA score[a]					
Just before transfusion	5	10	3	3	2
Day 1 posttransfusion	4	12	4	3	2
Day 3 posttransfusion	6	10	3	2	2
Day 5 posttransfusion	5	11	2	2	2
Day 7 posttransfusion	3	7	2	2	1
Day 12 posttransfusion	2	4	2	1	1
PAO_2/FiO_2[b]					
Just before transfusion	276	209	172	188	205
Day 1 posttransfusion	300	134	184	242	292
Day 3 posttransfusion	220	230	164	233	304
Day 7 posttransfusion	245	206	220	290	230
Day 12 posttransfusion	284	316	342	322	366
Ct value[c] (viral load proxy)					
On admission to hospital	23.0	19.7	18.9	38.0	28.0
Lowest value during hospitalization[d] (highest viral load)	19.2	19.7	18.9	26.6	26.5
Just before transfusion	28.5	22.0	33.0	26.6	35.9
Day 1 posttransfusion	30.0	23.7	38.5	28.0	Negative
Day 3 posttransfusion	34.4	25.0	Negative	Negative	Negative
Day 7 posttransfusion	38.0	32.0	Negative	Negative	Negative
Day 12 posttransfusion	Negative	Negative	Negative	Negative	Negative
Mechanical ventilation					
Onset, days before transfusion	11	2	12	9	2
Removal, days posttransfusion	Intubated	Intubated	2	9	9
ECMO					
Onset, days before transfusion	Not received	1	Not received	Not received	Not received
Removal, days posttransfusion	NA	5	NA	NA	NA
Laboratory findings					
C-reactive protein, mg/L (normal range <8)					
Before transfusion	163.4	242.8	65.0	156.0	173.1
Day 1 posttransfusion	146.2	223.0	108.3	NT	186.8
Day 3 posttransfusion	115.1	75.2	78.7	160.8	233.7
Day 5 posttransfusion	31.3	10.4	74.7	NT	260.4
Day 7 posttransfusion	31.2	13.9	6.2	9.6	5.5
Day 12 posttransfusion	5.3	33.1	NT	5.8	3.2
Procalcitonin, ng/mL (normal range <0.1)					
Before transfusion	1.2	7.3	0.1	0.2	0.2
Day 1 posttransfusion	1.3	19.7	0.1	0.08	0.4
Day 3 posttransfusion	1.6	13.9	0.09	0.07	1.5
Day 5 posttransfusion	0.9	1.8	0.08	NT	0.9
Day 7 posttransfusion	1.1	0.1	0.04	0.04	0.09
Day 12 posttransfusion	0.4	0.2	NT	0.04	0.07
IL-6, pg/mL (normal range 0-7)					
Before transfusion	70.5	438.2	63.9	79.1	87.8
Day 1 posttransfusion	74.9	NT	118.5	39.3	NT
Day 3 posttransfusion	34.5	1045.0	67.0	25.8	797.9
Day 5 posttransfusion	24.1	334.1	590.5	NT	NT
Day 7 posttransfusion	30.8	29.8	174.3	34.0	69.9
Day 12 posttransfusion	6.1	31.8	NT	2.7	54.9
Length of hospital stay, d	Remains hospitalized	Remains hospitalized	53	51	55
Current status as of March 25, 2020	Stable, still receiving mechanical ventilation	Stable, still receiving mechanical ventilation	Discharge home	Discharge home	Discharge home

Note: Ct=cycle threshold; ECMO=extracorporeal membrane oxygenation; NT=not tested.

[a] The SOFA socre is calculated using 6 systems: respiratory, coagulation, hepatic, cardiovascular, central nervous system, and kidney. A socre of 0 is given for normal function through to 4 for most abnormal for each system. The worst values on eacj day are recorded, and the final SIFA socre is the sum of the score of each system.

[b] PAO_2/FiO_2 ratio was defined as the ratio of the partial pressure of arterial oxygen to the percentage of inspired oxygen.

[c] Cycle threshold is the number of polymerase chain reaction cycles required for gone amplification. A higher Ct value is correlated with a lower viral load.

[d] Lowest value (highest viral load) between hospital admission and plasma transfusion.

Four patients with ARDS showed improvement by the 12th day after transfusion, and three patients could discontinue mechanical breathing after the second week of treatment. After 53, 51, and 55 days in the hospital, three of the five patients have been discharged, and 37 days after getting the blood transfusion, both of the remaining patients are doing well. Table 1 shows the variations in parameters before and after a CP transfusion.An experiment was conducted and recorded by Simonovic et al. (2020) in which people with severe pneumonia caused by COVID-19 were randomly allocated to receive either CP or a placebo. Thirty days after the intervention, the patient's clinical state was evaluated using a six-point ordinal scale to determine the study's result.[28]

One hundred and five of the 228 convalescent plasma patients were given a placebo. The median antibody titer for SARS-CoV-2 in recovered individuals is 1:3200. (at now, between 1:800 and 3:1200) A severe study is defined by the presence of hypoxemia. Every patient is followed up with regularly. At day 30, there was no statistically significant difference between the two groups (control and convalescent plasma; odds ratio, 0.83; 95% CI=0.52–1.35; *P*=0.46). Those who were given convalescent plasma had a 10% death rate, whereas those who were given a placebo had an 11% mortality rate. Both groups had the same drawbacks.[28] A comparison of the clinical outcomes of patients treated with convalescent plasma and those treated with a placebo is shown in Figure 3.

A review of the literature by Rajendran et al. Using electronic databases (PubMed, Embase, and Medline), a 2020 study of convalescent plasma reviewed five papers reporting 27 individuals. The amount of recovered plasma utilized in each study had a different dosage. There was a single 200 mL CP dose utilized in a Chinese study, and the antibody titer was more than 1:640, while another Chinese study utilized a dose of 2400 mL in a male patient who was 73 years old. Convalescent plasma was administered to the patient during the sixth and 50th days following the start of symptoms or hospitalization.[29]

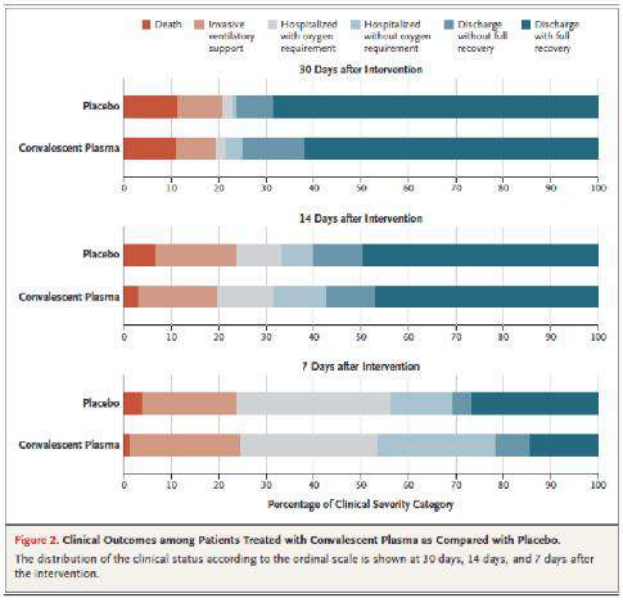

Figure 3. Comparing the Clinical Outcomes of Patients Treated with Convalescent Plasma with a Placebo[28]

Seventeen of the 21 patients receiving convalescent plasma treatment required mechanical ventilation due to the severity of their symptoms. Seventeen ARDS patients were given ECMO therapy. While hospitalization duration data was lacking, hospital discharge times were documented in almost all trials (15 total).[29]

All five investigations showed a considerable and unfavorable decline in viral load between day one and day 30 following plasma injection. In a concise amount of time, almost all patients returned to baseline clinically, with improvements in temperature regulation, absorption of lung lesions, ARDS, and the ability to wean off of mechanical ventilation. After receiving a blood transfusion, the recovery time might range from 1 to 35 days.[29]

CONVALESCENT PLASMA THERAPY IN PREGNANT WOMEN WITH COVID-19

Particular attention should be paid to controlling COVID-19 in pregnant women because of the risk of teratogenic consequences from antiviral drugs and immunosuppression caused by pregnancy. Recovery plasma EBM was studied by Franchini et al (2021) in a clinical setting during pregnancy (see Table 2). Twelve pregnant women were reported as case reports in the research. Preeclampsia affected two women, but six mothers reported feeling OK.[30]

Table 2. Synopsis of Convalescent Plasma Treatment for COVID-19 in Expectant Mothers.[30]

Author, Year [Ref]	Design	Country	Age, y	Gestational Age	Severity of Disease	Comorbidity	Procedures	CP Treatment				Other Medications	Outcome	
								Units Tranfused	NAbT	Days Hospitalization	AR		Maternal	Fetal/Neonatal
Grisolia, 2020 [17]	CR	Italy	29	24 w and 2 d	Mild ARDS	Class I obesity	VD	2	160	+1, +4	None	Ceftriaxone, azithromycin, hydroxychloroquine, methylprednisolone, LMWH	Maternal well-being	Full-term, well neonate with VD
Zhang, 2020 [25]	CR	China	31	35 w and 2d	Severe ARDS	--	CD (35 w), IMV, ECMO	1	NR	+17	None	Lopinavir/ritonavir, ribavirin, imipenem, vancomycin	Maternal survival	Neonatal death due to intrauterine asphyxia
Anderson, 2020 [26]	CR	USA	35	22 w and 2 d	Severe ARDS	Type 2 DM, asthma, class III obesity	Forego delivery (25 w)	1	NR	+1	None	Remdesivir, ceftriaxone, azithromycin, hydroxychloroquine, hydrocortisone, LMWH	Maternal well-being	Normal ongoing pregnancy
Donzelli, 2020 [22]	CR	Italy	34	27 w and 4 d	Severe ARDS	--	IMV, PP, tracheostomy, CD (30 w)	2	NR	+2, +3	None	Clarithromycin, ceftriaxone, betamethasone, LMWH	Maternal well-being	Normal ongoing pregnancy
Jacobson, 2021 [27]	CR	USA	42	26 w	Severe ARDS	--	CD (29 w), IMV, PP, ECMO, tracheostomy	1	NR	+2	None	Remdesivir, dexamethasone, azithromycin, ceftriaxone	Discharged with home oxygen	Neonatal adrenal insufficiency, then good condition
Magallanes-Garza, 2020 [23]	CR	Mexico	33	27 w and 4 d	Severe ARDS	--	VD (39 w), IMV	2	NR	+4, +5	None	Lopinavir/ritonavir, LMWH, azithromycin, ceftaroline, methylprednisolone	Maternal well-being	Neonatal GR
Pelayo, 2020 [24]	CR	USA	35	37 w and 2 d	Severe ARDS, PE	Asthma, class III obesity, ileal carcinoma, HCV	IMV, CD (36 w)	1	NR	NR	NR	Methylprednisolone, remdesivir, heparin, vancomycin, ceftriaxone	Discharged to acute inpatient rehabilitation unit	Neonate intubation due to hypoxia, then positive outcome
Jafari, 2020 [18]	CR	Iran	26	36 w and 1 d	Moderate ARDS	--	CD (36 w)	NR	NR	NR	NR	Favipiravir, meropenem, azithromycin, hydroxychloroquine	Maternal well-being	Neonate well
Easterlin, 2020 [20]	CR	USA	22	23 w and 6 d	Severe ARDS	Tuberous sclerosis, nephrectomy, leiomyosarcoma	CD (25 w), PP, tracheostomy	NR	NR	NR	NR	Azithromycin, hydroxychloroquine, remdesivir, tocilizumab, LMWH	Pre-eclampsia, postdelivery critically ill condition	Critically ill preterm neonate with severe respiratory failure
Soleimani, 2020 [16]	CR	Iran	30	21 w and 2 d	Severe ARDS	Class II obesity	--	2	NR	+10, +11	NR	Lopinavir/ritonavir, LMWH, azithromycin, methylprednisolone	Maternal well-being	Normal ongoing pregnancy
Lam, 2020 [19]	CR	USA	30	23 w and 1 d	Severe ARDS	Type 2 DM, hypertension, pre-eclampsia	CD (25 w)	NR	NR	+1	NR	Remdesivir, dexamethasone, azithromycin, ceftriaxone	Pre-eclampsia, discharged on day +28	Neonate intubation due to hypoxia, stable condition
Yaqoub, 2020 [21]	CR	Qatar	33	32 w	Severe ARDS	Asthma, gestational diabetes	CD (32 w(, IMV, ECMO	2	NR	+5	NR	Lopinavir/ritonavir, tocilizumab, hydroxychloroquine, azithromycin, ceftriaxone	Clinical improvement, discharged on day +40	Neonate intubation due to hypoxia, then positive outcome

Note: AR=adverse reactions to CP infusion; ARDS=acute respiratory distress syndrome; CD=Cesarean delivery; CR=case report; d=days; DM=diabetes mellitus; ECMO=extracorporeal membrane oxygenation; GR=growth restriction; IMV=invasive mechanical ventilation; LMWH=low-molecular weight heparin; NAbT=neutralizing antibody titer; NR=not reported; PE=pulmonary embolism; PP=prone positioning; VD=vaginal delivery; y=years; w=weeks.

The future outlook for each mom is laid forth in detail. Survival, clinical progress, oxygenation, and recuperation are all parts of a full prognosis. Two infants were described as healthy, four as experiencing mild sickness, two as being in severe condition, one as having passed away, and three as not being noticed. All three pregnancies were healthy, and the baby is expected to do well.[30]

Eleven women and one mother experienced severe ARDS before beginning CP treatment. No co-morbid conditions were reported in any of the five patients. In our sample, five mothers had several chronic diseases, whereas the other two had simply obesity as a chronic illness. In CP treatment, gestational age may be anywhere from 21 weeks and 36 weeks and two days. Steroids (n=8), heparin (n=7), hydroxychloroquine (n=5), human monoclonal antibodies (tocilizumab, n=2), and antivirals from the analog family of nucleotides (redeliver, n=5) were all used throughout the patients' hospital stays. Three of these nine patients had tracheostomies, and three had extracorporeal membrane oxygenation/ECMO. Six patients required invasive mechanical ventilation.[30]

SARS-CoV-2 seems to exacerbate clinical symptoms in both mothers and their babies. Premature delivery, maternal death, fetal death in utero, and newborn mortality are expected outcomes of pregnancies interrupted by SAR-COV-2. There was a 5% maternal and 6% infant mortality rate, respectively. Although passive immunotherapy with CP transfusion is often deemed appropriate in patient groups with such specific characteristics, only twelve cases of CP recorded in pregnant women were described. The average gestational age was 27.9 weeks, with a range of 22–36 weeks, and the average age of the patients was 32.0 years (range, 22–42 years). However, most reported cases (i.e., in the third trimester of pregnancy) were in women younger than 35. Research shows that third-trimester SARS-CoV-2 infections are dangerous.[31,32] Critically ill patients with moderate to severe ARDS have always been given CP. The high proportion of invasive operations (7/12.58.3%) needed to cure life-threatening hypoxia demonstrates the severity of respiratory disorders. These procedures include invasive mechanical ventilation, tracheostomy, and extracorporeal membrane oxygenation.

According to previous research, COVID-19 in pregnancy and an accompanying illness showed a greater risk of having complications with their pregnancy. Seven of the twelve pregnant women polled had several medical problems (most commonly obesity, diabetes, and asthma). Six of nine doctors agree that two CP units are necessary for clinical improvement (56%). There is a wide range (1–17 days) between hospital admission and the first transfusion in a CP unit, although typically, it takes two days. The antiviral advantages of plasma hyperimmune are maximized when it is infused as soon as possible after hospitalization (ideally within 72 hours).[33–35]

Unfortunately, only two CP units have the anti-SARSCov-2 neutralizing titer, a key metric for assessing CP effectiveness. However, CP transfusion has not been linked to adverse effects, demonstrating its safety as a treatment option. In addition to hyperimmune plasma, several other medications, such as 1) antibiotics; 2) steroids; anticoagulants employing low molecular weight heparin (LMWH); 3) hydroxychloroquine; and 4) antiviral medicines employing lopinavir, ritonavir, or remdesivir, are utilized. These medications are used either in conjunction with hyperimmune plasma or as a second-line therapy after the initial one has been in every case investigated and recorded; the only person who prevailed was the mother.

According to a review of the relevant data, convalescent plasma treatment during pregnancy with severe COVID-19 benefits both mother and baby. Since current research is based on a single case report, they may be biased. Well-designed and well-funded registries and research, including pregnant women, may help comprehend CP's role in treating COVID-19 throughout pregnancy.

CONCLUSION

Patients with severe COVID-19 symptoms and emergencies responded more quickly (within 28

days) to convalescent plasma therapy than standard medical care. Convalescent plasma might be looked into when managing COVID-19. However, further clinical studies are still required to offer more concrete evidence of convalescent plasma effectiveness.

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CONFLICT OF INTEREST

None

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Literature Review

Indonesian Society of Respirology (ISR) Consensus Statement on Lung Cancer Screening and Early Detection in Indonesia

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Abstract

Lung cancer is the leading cause of mortality for all cancer globally and in Indonesia. In Indonesia, lung cancer contributes to 12.6% of death of all cancer, making it the number one cause of cancer death, and 8.6% of all cancer incidence in 2018, behind breast, cervical, and colorectal cancer. The total cases per year are expected to almost double from 30,023 in 2018 to 54,983 cases in 2040. Smoking is among the risk factors for lung cancer, after occupational/environmental risk factors, history of lung fibrosis, and family history of cancer. There was a tendency of younger smokers in Indonesia and increased lung cancer incidence and prevalence in the younger population. The median age of lung cancer in Indonesia was younger than in any country, probably due to the younger age of smoking, early onset of carcinogens, asbestos use, and environmental. Lung cancer screening is a voluntary measure to detect lung cancer in the earliest stage, to find cancer at curable disease before symptoms appear in high-risk individuals. Lung cancer early detection is strategies to find cancer earlier after symptoms appear (cough, hemoptysis, dyspnea, chest pain). Low-dose computerized tomography of the thorax (LDCT) screening has been known to reduce lung cancer mortality compared to a chest x-ray (CXR). This Indonesian Society of Respirology consensus statement was aimed to give recommendations on lung cancer screening and early diagnosis in Indonesia.

Keywords: early detection, LDCT, screening

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INTRODUCTION

Epidemiology

With an estimated 2.2 million new cases and 1.8 million deaths in 2020, lung cancer is the leading cause of cancer death and the second most commonly diagnosed cancer worldwide.[1] In Indonesia, lung cancer contributes to 12.6% of death of all cancer, making it the number one cause of cancer death, and 8.6% of all cancer incidence in 2018, behind breast, cervical, and colorectal cancer. The total cases per year are expected to almost double from 30,023 in 2018 to 54,983 cases in 2040.[2–4] Eighty percent of smokers aged ≥15 live in low to middle-income countries.[2]

In countries like Indonesia, where smoking continues to rise and younger, the next few decades could see an increasing number of lung cancer rates.[3] Common risk factor for lung cancer includes occupational exposures (miners, heavy metal workers), smoking, second-hand smoke, family history, dietary factors, radon gas, aging, other lung diseases (COPD, TB, fibrosis), pollution, and radiation exposure.[1]

Accurate tumor staging at the time of diagnosis is of utmost importance, for it will guide the initial therapy and the prognosis.[3–5] Poorer prognosis is observed with each centimeter increase in tumor size. However, for tumors sizing beyond 6 cm, no difference in survival was observed. Five-year estimated survival of 92% in those diagnosed with T1a stages dropped significantly to just 52% and 38% for those with T3 and T4 stages, respectively.[3,6,7]

The N component assesses the involvement of regional hilar and mediastinal nodes.[8] The more nodal stations are involved, the worse the prognosis of the tumor is.[7,9] It is shown that those with several metastases have a worse prognosis than those with only single extrathoracic metastasis, with a mean survival of 6.3 months instead of 11.4 months.[5,7,10] This phenomenon further reiterates the need to be able to diagnose patients with lung cancer at the earliest possible stages as tumors in the lower stages of a curable disease.

Lung Cancer Control

Lung cancer multistep management includes lung cancer prevention, diagnosis, prompt treatments, and end-of-life care. Lung cancer preventive measures include risk identification and stratification and lung cancer screening, whereas Lung cancer diagnosis consisted of early diagnostic procedures and diagnostic procedures.

In 2021, the US Preventive Services Task Force (USPSTF) updated its 2013 recommendation on screening accuracy for lung cancer with low-dose computed tomography (LDCT).[9,11–13] USPSTF has decided not to use other known risk factors for lung cancer, such as environmental exposures, prior radiation therapy, other (noncancer) lung disease, and family history, to be weighted as additional risk factors when screening.[11] Nevertheless, this decision could miss the 'real-world' high-risk population, especially the non-smoker population.[14]

In Indonesia, there was a tendency for younger lung cancer age due to possible early exposure to smoking, indoor air pollution, asbestos, and occupational and family history of cancer to have distinct lung cancer screening approaches.[15]

Risk factors of lung cancer are aging, smoking, family history, occupational exposure, indoor air pollution, outdoor air pollution, and chronic lung diseases. The definition of a high-risk group includes age group, smoking history, and family history of lung cancer.

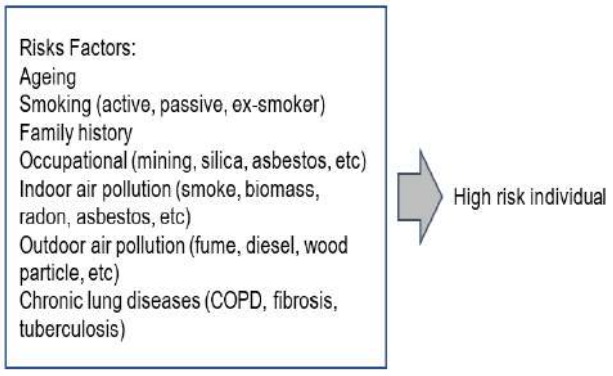

Figure 1. Risk factors and identification of high-risk individuals

A family history of lung cancer was associated with an increased risk of lung cancer, and this association was stronger in women and in never smokers.[14]

CONSENSUS STATEMENT ON RECOMMENDATIONS FOR LUNG CANCER SCREENING IN INDONESIA

Lung Cancer Screening in High-Risk Individuals

The high-risk population is strongly suggested to undergo lung cancer screening. Based on risk stratification, Group A consisted of any individuals age >45, smokers/passive smokers/ex-smokers <10 years; and Group B consisted of any individuals with age >40years old, family history/genetics of lung cancer, as follows (Figure 1).

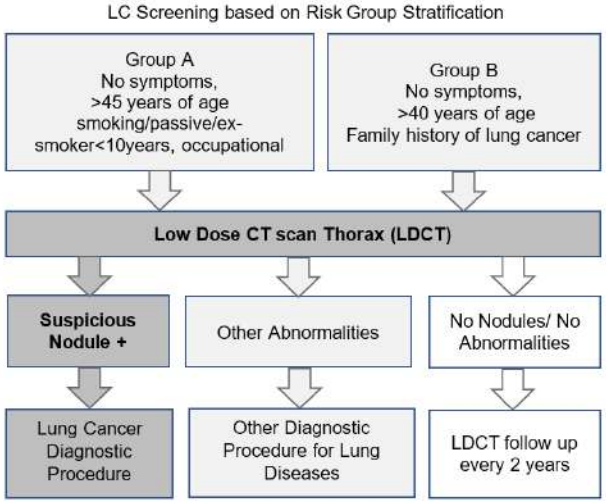

Figure 2. Screening based on risk group stratification

High-risk individuals include males aged >45 years old, a history of smoking/second-hand smoke or occupational/environmental exposure, and a history of fibrosis lung diseases. The younger age group (>40years) should be monitored with the above risks and genetic or family history of cancer. The risk assessment determines which individuals are at high risk for lung cancer. Factors such as age and tobacco smoking are weighted; lung cancer is relatively rare in individuals younger than 45 years, and smokers have a 10- to 35-fold increased risk of lung cancer compared to non-smokers, including second-hand smokers.[15]

Within five years since quitting, former smokers have a 39.1% lower risk of lung carcinoma incidents than current smokers. This risk even continues to fall with increasing years since quitting. However, compared to never-smokers, the risk of developing cancer in former smokers remains high, even after 25 years after quitting, reaching over three-fold higher than never-smokers.[16]

Other than smoking, occupational exposure to carcinogens, asbestos was historically the most common, is considered another risk factor for lung cancer as it is estimated to be found in 5 to 10% of lung cancer patients.[12] A meta-analysis of 14 case-control studies in Europe and Canada, consisting of 17,705 lung cancer cases and 21,813 controls, has found that over-exposure to asbestos was associated with a 24% and 12% increased risk of lung cancer in men and women, respectively.[17]

With its cases still prevalent in Indonesia, it is essential to know that tuberculosis could have a role in the pathogenesis of lung cancer by promoting chronic inflammation and pulmonary fibrosis, which lead to higher rates of genetic alterations and mutations.[18] Genetic is another risk factor as an inherited susceptible locus responsible for lung cancer disease has been discovered. The Genetic Epidemiology of Lung Cancer Consortium revealed a vital susceptibility locus influencing lung cancer risk, which is a region on 6q23-25 after conducting a genome-wide linkage analysis of 52 families in which several lung cancer cases occur in first-degree relatives.[19]

For people meeting the abovementioned high-risk criteria, LDCT is strongly recommended to be undergone every two years. In order to ensure compliance and screening program effectiveness, it is recommended for institutions performing lung cancer screening employ a multidisciplinary approach in which a patient is managed by specialties such as chest radiology, pulmonary medicine, and thoracic surgery.[20]

Pulmonary nodules are often defined as rounded or irregular opacities, well or poorly defined, measuring up to 3 cm in diameter.[21] They are best classified according to size, attenuation, and presence (or absence) of calcification. One of the

objectives of LDCT is to detect non-calcified nodules that might be suspicious for lung cancer, most of which are solid. Non-calcified nodules are common and present in 25–50% of LDCT scans.[22] If a single lung nodule or multiple nodes are found, further diagnosis is needed to define whether the nodule is of inflammatory or malignancy origin. After that, a follow-up LDCT is conducted after 1–2 months for further treatment. On the contrary, if no lung nodules or other non-cancerous abnormalities are detected (for example, aortic aneurysm, coronary artery calcification, or tumors/benign disease outside of the chest), a follow-up for other respiratory diseases is recommended after every 2-yearly control with LDCT.[20]

Lung Cancer Early Diagnosis in Individuals with Respiratory Symptoms

Most lung cancer is diagnosed patients present with symptoms such as persistent cough, chest pain, hemoptysis, dyspnea, or weight loss. Unfortunately, symptom occurrence usually means that their stages are already advanced. Therefore, early diagnosis achieved through screening will increase the time interval before symptoms ensue and improve survival. An ideal and effective screening will allow earlier detection of lung cancer long before patients experience symptoms, hopefully decreasing the mortality rate.[20]

However, particularly in Indonesia, the same groups of symptoms could also lead to an infectious cause that is still prevalent: tuberculosis. Therefore, once a patient has one or more of these symptoms for over two weeks, Xpert MTB/RIF Assay will be done to exclude tuberculosis as a diagnosis. After the diagnosis is confirmed for tuberculosis, these patients will undergo further investigation and evaluation for clinical tuberculosis and LDCT. The Xpert MTB/RIF assay is the opted test, which is considered sensitive and rapid (results are available in less than 2 hours). Additionally, this assay may contribute to cost savings by avoiding unnecessary treatment and misdiagnosis for people who are eventually found not to have tuberculosis.[23] Finally, if the Xpert MTB/RIF assay results are negative, patients will still be observed and assessed to decide whether the patient has clinical tuberculosis or lung cancer is suspected through LDCT.

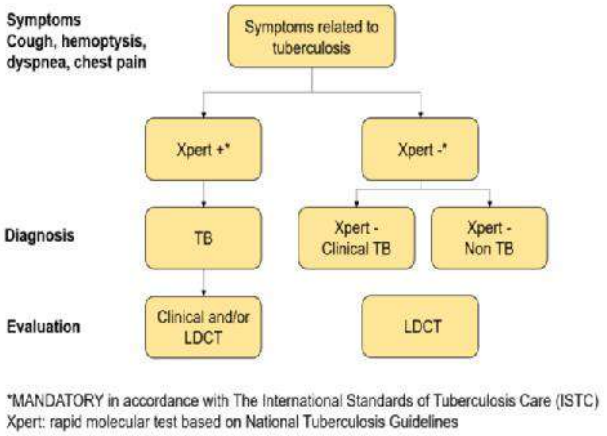

Figure 3. Algorithm of early diagnosis in individuals with respiratory symptoms[25]

Lung Cancer Screening in High-Risk Individuals with Respiratory Symptoms

In high-risk populations with both risk factors mentioned before and symptoms, LDCT will be conducted to detect nodules and early abnormalities. If nodules are found, further diagnosis with MDT will determine whether they are of inflammatory or malignancy origins before a follow-up treatment continues. If the results were negative for nodules or other abnormalities, the patient would be examined for other respiratory diseases that could explain the symptoms presenting. If so, tailored treatments will be provided.

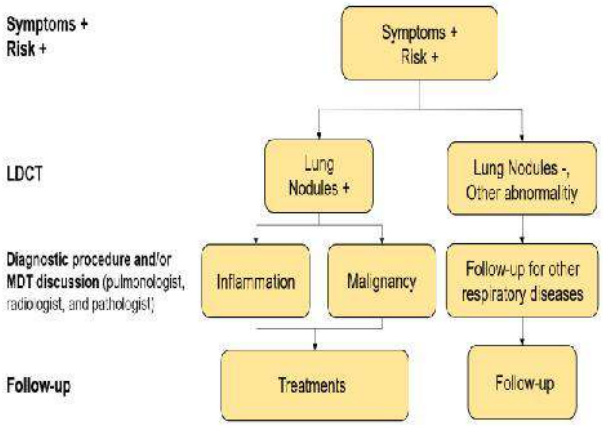

Figure 4. Algorithm of early diagnosis in high-risk individuals with respiratory symptoms[24]

Risks and Benefits of Screening

The National Lung Screening Trial (NLST) showed the benefits of LDCT screening and improved lung cancer mortality. The study, which followed 53,454 participants at high risk for lung cancer at 33 US medical centers, showed that those receiving annual LCDT have a relative reduction in mortality of 20% (p=0.004) compared to those who received single-view posteroanterior chest radiography, as also shown at NELSON trial.[25,26]

Besides the apparent reduction of mortality, a more critical, intangible parameter, quality of life (QoL), was also shown to benefit from early screening.[25] Moreover, lung cancer screening may bring another lung- or non-lung-related clinical conditions that require follow-ups to the surface, such as coronary artery calcification, COPD, or other cancers.[25,27]

The main concerning harm from screening is the unneeded invasive procedure that entails false-positive findings.[28,29] The false-positive rate in the NLST in those receiving LDCT was 23.3%. From these false-positive tests, 0.06% experienced a 'major complication after an invasive procedure.[25,26] Besides physical drawbacks, some evidence argues that lung cancer screening participation could have adverse psychological effects.[30,31] Concerns on radiation exposure have been estimated to be around eight mSv over the three screening scans in the NLST study. It could result in one death due to radiation per 2,500 people screened over a 10- to 20-year period.[32,33] In every 108 lung cancers detected by screening, one radiation-induced cancer arises.[34]

FUTURE DIRECTIONS

Unlike population-based screening programs such as breast, cervix, and colon cancer in which all individuals of a specific sex and age, regardless of any risk factors, lung cancer screening program only targets those most at risk.[35]

Another developing alternative for lung cancer screening is detecting specific biomarkers only in lung cancer. This use of blood-borne biomarkers, called 'liquid biopsies' by some, which detect circulating nucleic acids, proteins, or tumor cells, has gained popularity for monitoring advanced-stage lung cancer (Table 5).[35]

One example is the detection of specific circulating microRNAs, such as let7 miRNA, which is downregulated in lung cancer tissue, or miRNA-21, that has been shown to appear in both lung cancer cell lines and tissue.[36,37] Another non-invasive method that has been proposed is exhaled breath analysis. Ion mobility spectrometry is one of the sensitive tools in detecting volatile components (VOC) in exhaled breath of lung cancer patients; one pilot study has shown that VOCs of patients with lung cancer are easily distinguished from controls.[38]

Table 1. Potential targets of biomarkers for the early detection of lung cancer[35]

Base	Potential target biomarker
Cell-free nucleic acid	circulating tumor DNA, circulating microRNA,
Tumor-specific antibodies	antibodies to TSA, tumor-specific antigen
Circulating tumor cells	Circulating tumor cell
Exhaled-breath analysis	Exhaled-breath condensate, volatile gas

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CONFLICT OF INTEREST

None

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Literature Review

Anatomical Pathology Differences in Lung Alveoli Damage with Exposure to Conventional and Electric Cigarettes

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Abstract

In conventional cigarettes, tobacco is a major risk factor in the development of diseases involving the lungs, including pulmonary emphysema, fibrosis and lung cancer. Many people think that using e-cigarettes is much safer than conventional cigarettes. Whereas smoking with electronic cigarettes can cause the same feeling of cotton mouth as felt by conventional smokers, with symptoms such as itchy throat, cough and complications to the lungs. This literature review conducted a literature search with the keywords cigarette, e-cigarette, popcorn lung, and alveoli. Conventional cigarettes and electronic cigarettes (e-cigarettes) cause damage to the pulmonary alveoli in the form of alveolar spaces; this depends on the nicotine content in them. Electronic cigarettes and conventional cigarettes exert different effects on the oxidative stress response of the airway epithelium. In addition, the image of popcorn lung can be found due to the presence of diacetyl that appears when heating e-juices in e-cigarettes.

Keywords: alveoli, cigarette, e-cigarette, popcorn lung

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INTRODUCTION

Based on data from RISKESDAS 2018, the national average of smokers aged over 15 years was 32.2% and almost 50% of provinces showed numbers above the national average. The increase in the number of businesses from 2013 to 2018 was 0.7% for those aged 10-14 years and 1.4% for those aged 15–19 years.[1]

In 2018, Indonesia had a proportion of the population that consumed tobacco (sucking and chewing) of 62.9% for men and 4.8% for women. These data indicate that the number of male smokers in Indonesia is higher than that of women, and these data indicate that the number of smokers in Indonesia is higher than that of non-smokers.[1]

In addition to tobacco smokers, in Indonesia there are also many users of e-cigarettes. It was recorded that in 2018, the national average prevalence of electronic cigarette users in Indonesia reached 2.8%. Although the number of tobacco smokers had increased, e-cigarette users in 13 provinces were recorded of being above the national average prevalence. Most of the areas that had the highest prevalence of e-cigarette users were on the island of Java.[1]

Many people think that e-cigarettes are safer than conventional cigarettes. Recent infographic data reveal that smoking using e-cigarettes can elicit the same feelings from a cottonmouth as conventional smokers, including symptoms such as an itchy throat and cough. Electronic cigarettes can cause complications for the lungs. Smoking with electronic cigarettes (vaping) can cause serious damage to these organs.[2]

Chemicals in e-cigarettes can damage lung tissue by triggering inflammation. The damage can reduce the ability of the lungs in preventing infection from germs and other harmful substances. Nicotine in tobacco cigarettes and e-cigarettes is harmful to

adolescent brain development according to the U.S. The Food and Drug Administration. Although there is a liquid in electronic cigarettes that does not contain nicotine, the use of e-cigarettes can interfere with the lung functions.[3]

Vaping of propylene glycol and glycerol aerosols at high doses and in large amounts has been shown to cause sustained impaired gas exchange and lower respiratory tract epithelial injury. Previous investigations revealed sequelae and abnormalities on radiographs and pulmonary function tests at a later time.[4] In conventional cigarettes, tobacco is a major risk factor in the development of diseases involving the lungs, including pulmonary emphysema, fibrosis, and lung cancer.[5]

Based on the explanation above, this study was aimed to prove that consuming electronic cigarettes and conventional cigarettes could trigger damage to the alveoli and tissues in human lungs.

METHODS

This literature review conducted a literature search and obtained 27 journals and 7 textbooks. Journals were obtained from PubMed, Elsevier and Google Scholar searches with the keywords cigarette, e-cigarette, popcorn lung, and alveoli, which were selected with the criteria of national journals accredited by SINTA and international journals with a good reputation and indexed by Scopus and non-Scopus. The study was conducted by interpreting and identifying previous studies related to the anatomical pathology of the alveoli exposed to conventional cigarette smoke and e-cigarettes.

RESULTS

A study conducted by Andrault et al discussed about the induction of cigarette smoke on the overexpression of active Cathepsin S (CatS) in human lungs. Simple levels of immunoreactive CatS were observed in non-smokers (NS) lungs, while higher expression of CatS was readily detectable in non-COPD current smokers (CS) and CS with COPD.[7]

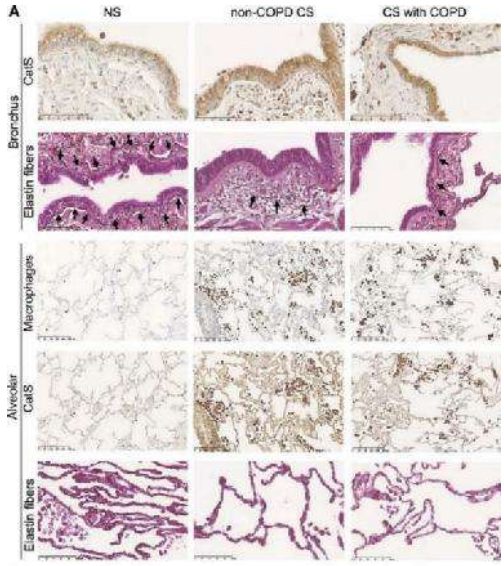

Figure 1. Expression of Cathepsin S protein in peripheral lung tissue from non-smokers and smokers. Representation of histology sections of the bronchial and alveolar epithelium. Elastin Fiber is indicated by a pointing arrow.[6]

In this study, the highest CatS expression was observed in bronchial epithelial lining, type II pneumocytes, and alveolar macrophages. CatS immunoreactivity was also detected in the submucosal glands, whereas the non-ciliated club cells of the bronchiolar epithelium stained weakly. The important factor in the pathogenesis of cigarette smoke-induced emphysema is the degradation of the pulmonary interstitium by elastinolytic proteases, including CatS. Accordingly, more areas of disruption and fragmentation of elastin fibers in lung tissue were observed in non-COPD CS and CS with COPD compared to NS.[7]

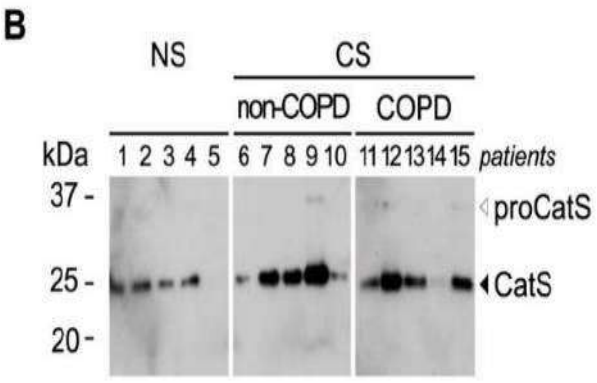

Figure 2. Western blot representation of mature CatS in pulmonary peripheral tissue lysates.[7]

Figure 2 discusses CatS levels in lung tissue of never-smokers and smokers. Western-blot analysis confirmed a higher CatS protein expression in selected samples of non-COPD and COPD

smokers versus NS. The mature form of CatS (25 kDa) was strongly stained; the staining of its proform was fainter.[7]

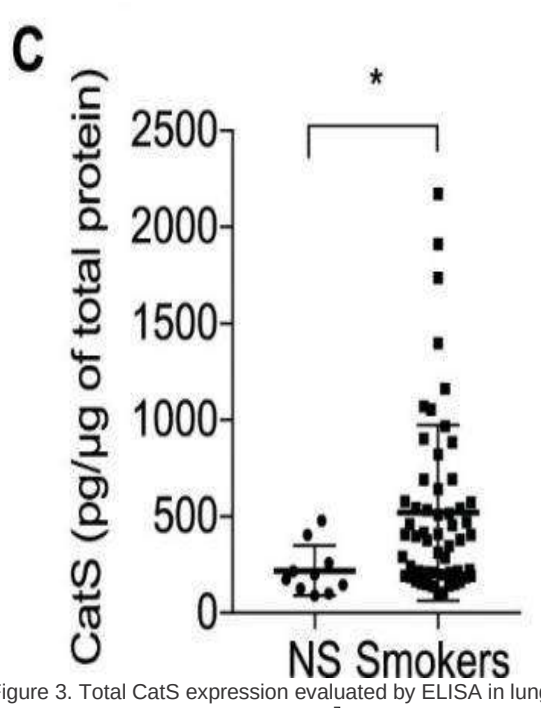

Figure 3. Total CatS expression evaluated by ELISA in lung tissue lysates.[7]

Moreover, the levels of immunoreactive CatS determined by ELISA were significantly (2.5 fold) higher in lung tissue lysates from the cohort of cigarette smokers compared to NS.

Table 1. Descriptive data on histopathological observations of widening, thickening, infiltration of the lumen, and the wall of alveolar lymphocytes

Histopathological observations of widening	Thickening	Infiltration of the lumen	The wall of alveolar lymphocytes
Kn	1	1	1
E0	1	1	1
E3	2	2	2
Kv	2	2	2

Note: Treatment groups=Control (Kn), 0 mg nicotine (E0) e-cigarettes, 3 mg nicotine e-cigarettes (E3), and conventional cigarettes (Kv). Scoring=none (0), low (1), and large (2).[8]

Triantara et al also conducted a study on the lung histopathology of white rats exposed to conventional cigarettes and electronic cigarettes, showing data as written in Table 1 and Figure 4. In this study, bronchial wall thickening, bronchial lumen dilation, and lymphocyte infiltration were assessed in the control animal group, e-cigarettes with 0 mg nicotine, e-cigarettes with 3 mg nicotine and conventional cigarettes.[8]

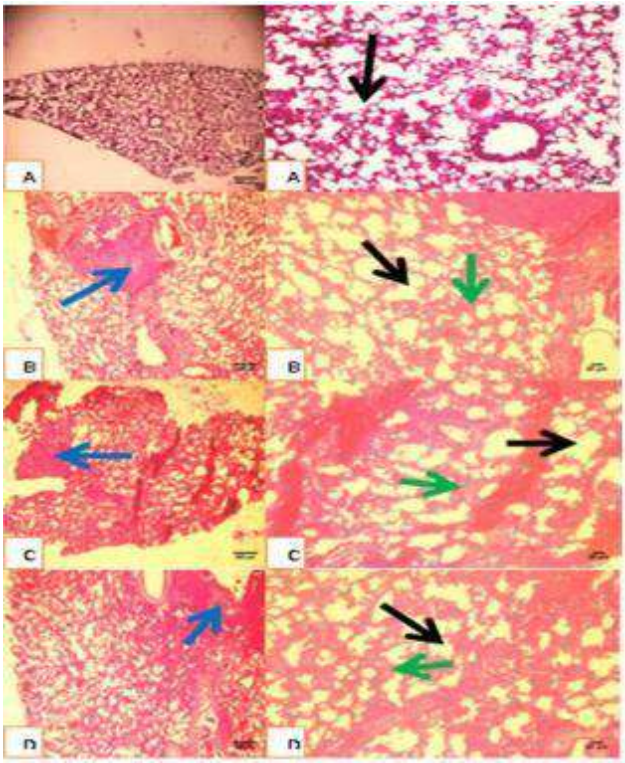

Figure 4. Microphotos with 40- and 100-fold magnification and with Hematoxylin-Eosin staining, the histopathological picture of the treatment group: A. Control (Kn), B. E-cigarette with 0 mg of nicotine (E0), C. E-cigarettes with 3 mg of nicotine (E3), and D. Conventional cigarettes (Kv).[8]

Figure 5 shows the results as seen in emphysema patients; both airways and vascular cells are affected, resulting in enlargement of the alveolar air spaces and loss of peripheral blood vessels. In this study, it could be concluded that electronic cigarettes had the same toxic effect as tobacco cigarettes or conventional cigarettes, and long-term exposure to nicotine vapor could cause significant lung damage.[9]

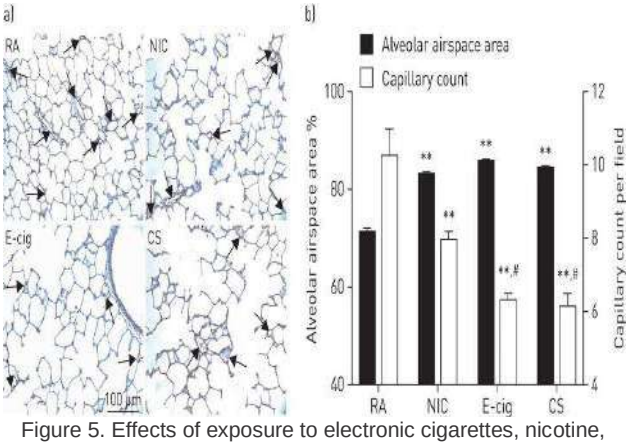

Figure 5. Effects of exposure to electronic cigarettes, nicotine, and tobacco cigarettes on lung structure and number of blood vessels compared to room air. Figure A. Morphology and pulmonary vasculature (visualized by staining for von Willebrand factor) after 5 days of exposure. The arrow in figure A shows the capillaries. Figure B. Enlargement of the alveolar air spaces.[9]

DISCUSSION

In a study conducted by Reinikovaite et al on experimental mice, it was observed that the nicotine contained in electronic cigarettes was as harmful to the microcirculation as conventional cigarettes. Exposure to the use of e-cigarettes or the production of nicotine has the same damaging effect on the structure of the lungs and blood vessels as conventional cigarettes.[9]

Conventional cigarettes or tobacco cigarettes are known to cause damaging effects on the cardiovascular system, angiogenesis, and skin capillary perfusion by causing direct injury to blood vessel walls, increasing platelet aggregation, microvascular thrombosis, and inflammation. Meanwhile, the consequences of exposure to e-cigarette vapor have not been widely explored.[9]

Research conducted by Taylor et al stated that, under comparable conditions, compared to conventional cigarettes, e-cigarettes did not activate the cellular stress response in an in vitro model of the airway epithelium.[10]

Conventional cigarettes or tobacco cigarettes have an impact on the lungs by increasing the risk of lung cancer and also causing Chronic Obstructive Pulmonary Disease (COPD) which includes emphysema and chronic bronchitis.[6] In addition, quoted from the research by Andrault et al, tobacco cigarettes also induced overexpression of active CatS in human lungs. Cathepsin S itself is a cysteine protease enzyme involved in the remodeling or degradation of connective tissue and basement membranes. CatS expression was found to be significantly higher in smokers (both with COPD and non-COPD) than in never-smokers.[7]

In a study conducted by Zhang et al conventional cigarette smoke was also a strong risk factor for Idiopathic Pulmonary Fibrosis (IPF) and was a pro-senescent factor. Aging type II pneumocytes are involved in the pathogenesis of idiopathic pulmonary fibrosis (IPF).[11] In addition, smoking is noted to cause emphysema, as in the study by Kosmider et al, which discovered high DNA damage and impaired DNA damage repair in mitochondria in type II pneumocyte cells isolated from emphysema patients contributing to mitochondrial dynamics abnormal.[12]

Andrault et al was also pointed out that exposure of human primary bronchial epithelial cells to cigarette smoke extracts triggered P2X7 receptor activation which could upregulate CatS. The highest expression of CatS was observed in bronchial epithelial layers, type II pneumocytes, and alveolar macrophages.[7]

In emphysema, the walls of the air sacs (alveolar septa) appear to be destroyed and the air spaces (alveoli) become wider but irregular and reduced in number. This wider space results in less efficient gas exchange in the alveoli.[13] Nevertheless, high levels of inflammatory cytokines such as IL8 are also found in emphysema. It is noted that the impact of smoking will produce IL6, IL10, and IL33, which increase the risk of lung cancer or other lung diseases.[14] Along with the widening of the airway space, a reduction in peripheral blood vessels was obtained.[9]

In emphysema, the walls of the air sacs (alveolar septa) are destroyed. This situation interferes with the gas exchange of O_2 and CO_2. Alveoli are abnormal and protrude at the top for a complex reason.

Cigarette smoke contains a lot of dirt particles that are inhaled in large quantities by the lungs. Therefore, the alveolar space of smokers contains many macrophage cells that are filled with particles as a result of the phagocytosis process.[13]

Under a microscope with strong magnification, the observed black and brown particles are phagocytized by macrophages. Smoker's lungs have so many particles that they look blackish-gray. In addition, in a large prospective study of high-risk smokers, it was reported that there was a strong linear relationship between increased severity of airflow limitation and lung cancer risk.[15]

Triantara et al concluded that exposure to conventional cigarette smoke caused the greatest damage to the lungs of *Rattus norvegicus* based on alveolar macrophages and histopathological markers, but was not different from exposure to e-cigarette

smoke with a concentration of 3 mg nicotine. E-cigarettes with a nicotine content of 0 mg can cause damage lower than or equal to the control group based on histopathological markers.[8]

According to Lerner et al, the vapor produced from electronic cigarettes and flavored e-juices could induce toxicity, oxidative stress, and inflammatory responses in bronchial airway epithelial cells (H292) and fetal lung fibroblasts (HFL1) in experimental animals. It is known that oxidative stress and inflammatory response are key events in the pathogenesis of chronic airway disease.[16]

Reinikovaite et al measured the average alveolar air enlargement using automated image analyzer software and calculated it as a percentage of total air space versus tissue density. Although less sensitive than stereological methods, measurement of the alveolar air space area accurately reflects changes in lung morphology.[9]

In a study conducted by Taylor et al with comparable conditions, e-cigarettes did not activate the cell stress response in the airway epithelium.[10]

E-cigarettes are known to contain harmful substances, including nicotine, vitamin E acetate, volatile organic compounds, heavy metals, ultra-fine particles, and carbonyl compounds. Of particular concern is the use of flavoring agents in e-liquids. There are more than 7,700 e-liquid flavors across 60 brands. While many of these flavors are "generally recognized as safe" under the United States Federal Food, Drug, and Cosmetic Act, it is important to understand that these only apply to consumption; aerosolization of safe-to-digest flavors can produce adverse health effects.[17]

A cluster of cases of acute lung injury related to e-cigarette use have been reported since April 2019 across the United States. As of August 2019, more than 120 cases in at least 15 states had been identified. As of September 2019, more than 450 cases of vaping-related acute lung injury (EVALI) had been reported to the CDC from 33 states across the country, including 7 deaths. In general, most of the previous patients were healthy adolescents, who experienced rapid onset of symptoms, including cough and severe dyspnea, after vaping.[18]

In e-cigarettes, data show that some flavorings can induce inflammation of the lungs. Diacetyl-containing e-liquids such as caramel, butterscotch, watermelon, pina colada, and strawberries receive wide attention because they can cause bronchiolitis obliterans (popcorn lung).[14] The term popcorn lung has been given to another term for bronchitis obliterans because this disease usually occurs in popcorn factory workers who are exposed to butter-flavored volatiles, particularly diacetyl, which can impair lung epithelial barrier function.[19] This diacetyl content causes symptoms of popcorn lung in e-cigarette users.

Diacetyl and another flavoring agent, 2,3 Pentanedione, can alter gene expression pathways associated with ciliary and cytoskeletal processes in normal human bronchial epithelial cells and cause epithelial cell injury and bronchiolitis obliterans in mice. Inhaled diacetyl affects human cellular matrix remodeling and can stimulate fibroproliferative changes in the human airways.[17]

Diacetyl has been identified in e-liquids at levels higher than the recommended safety limits, including in some products where the packaging clearly states that diacetyl is not an ingredient. One study found it in more than 60% of the e-cigarette flavor samples analyzed, and another study showed that diacetyl is produced in e-liquids over time from another flavoring agent, acetoin. The chemical synthesis of diacetyl from acetoin is accelerated when nicotine is added to the vaping liquid, with the diacetyl concentration increasing over time. Vaping liquids stored for long periods can accumulate high levels of diacetyl, which, when vaporized, can increase the risk of pulmonary toxicity.[17]

The pathophysiology of bronchiolitis obliterans is inflammation of the sub-epithelial structures and repair of dysregulation in response to injury from inhaled toxins or an autoimmune response, leading to fibroproliferative proliferation and abnormal regeneration of the small airway epithelium.[20]

Bronchial smooth muscle hypertrophy, peribronchiolar inflammatory infiltrate, accumulation of mucus in the bronchial lumen, and bronchial scarring can be observed in bronchiolitis obliterans.

There is the concentric narrowing of the bronchial lumen by inflammatory fibrosis. There may even be total lumen occlusion in some cases.[20]

Inhalation of diacetyl-containing products is associated with an occupational risk of bronchiolitis obliterans (BO) and the impact of fixed airway obstruction on public health.[21] In patients with popcorn lungs, the airways become irritated and inflamed, causing scar tissue that narrows the airways, making it difficult for the person to breathe.

CONCLUSION

Conventional cigarettes and electronic cigarettes (e-cigarettes) cause damage to the pulmonary alveoli in the form of enlargement of the alveolar spaces; this depends on the nicotine content.

Electronic cigarettes and conventional cigarettes have different effects on the oxidative stress response of the airway epithelium. Conventional cigarettes have an impact on the oxidative stress response in the airway epithelium, while e-cigarettes do not activate the oxidative stress response in the airway epithelium.

The picture of popcorn lung (bronchiolitis obliterans) can be found due to the presence of diacetyl that appears when heating e-juices in e-cigarettes. Meanwhile, conventional cigarettes do not have these symptoms.

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None

CONFLICT OF INTEREST

None

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