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Low dose Lung-CT as COVID-19 diagnostic tool while waiting for RT-PCR result

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Abstract--Reverse transcription-polymerase chain reaction (RT-PCR) assay as the standard of COVID19 diagnosis takes time, can only be done in limited laboratories, and sometimes produced false negative result; which made diagnosis and intervention become delayed. Meanwhile, chest CT takes little time and has high sensitivity in diagnosing COVID19. This study aimed to see the correlation of Chest CT with RT-PCR results in COVID19 patients. We performed a retrospective cohort study from symptomatic patients at Pantai Indah Kapuk Hospital in Jakarta, Indonesia. Multi-detector scanner CT was done, RT-PCR samples were taken and sent to the government appointed laboratory. Main outcome measures include correlation of CT patterns and CT severity index with RT-PCR. Data were processed with SPSS ver. 25.0 using gamma coefficient measure of agreement. Seventy-three patients were included and underwent chest CT and compared the result with RT-PCR. This study showed the very strong correlation (Gamma +0.897, p-value <0.05, CI 95%) between CT pattern with RT-PCR and no correlation (Gamma +0.241, p-value = 0.379, CI 95%) between CT severity index with RT-PCR. Chest CT has proven its superiority to be used as one of the most capable diagnostic devices for COVID19 patients. It is available in almost every regional hospital in Indonesia. Knowing the Chest CT pattern is a good indicator to predict COVID-19.

Keywords---lung-CT, COVID-19, RT-PCR, multi-detector scanner.

Introduction

A novel strain of human coronaviruses, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has emerged and caused a pandemic referred to as coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO).

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Commented [A1]: R1: 1. The authors need to include a background. I strongly suggest using a scientific reference (textbook, guidelines, etc) to support the author's statement. non-academic literature (Ref.1). Kept in mind, this is journal writing.
2. When say "the main action needed" and "another chosen" --> this is subjective to the author and not a by the government. Should be more scientific.
3. In paragraph 2 in the background, the author write limitation of health facilities and medical profession statement should be supported by clear evidence or
4. In paragraph 2 in the background, the author write reverse transcription-polymerase chain reaction (RT-PCR) the standard for diagnosing COVID19, but it takes time to be done in laboratories pointed by the government." should elaborate more on the turn around time (TAT) in the normal setting and what is the current TAT after regarding the influx of patients.
5. In paragraph 3: "fast diagnostic tool" ==> fast-dia
6. In paragraph 3: Study from Ai et al2 had found that 98% for chest CT, while RT-PCR sensitivity was on early state of disease" --> it's not well cited! put more results.
7. In paragraph 3: "Another benefit of chest CT is the low dose radiation" --> "immediate" ==> "immediate" statement is unnecessary and is not linked with the p statement. : Following this statement, the authors should research question or clear statement why this study is. Should be clearer what is the novelty of this study.
8. In paragraph 3: "almost all" --> is it almost or all? support your statement with clear evidence.

Many victims and deaths have occurred due to this virus. The main action needed is to make a rapid diagnosis, so that prompt treatment can be given and isolation for patients and families can be done in order to stop the transmission chain of this virus.

Indonesia ranked as the fourth most populated country in the world and home to the world's second largest urban area, Greater Jakarta is now facing this problem. So far, Indonesia has recorded more cases than any other South East Asian (SEA) country with the highest fatality rate in SEA.¹ With the limitation of health facilities and medical professional, the main target is to suppress the transmission. Real-time reverse transcription-polymerase chain reaction (RT-PCR) assay is the standard for diagnosing COVID19, but it takes time and can only be done in laboratories pointed by the government. To be able to overcome the situation, another strategy has to be chosen.

As chest computed tomography (CT) is available in almost all regional hospital in Indonesia, we suggest the use of low dose chest CT as a fast diagnostic tool. Study from Ai et al² had found the sensitivity of 98% for chest CT, while RT-PCR sensitivity was only 71%, at the early state of disease.²⁻⁴ Another benefit of chest CT is the immediate result and low dose radiation.³ We aimed to see the correlation between CT pattern and RT-PCR result, along with CT severity category and RT-PCR result.

Methods

This hospital-based retrospective cohort study was conducted at Pantai Indah Kapuk Hospital, North Jakarta, Indonesia between March 15th – April 30th 2020. All patient admitted to the hospital with clinically suspected COVID19 infection who undergone both chest CT scan and nasopharyngeal swab for RT-PCR test were included. The low-dose CT parameters of protocols used is according to recommendation from Kang et al³. A high-resolution CT scan was performed in all patients with multi-detector row CT scanners (Siemens - SOMATOM Definition AS⁺ 128). Patients were scanned in the supine position, during breath hold, from the lung apices down to the costophrenic angles. The acquisition parameters using core dose were as follows: tube voltage 100 kV, mAs/ref 112/96. Dose length product (DLP) 14.5 milligray (mGy) 4.5, inversion time 0.25 s, collimation slice 0.6 mm, signal-to-noise ratio (SNR) 0.47. The 0.6 mm thick images were reconstructed using a high-frequency reconstruction algorithm and lung windowing and stored in the picture archiving and communication system (PACS).

Unenhanced CT scans were obtained for all patients. Image viewing and evaluation was done on a PACS workstation (Synapses, Fujifilm) with multiplanar reconstruction tools and reached a decision in consensus. The images were viewed in lung window settings (width, 1,000–1,500 HU; level, 700 to –550 HU) and mediastinal window settings (width, 300–350 HU; level, 30–40 HU). Two radiologists with 16 and five years of experience in radiology retrospectively reviewed all images independently blind to RT-PCR results and decided on positive or negative CT findings by consensus. The epidemiological history and chief clinical symptoms (fever and/or cough) were available for both readers.

Commented [A2]: R1: 1. This study was conducted at top private hospitals in Jakarta. So please be wise with statement in the background. (see "the limitation of health facilities and " Chest CT is available in almost all regional hospitals in Indonesia." 2. Is it contrast or non-contrast chest CT scan: please specify that not all the readers are radiologists. 3. In paragraph 2: "The 0.6 mm thick images " --> 0.6 mm thickness (not thick images) 4. HU --> Hounsfield Unit (put in the abbreviation list) 5. In paragraph 4: "Two radiologists with 16 and five years of experience in radiology"--> chest radiologists? Or general radiologists? 6. The method is not precise. What happened if there was a discrepancy between two readers? --> excluded cases? Is it necessary to suggest taking one more reader (perhaps independent) to determine the discrepancy between the two original readers? 7. Please elaborate more on the consensus; Regrading criteria used in this study to define Chest CT --> is it established or proposed original criteria? 8. The statement regarding the subject or sample size is not clearly stated

Images were reviewed independently, and final decisions were reached by consensus. They reviewed all chest CT image and described CT pattern type and CT severity category. For any disagreement between the two radiologist interpretations, the case was excluded.

Normal Chest CT pattern is defined as no abnormalities found in the lung parenchyma. Classic COVID19 infection is lower lobe, peripheral predominant, multiple, bilateral foci of ground glass opacities (GGO) AND crazy-paving pattern or peripheral consolidation or air bronchograms or reverse halo or perilobular pattern. Probable COVID19 infection is lower lobe predominant mix of bronchocentric and peripheral consolidation or reverse halo or perilobular pattern or scarce GGO. For classic and probable COVID19 pattern, mild severity category defined as pure GGO, up to 3 focal abnormalities \leq 3cm in max diameter; moderate or severe as pure GGO, more than 3 focal abnormalities or $>$ 3cm in diameter with consolidation; and severe as diffuse GGO or consolidation with signs of architectural distortion. Indeterminate for COVID19 infection means that the chest CT pattern do not fit classic or non-COVID19 patterns or clinical context; non-peripheral GGO or complex/unilateral or other patterns. For indeterminate pattern, mild category is defined as up to 3 focal abnormalities \leq 3cm in max diameter, and moderate/severe as more than 3 focal abnormalities or $>$ 3cm in diameter. In accordance to BSTI COVID19 diagnosis, the difference between moderate and severe is subjective and were used in conjunction with clinical assessment.^{4,5} Non-COVID19 infection is other chest CT pattern that includes lobar pneumonia, cavitating infections, tree-in bud / centrilobular nodularity, lymphadenopathy, effusion, or established pulmonary fibrosis.⁵

Nasopharyngeal swabs were taken by trained laboratory personnel; blinded from the patient's symptoms and CT scan results. Each patient has two nasal swab samples taken from each nostril, and the samples were then put in viral transport media and were transported within the same day to the government appointed laboratory to under-run RT-PCR for SARS COV-2. The RT-PCR results were reported back to the hospital's COVID19 response team, which were then included in the patient's medical records. All statistical analysis was done using Statistical Package for the Social Science (SPSS) version 25.0 (SPSS Inc., Chicago, IL, USA). CT pattern (classic, probable, indeterminate, non-COVID19), CT severity category (mild, moderate, severe) and RT-PCR results (positive, negative) were taken as variables. Gamma coefficient analysis were done to determine the correlation between CT pattern and RT-PCR result, along with the correlation between CT severity category and RT-PCR result, as each variable can act as both dependent and independent variable. This study was approved by Atma Jaya Ethical Committee, Jakarta, Indonesia with a reference No. 03/04/KEP-FKUAJ/2020. Written informed consent was obtained from all parents of the study subjects.

Results

The data of patients were collected from our hospital in North Jakarta, Indonesia from March 15th to April 31st, 2020. The electronic medical records were reviewed and analysed. A total of 73 patients undergone chest-CT and nasopharyngeal

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2. "The electronic medical records were reviewed and analyzed" -> "The electronic medical records were reviewed"
 3. "Fifty out of 73 subjects resulted from positive COVID-19 according to the RT-PCT run by the government," -> "Who is the government here?"
 4. "in which 36 (72%) are male --> 36 subjects!"
 5. Just used median (drop the range)
 6. "Three patients with positive RT-PCR results died of care; all of them were male, with age 56, 73 and 80. please be clear if these three patients are from the 50 positive PCR?"
 7. It's so confusing, at first the author mentioned 50 subjects then the second paragraph 51 subjects ???
 8. Most grateful if the author can explain more on the analysis? why Gamma coeff is used? ; Gamma tests association between points and also tells us the strength of association NOT correlation.
 9. rewrite the results please

swabs RT-PCR. (Table 1). Some of the CT scan result images are shown in Figure 2.

(Table 1)
(Figure 1)
(Figure 2)

Fifty out of 73 subjects resulted positive COVID19 according to the RT-PCT run by the government, in which 36 (72%) are male with the mean age of 53.56 years old (median 55.0 years old, range: 26-83 years old), and 14 (28%) are female with the mean age of 51.71 years (median 53 years old, range: 25-80 years old). Three patients with positive RT-PCR results died within six days of care; all of them were male, with age 56, 73 and 83 year old. There are 51 subjects that has classic COVID19 chest CT pattern, in which 44 (86.3%) resulted positive COVID19 according to RT-PCR. Further analysis found that chest CT pattern has significant correlation (Gamma +0.897, $p < 0.05$, CI 95%) with RT-PCR result; the more 'classic' the chest CT appearance, the more likely the RT-PCR to be positive. (Table 2)

Out of 51 patients with classic COVID19 Chest CT pattern, 13 (25.5%) were classified as mild, 31 (60.8%) as moderate, and 7 (13.7%) as severe. Patients with probable COVID19 Chest CT pattern were half of mild severity and half of moderate severity. (Table 3). (Table 3). There are 19 patients classified as mild severity COVID19 according to chest CT in which 15 (78.9%) resulted positive in RT-PCR. From 36 moderate severity COVID19 CT pattern, 28 (77.8%) were RT-PCR positive. All seven patients in severe category are positive in RT-PCR. This research, however, was unable to find correlation between CT severity category and RT-PCR result (Gamma +0.241, $p = 0.379$, CI 95%). (Table 4)

Discussion

Indonesia has recorded more COVID19 cases than any other Southeast Asian country. The fatality rate is also one of the highest in the world.¹ With limited health facilities and medical worker, the main objective from WHO is to slow and stop the transmission. Upper respiratory tract (URT) specimens test by RT-PCR is the main art of diagnosis for COVID19, but RT-PCR takes times and can only be done in limited laboratories. Moreover, in Indonesia, only government appointed laboratory can run RT-PCR for SARS-COV-2. Considering the time needed to wait for RT-PCR result and the possibility of a false negative result, another diagnostic tool is needed to help diagnosing COVID19.

The detection rate of URT (nasal or pharyngeal swab) sample RT-PCR varies between 32%-62%,^{6,7} a false negative may initially occur. Other problems that occur with RT-PCR as standard of diagnosis are: genetic diversity and rapid evolution of this novel coronavirus, irregular study samples, inadequate viral material in the specimen, laboratory errors, extraction of nucleic acids that did not match clinical material, and contamination and technical problems.^{8,9} It is recommended that in the case of negative RT-PCR result on upper respiratory tract samples with clinical features suspicion for COVID19, especially from CT

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2. Does the manuscript make valid comparisons to o recent studies? --> Not really. Small sample size and proposed in this study is not well established yet cle COVID-19 on Chest CT.
3. Does the section discuss the potential impact or be study to relevant stakeholders? --> probably only fo similar healthcare settings;
4. Does the section discuss the limitations of the stu
5. Is the conclusion accurate? Is it potentially mislea how? - I strongly suggest using "diagnostic tool" rat "diagnostic devices"; The conclusion is very subject authors, and it's not applicable to "almost every regio Indonesia."
6. This study aims to see the association between Ch with RT-PCR. Not a correlation based on the used m when say "good indicator", the author did not run a to measure prediction

image, multiple sample types in different time points, including from the lower respiratory tract if possible, should be tested.^{9,10} Thus, negative RT-PCR result does not necessarily exclude COVID19 from the patient's differential diagnosis.

Based on available data published in recent literature, almost all patients with COVID19 had characteristic CT features in the disease process, such as different degrees of GGO with/without crazy-paving sign, multifocal organizing pneumonia, and architectural distortion in a peripheral distribution, which we called 'classic COVID19 chest CT pattern'.^{2,11,12} Classic chest CT pattern for COVID19 has 100% confidence for COVID19 and probable COVID19 chest CT pattern has 71-99% confidence for COVID19.⁵ Study from Ai et al² had found the sensitivity of 98% for chest CT, while RT-PCR sensitivity was only 71% at the early state of disease, where viral load is lower.^{2,3,9} As chest CT is almost available in all regional hospital in Indonesia, a low dose chest CT can be used as a fast diagnostic tool for COVID19. Even though the use of chest CT as a screening tool has not been recommended, recent studies have demonstrated a central role of CT in the early detection and management of COVID19.

This study has supported the correlation between chest CT pattern for COVID19 pneumonia with RT-PCR diagnosis of COVID19 (Gamma +0.897, $p < 0.05$, CI 95%). Although there is a strong correlation between the two, further study needed to determine the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of chest CT scan in diagnosing COVID19. One meta-analysis showed that the pooled sensitivity was 94% for chest CT and 89% for RT-PCR. For chest CT, specificity was 37%, PPV ranged from 1.5% to 30.7%, and the NPV ranged from 95.4% to 99.8%. For RT-PCR, the PPV ranged from 47.3% to 96.4%, while the NPV ranged from 96.8% to 99.9%.¹³ It was stated that the sensitivity of chest CT was affected by the distribution of disease severity, the proportion of patients with comorbidities, and the proportion of asymptomatic patients.

Disease severity has been reported to be related to the viral load of a patient; the higher the viral load, the more severe the disease.¹⁴ The higher the viral load, the easier it is to detect SARS-COV-2 virus in RT-PCR. This research, however, was unable to find correlation between CT severity category and RT-PCR result (Gamma +0.241, $p = 0.379$, CI 95%). It should be noted that in this study, RT-PCR samples were only taken from nasal swabs, remember that nasal swab positivity rate ranges from 53.6%-73.3%, and multiple sample types should be taken, especially sputum sample which has higher positivity range (72%-88.9%).^{6,9,15} It should also be noted that the number of samples in the severe category is far less than those in mild and moderate severity, which may affect the statistical analysis. The limitation of this study is as stated above; the limited sample taken to undergone RT-PCR, and also the limited number of samples. There is no conflict of interest in this study.

In conclusion, chest CT has proven its superiority to be used as one of the most capable diagnostic devices of COVID19. To add, it has a low-dose of radiation and is available in almost every regional hospital in Indonesia. Knowing the chest CT pattern is a good indicator to help diagnose COVID19. Further study is needed in the use of chest CT as clinical severity predictor.

Conflicts of interest

All of the authors have no conflict of interest regarding this manuscript

Funding Source

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Table 1
Demographic of subject according to RT-PCR result

			Male	Female	Total
RT-PCR result	Negative	n	14	9	23
		%	60.9%	39.1%	100.0%
	Positive	n	36	14	50
		%	72.0%	28.0%	100.0%
Total	n	50	23	73	
		%	68.5%	31.5%	100.0%

RT-PCR= real time polymerase chain reaction

Table 2
Subject distribution according to CT pattern and RT-PCR result

		RT-PCR result			Gamma coefficient	p	
		Negative	Positive	Total			
CT Pattern	Non-COVID19	n	11	0	11	+0.897	0.000
		%	100.0%	0.0%	100.0%		
	Indeterminate	n	1	0	1		
		%	100.0%	0.0%	100.0%		
	Probable COVID19	n	4	6	10		
		%	40.0%	60.0%	100.0%		
	Classic COVID19	n	7	44	51		
		%	13.7%	86.3%	100.0%		

CT pattern= computed tomography pattern according to BSTI; RT-PCR= real time polymerase chain reaction; COVID19=Coronavirus disease 2019