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Clinical Symptoms are Better Than CT Images for Treatment Evaluation and Hospital Discharge in Patients with Coronavirus Disease 2019 (COVID-19)

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1. Abstract

1.1. Objective: To determine whether changes in CT are better than clinical symptoms for treatment evaluation, and whether CT is necessary to determine the discharge of patient undergoing COVID-19 treatment.

1.2. Methods: Forty-two adult COVID-19 patients and at least two CT examinations were retrospectively recruited in this observational cohort study. We compared analyzed changes in CT data with clinical symptoms at four different time points (at admission, during treatment, discharge, and post-discharge). This study was approved by the institutional ethics boards committees, and informed consent was obtained from each patient.

1.3. Results: The median (IQR) time required for the resolution of clinical symptoms (4 (3-17) days) was shorter than 20%, 40%, 60% and 80% CT improvement (10 (6-18), 13 (8-20), 14 (9-29) and 16 (9-31) days, respectively) (P =0.021, 0.002, <0.001, and <0.001 respectively). Abnormal CT remained in 88% and 50% of patients at discharge and at least 14 days post-discharge, respectively. Binary logistic regression analysis demonstrated that i) there was an association between quality discharge and days required for the resolution of clinical symptoms (P =0.019), but not between quality discharge (defined below) and days needed for CT improvement (20%: P =0.060, 40%: P =0.129, 60%: P =0.152, 80%: P =0.686, respectively); ii) there was no association between quality discharge and CT improvement during treatment (20%: P =0.301; 40%: P =0.450).

1.4. Conclusions: CT is not better than clinical symptoms for treatment evaluation or discharge of COVID-19 patients. Chest CT is not recommended for clinical management of COVID-19 patients unless pneumonia is required.

2. Introduction

Since initially identified in Wuhan city of China's Hubei province in December 2019, the 2019 novel coronavirus (COVID-19) has resulted in 252,902,685 confirmed cases and 5, 094, 826 deaths as of 11:58am CET, 15 November 2021 according to the World Health Organization (WHO). The ongoing wave of coronavirus in some countries shows no signs of slowing, and the second wave of the COVID-19 pandemic has already begun [1]. The lungs are one of the foremost organs targeted by the COVID-19 virus. A study of 1663 hospitalized COVID-19 patients showed abnormal chest

computerized tomography (CT) scans in 99.8% of patients [2]. Studies have also indicated that 94% of discharged patients had residual disease on final CT scans [3], and 35%-47% of recovered patients had abnormal CT scans after [3-4] weeks of discharge from the hospital [4,5]. It is generally accepted that chest computerized tomography (CT) is the most powerful tool to visualize COVID-19 infection in the chest [6,7]. However, this has raised concerns of chest CT overuse and unnecessary radiation exposure. A proper balance must be addressed among its clinical benefit as a visualization tool, and the risk of cancer associated with exposure to ionized radiation. Additionally, the amount of people exposed to the individual with COVID-19 increases with every imaging appointment, not to mention the increased cost to patients and societies as a whole.

A substantial number of papers have either intentionally or unintentionally promoted the use of chest CT. By all appearances, this promotion is reasonable since chest CT can indeed provide impressive images of COVID-19-induced pneumonia. Additionally chest CT has been required in certain situations, for example, during the beginning of the outbreak when knowledge of COVID-19 infection was severely limited, and RT-PCR tests were less reliable or not available [8]. Consequently, however, CT has been overused by some physicians [9-11]. For example, most patients confirmed to have COVID-19 infection in China had one chest CT within three days of hospital admission, and another CT within three days of hospital discharge. A considerable percentage of patients also had a chest CT during treatment, after finishing a 14-day observation following hospital discharge, or both [11]. Unnecessary use of CT is not only financially costly to both patients and healthcare systems but also increases the risk of developing cancer by 0.1% [12] and the chance of exposing additional medical personnel to COVID-19. Many guidelines and consensuses have been published for the proper use of chest imaging to direct patient management during the COVID-19 pandemic in different practice settings, different phases of the outbreak, and environments of varying critical resource availability [7,8,13].

To the best of our knowledge, most related studies focus on whether or not to utilize chest CT for the diagnosis or screening of COVID-19 infection [14-17], with only a few exceptions on treatment evaluation or hospital discharge [18,19]. As such, studies are needed to improve and guide evidence-based practices. Consequently, even the most recent WHO guideline for the use of chest imaging for treatment evaluation is based on “very low certainty evidence” and thus is considered a “conditional recommendation” [8]. This study aims to determine whether: 1) changes in CT over time are better than the observation of clinical symptoms alone (fever, cough, diarrhea and fatigue et al.) for treatment evaluation; 2) CT is necessary to determine the discharge of an adult patient undergoing treatment for COVID-19.

3. Materials and Methods

3.1. Patients and Methods

Forty-five of 50 adult patients with RT-PCR confirmed COVID-19 infection were hospitalized from January 23 to April 8, 2020, after excluding five asymptotic patients. Forty-two (93%) of the 45 adult patients with at least two chest CT examinations were retrospectively recruited for this study. All clinical data were extracted from the hospital’s electronic medical record system. Twenty-five (59%) of the 42 patients had at least three CT scans with one CT taken within two days of hospital discharge. Sixteen (38%) of the 42 patients had four CT scans with their last CT scan at least 14 days after hospital discharge. Thirty-five of the 42 patients had a CT scan at discharge or at least 14 days after hospital discharge. All 42 patients recovered and were discharged.

All CT images were first analyzed by a deep learning algorithm (InfervisionTM, Beijing, China). The algorithm has also been used in CT lung lesion detection [20-21]. A COVID-19 segmentation module was explicitly optimized for COVID-19 to automatically outline pneumonia regions and calculate the volume and proportion of pneumonia in the lung and each lobe [22]. This COVID-19 module was utilized in this study. CT images were then reviewed by two independent radiologists with more than ten years of experience to ensure the accuracy of the lesion boundaries. The opacity percentage of the whole lung was calculated at the beginning of COVID onset and the follow-up CT, the baseline CT was taken at the onset of clinical symptoms [23].

Patient discharge criteria were based on overall clinical recovery as evaluated by physicians following the guidelines for China [24]. They included: normal body temperature without any clinical symptoms for three days and at least two negative RT-PCR results within 24h intervals. Quality discharge was defined as those patients who met the discharge criteria, and showed a 60% or more reduction in CT lesion volume at the time of discharge. Only final decisions reached by consensus were reported. This study was approved by the institutional ethics board of three hospitals. Informed consent was obtained from each patient.

4. Statistical Method

Statistical analysis was performed using SPSS 25.0 (IBM, New York, NY). The log-rank analysis was used to compare Kaplan-Meier curves for statistical significance between the time required for CT image improvement and the time needed for the resolution of clinical symptoms. Univariable and multivariable binary logistic regression was used to determine the association between age, sex, clinical severity, clinical duration, the time required for CT improvement, CT changes during treatment, CT changes at discharge, and quality discharge. A *P*-value of less than 0.05 was considered statistically significant.

5. Study Design

For treatment evaluation, we answered the study question using two distinctive approaches. The first approach was to determine whether changes in CT during treatment could be utilized sooner by physicians than changes in symptoms during treatment for predicting hospital discharge of all 42 patients. Specifically, the log-rank analysis was used to compare Kaplan-Meier curves to determine whether there were significant differences between the time required for CT image improvement (at least 20%, 40%, 60%, or 80% reduction in CT lesion volume) and the time required for the resolution of clinical symptoms in the 42 patients with at least two chest CT scans.

The second approach was to determine whether CT changes during treatment can predict quality hospital discharge. Specifically, univariable and multivariable binary logistic regression was used to determine whether there was an association between CT change (at least 20% or 40% reduction in CT lesion volume) during the treatment and quality discharge, with and without adjusting for sex, age, and clinical severity.

For hospital discharge decision-making, we answered the question using univariable and multivariable binary logistic regression to determine whether there was an association between the time required for CT improvement (at least 20%, 40%, 60%, or 80% reduction in lesion volume), the time needed for the resolution of clinical symptoms, quality patient discharge, and whether there was an association between CT changes during treatment (at least 20% and 40% reduction in CT lesion volume) and quality discharge, with and without adjusting for sex, age, and clinical severity.

6. Results

6.1. Baseline Characteristics

The clinical and CT characteristics of 42 adult patients with COVID-19 at admission are given in Table 1. The 42 patients' ages ranged from 19-81 years old (median age: 44 years old). The most common symptoms included fever, 35 cases (83.3%), and cough, 32 cases (76.2%). Thirty-eight cases (90.4%) presented with ground-glass opacity (GGO) on chest CT images. Temporal chest CT changes of a typical COVID-19 patient without resolution of CT manifestation at discharge are shown in Figure 1.

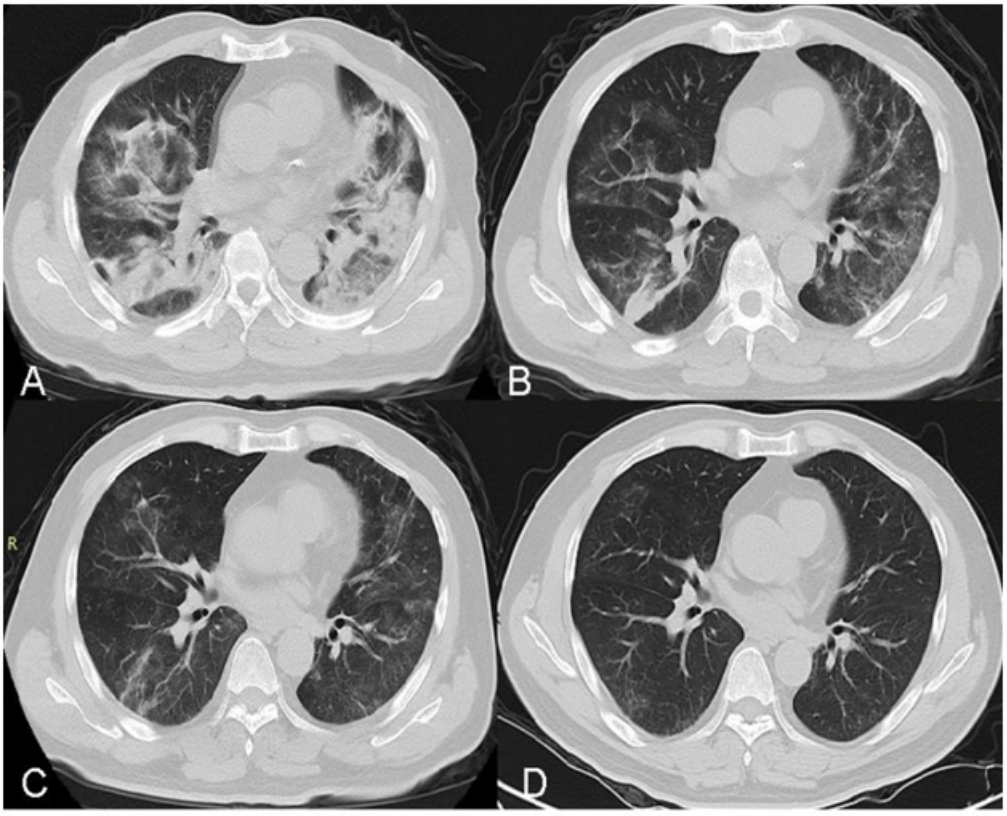

Figure 1: Typical chronological Chest CT changes of a COVID-19 patient without the resolution of CT manifestation at discharge; a 53-year-old patient who had severe COVID-19 infection, fever for five days and diarrhea for one day. (A): at hospital admission, chest CT showed diffuse consolidation and mixed ground-glass opacities (mGGO) in bilateral lung fields. (B): 11 days post-admission, chest CT showed that most of the lesions became smaller, and the density was noticeably decreased, but also contained fibrous streaks. (C): at discharge (18 days post-admission), chest CT showed slight GGO and fibrous stripes. (D): 33 days after discharge, chest CT showed that all lesions were almost completely absorbed.

Table 1: The clinical and CT characteristics of 42 patients at admission

Clinical characteristics	**Median (Range/No.)**
Age	44 years (19-81years)
Sex	Male (23); Female (19)
Duration of hospitalization	16 days (5-41days)
Exposure or contact information	**No. (%)**
From epidemic area	22(52.4)
Contact with locally confirmed cases	20(47.6)
Signs and clinical symptoms	
Fever	35(83.3)
Cough	32(76.2)
Diarrhea	11(26.2)
Chest CT characteristics	
Ground glass opacity (GGO)	38(90.4)
Solid lesions	9(20.9)
Interstitial abnormalities	16(38.1)

6.2. The time required for clinical symptom improvement compared to CT improvement

The results of the Kaplan–Meier method indicate that the time required for the resolution of clinical symptoms was significantly faster than the time required for CT image improvement (20%, 40%, 60%, or 80% or more reduction in CT lesion volume) in the 42 patients (Figure 2). The median (IQR) time required for the resolution of clinical symptoms was 4 (3-17) days. In contrast, the median (IQR) time required for 20%, 40%, 60% or 80% CT improvement was 10 (6-18), 13 (8-20), 14 (9-29) and 16 (9-31) days, respectively (P=0.021, 0.002, <0.001, and <0.001 respectively). All Kaplan-Meier curves had P <0.001 (Figure 2).

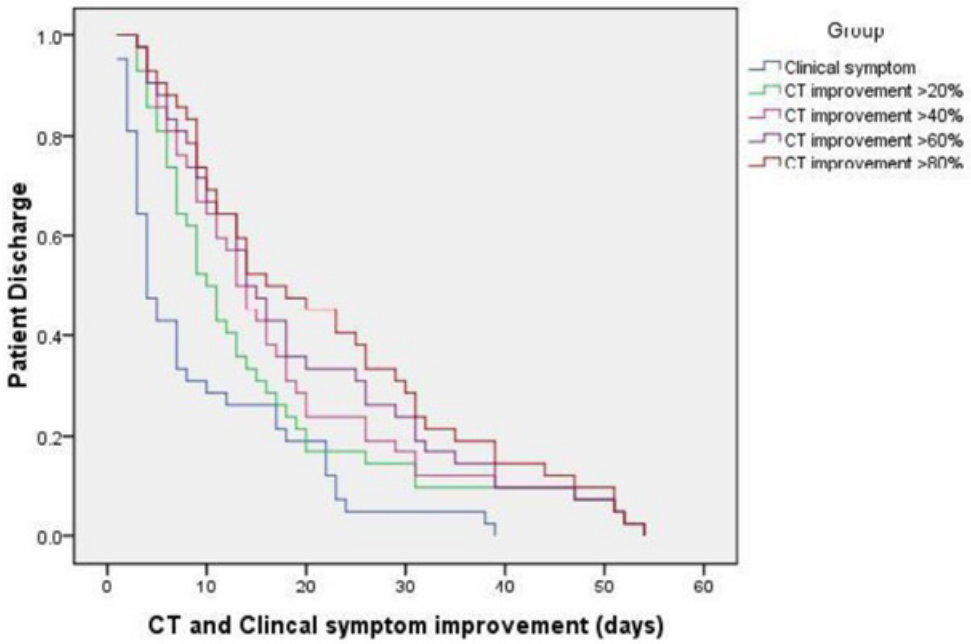

Figure 2: The Kaplan-Meier statistical analysis of the 42 patients showing that CT is slower than symptoms in predicting hospital discharge. The time required for the resolution of clinical symptoms (median: 4 days) was significantly faster than the time required for achieving 20%, 40%, 60%, or 80% reduction in CT lesion volume to predict hospital discharge (median: 10 days, 13 days, 14 days, 16 days; P =0.021, 0.002, <0.001, and <0.001, respectively).

6.3. Chest CT lesions in Recovered COVID-19 Patients

Analysis of progressive CT changes (Table 2) showed that abnormal CT scans remained in 88% and 50% of patients at discharge and at least 14 days post-discharge, respectively. Specifically, seven (28%) of the 25 patients (having at least three CT scans with one CT taken within two days of hospital discharge) did not have substantial (>60%) absorption in their CT lesion volumes at the time of their hospital discharge. Four (25%) of the 16 patients (having four CT scans with their last CT scan at least 14 days after hospital discharge) did not have substantial (>60%) absorption in their CT lesion volumes at least 14 days after hospital discharge. There were no significant changes in CT lesion volume at discharge (P =0.191) compared to images taken during treat-

ment. Still, there were significant differences in CT lesion volume between discharge and post discharge (P =0.006, at least 14 days post discharge), as well as during treatment and post discharge (P =0.038).

6.4. Association between Clinical Outcome and Clinical Symptom or CT Improvement

Binary logistic regression analysis after adjusting for age, sex, and clinical severity further demonstrated that for the 35 patients who had a CT scan at discharge or after hospital discharge, there was no association between quality discharge and CT improvement during treatment (20%: P=0.301; 40%: P =0.450). There is no association between quality discharge and the days needed for CT improvement (20%: P =0.060, 40%: P =0.129, 60%: P =0.152, 80%: P =0.686, respectively); but there was an association between quality discharge and the days required for the resolution of clinical symptoms (P =0.019), see Table 3.

Table 2: Progressive CT changes during treatment, at discharge, and post-discharge

CT changes at	No. of Cases	[1]Completely absorbed	[2]Substantially absorbed	[3]Slightly absorbed N (%)	No changes N (%)	Worse N (%)	[4]Not substantially absorbed
Admission compared to		N (%)	N (%)				N (%)
During treatment	42	3(7.2%)	16(38.1%)	14(33.3%)	5(11.9%)	4(9.5%)	23(54.7%)
[5]At discharge	25	3(12.0%)	15(60.0%)	6(24.0%)	0(0.0%)	1(4.0%)	7(28.0%)
[6]Post-discharge	16	8(50.0%)	4(25.0%)	3(18.8%)	1(6.2%)	0(0.0%)	4(25.0%)

1) Completely absorbed: more than 90% reduction in CT lesion volume; 2) Substantially absorbed: 60%-90% reduction in CT lesion volume; 3) Slightly absorbed: 10%-60% reduction in CT lesion volume; 4) Not substantially absorbed: less than 60% reduction, no change or worse in CT lesion volume; 5) At discharge: CT within two days of hospital discharge; 6) Post-discharge: CT at least 14 days after hospital discharge.

Table 3: Results of Univariable and Multivariable Regression Analysis.

	Univariable Analysis			**Multivariable Analysis**	
	OR (95%CI)	P -value		OR (95%CI)	P -value
Association between clinical outcome and CT improvement (N=35)					
CT changes (>20%) during treatment	3.45(0.58-20.50)	0.173		2.96(0.38-23.13)	0.301
CT changes (>40%) during treatment	4.00 (0.71-22.43)	0.115		2.12(0.30-14.82)	0.45
Association between high-quality discharge and days required (N=35)					
Days for resolution of symptoms	0.89(0.81-0.98)	**0.013**		0.83(0.71-0.97)	**0.019**
Days for CT improvement (>20%)	0.94(0.88-0.99)	**0.022**		0.93(0.86-1.00)	0.06
Days for CT improvement (>40%)	0.94(0.89-0.99)	**0.042**		0.95(0.89-1.02)	0.129
Days for CT improvement (>60%)	0.94(0.89-1.00)	0.053		0.94(0.87-1.02)	0.152
Days for CT improvement (>80%)	0.96(0.91-1.02)	0.169		0.99(0.93-1.05)	0.686

P values<0.05 indicate statistical significance. OR: Odds Ratio; CI: confidence interval; Multivariable Analysis adjusted for age, sex and clinical severity.

7. Discussion

The global pandemic of COVID-19 is not expected to withdraw for many months to come. Some scientists predict that as many as 250 million people worldwide will be infected by June 2021 [25]. Chest CT has been used for the diagnose and screen COVID-19 infection; to diagnose and characterize COVID-19 induced pneumonia; to evaluate disease progression, treatment and patient discharge. The overuse of CT does not benefit patients, medical personnel, or society as a whole. It is critical to promote evidence-based practices for COVID-19 patients, in an environment that makes CT use for COVID-19 patients look rather appealing. For example, many papers present impressive images of COVID-19 induced pneumonia before diagnosis, during treatment and after recovery. Without reliable data, patients or physicians can be swayed to order unnecessary CT scans. The main results of this study are: i) The time required for the resolution of clini-

cal symptoms was significantly faster than the time needed to observe improvements on CT images; ii) There was an association between quality discharge and the days required for the resolution of clinical symptoms, but not between quality discharge and the days needed for CT improvement; iii) There was no association between quality discharge and CT improvement during treatment; iv) Chest CT lesions remained in most recovered COVID-19 patients while all clinical symptoms had been resolved at least three days before discharge.

Our results are consistent with published studies [4,17, 26,27]. Studies have shown that the progression of CT patterns is much slower than clinical symptoms, particularly within the first two weeks of hospitalization [25]. In other words, clinical symptoms and chest CT findings were inconsistent at least in the early stage [28]. After patients became RT-PCR negative with a notable clinical improvement, pneumonia was still persistent [26], and patients who were discharged from the hospital still had residual lung abnormalities on their last CT scans [3-4 ,29]. Moreover, CT lesions were significantly improved after at least 14 days post-discharge compared to that during treatment and discharge [7,29]. The delay in CT change compared to clinical symptoms is believed to be due to the longer time required for any morphological changes of the lungs [18]. Finally, there were no differences in CT characteristics at discharge between patients with positive and negative RT-PCR results, indicating that CT was not better than clinical symptoms in identifying patients with recurrently positive RT-PCR [4]. CT may not be necessary for those retest RT-PCA positive patients, unless the clinical symptoms are worsening [30].

Our results are, in general, consistent with most published guidelines or consensuses [7-8,13]. For example, the latest WHO guideline for hospitalized patients with COVID-19 whose symptoms had resolved, suggests not using chest imaging in addition to clinical or laboratory assessment to inform the decision regarding discharge [8]. This “conditional recommendation, based on expert opinion” is in complete agreement with our results. Moreover, the team identified no study that evaluated any chest imaging modality to support a discharge home [8]. Our results are consistent with the statement from the Fleischner Society that “Imaging is indicated for patients with moderate to severe features of COVID-19 regardless of COVID-19 test results” [7], that, chest CT is the best tool to diagnose and characterize COVID-19-induced pneumonia. However, our study further demonstrates that chest CT is not better than clinical symptoms for predicting treatment outcome and hospital discharge decision-making. The lack of reliable results for whether or not using chest CT to evaluate treatment or hospital discharge has been recognized by virtually all guidelines, can be summarized by one: “the evidence base supporting the use of imaging across the scenarios presented is scant and the advice presented herein may undergo refinement through rigorous scientific investigation, exposing nuances of image interpretation that may lead to prognostic information and guide management decisions” [7]. Combining our results with published results and guidelines with reliable data on the diagnosis and screening of COVID-19 infection, we do not recommend chest CT for the clinical management of adult COVID-19 patients unless information on pneumonia is required. CT should not be used to diagnose or screen COVID-19 infection when standard laboratory tests such as RT-PCR are available and reliable [8]. A normal chest CT cannot rule out an individual with COVID-19 infection as there have been many documented asymptomatic cases. Similarly, an abnormal CT cannot definitively diagnose COVID-19 infection because of the possibility of overlapping CT features from other virus-induced types of pneumonia [31]. Low dose CT is recommended for the diagnosing or characterizing pneumonia whenever this information is required for clinical management [32]. The CT features of COVID-19 pneumonia include patchy local shadowing, lateral and bilateral ground-glass opacities. Most patients have lesions in the subpleural area, especially in the lower lung lobes with the highest percentage in the posterior segment.

Our study has limitations. This study has a small sample size, and the clinical severity is less severe than hospitalized patients in many countries. A long-term follow-up was not done because of the short time for data collection. Chest radiography was not included in this study because of the lack of data. Since radiography is less sensitive than CT, chest radiography is not expected to do better than chest CT for treatment evaluation or hospital discharge decision-making. In other words, the conclusion that chest CT is not better than clinical symptoms should also hold true for chest radiography.

8. Conclusion

Chest CT is a great tool to detect and characterize COVID-19 pneumonia but not to evaluate the resolution of illness for adult COVID-19 patients.

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