A Comprehensive Study on Prediction Reliability of The Severity of Computed Tomography Involvement in Patients with Covid-19

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Abstract

Purpose: Computed tomography (CT) emerges as a high–sensitivity tool in diagnosing SARS-CoV-2 virus on admission, even with the cases of negative reverse transcription polymerase chain reaction (RT-PCR). Moreover, CT plays a significant role in the evaluation of disease severity. In this study, we aimed to identify several parameters that could aid in evaluating the initial chest CT severity score (CT-SS).

Methods: A total of 348 RT-PCR positive patients were divided into three groups by evaluating the chest CT severity score (CT-SS) in detail. These three groups were defined as the CT-SS obtained 0-7, 8-15, 16-40 classified as mild, moderate and severe involvement, respectively. Patients with end-stage malignancy or immunodeficiency were excluded from the study. All CT images were evaluated by two chest radiologists, unaware of the clinical data.

Results: The analysis of categorical variables show that the chest CT-SS tends to increase with higher CHA2DS2VASC risk score (RS) (p= 0.001), M-CHA2DS2VASC RS (p = 0.001), and CHADS2 RS (p = 0.003). Moreover, age, hypertension, cardiothoracic ratio, aortic diameter, white blood cell count, neutrophil counts, neutrophil-lymphocyte ratio, c-reactive protein, D-dimer, ferritin, fibrinogen, blood urea nitrogen, and lactate dehydrogenase were also found to be associated with higher chest CT-SS. A 5-variable multivariable linear regression model, consisting of more frequently used variables, suggests a higher CHA2DS2VASC RS as the only statistically significant variable predicting a higher severity score

Conclusion: The CHA2DS2VASC RS may assist clinicians in predicting the CT-SS in COVID-19 patients, even if they are asymptomatic.

Introduction

The world is struggling with the contagious novel SARS-CoV-2 virus (COVID-19) since the first case was identified in December 2019. With the second wave, the COVID 19 pandemic continues to increase its impact across the world. Chest computed tomography (CT) is a prominent method in the diagnosis COVID-19, including the diagnosis in patients that are confirmed to have SARS-CoV-2 infection but with RT- reverse transcription polymerase chain reaction (RT-PCR) negative findings (1) Besides, the widespread CT involvement is associated with the mortality and hospitalization in intensive care (2). The chest CT severity score (CT-SS) was described by Yang et al. (3), which is a relatively easily applicable, semi-quantitative method for assessing severity.

CHA2DS2VASc RS (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke or transient ischemic attack (TIA), vascular disease, age 65 to 74 years, sex category) was developed to determine the thromboembolic risk in atrial fibrillation(4). Recently, studies have shown that the CHA2DS2VASc RS can also be used as a mortality risk assessment scale in COVID-19 patients (5). Tertiles of CHA2DS2VASc RS, except stroke and female gender, have a mortality association with COVID-19 (6–9). In contrast, male sex is associated with increased mortality (11). Therefore, several researchers have recently developed a modified (M) - CHA2DS2VASc RS that may predict mortality for use in COVID-19 patients (12). Moreover, mortality studies in COVID-19 have been associated with an increased risk of all-cause death during hospitalization of some demographic and laboratory parameters (such as chronic kidney disease, increased neutrophil-lymphocyte ratio, lactate dehydrogenase) (8–15). Ground-glass opacity (GGO) and consolidation are early predictors of clinical deterioration in CT imaging. In asymptomatic cases may have pneumonia, and clinical deterioration may occur rapidly.(16) We think, even if the patient is clinically stable, CT plays a crucial role in decision-making for hospitalization. Thus, with the data detected in this study, we planned to use CT more effectively and accurately.

Materials And Methods

Study population

This retrospective study enrolled a total of 367 COVID-19 patients who admitted to our hospital between October 2020 and November 2020. Following inclusion criteria were used for the study: I) to have a confirmed diagnosis of COVID-19 by RT-PCR using both nasopharyngeal and throat swab samples, II) to be evaluated by CT at admission, III) age ≥ 18 years old. Malignancy, immunodeficiency, pregnancy and absence of all medical records were determined as exclusion criteria for the study. A total 19 patients diagnosed with COVID-19 were excluded from the study for these reasons. All CT images were independently assessed by

two chest radiologists with more than five years of experience, blinded to the clinical data and laboratory indicator, and the demographic data of the patients were obtained from the National Health Database and the hospital database.

The study was conducted in accordance with the principles of the Helsinki Declaration and approved by the local Institutional Review Board.

Clinical and laboratory assessment

Demographics and medical records of the patients were reviewed and noted.
CHADS2 RS, CHA2DS2-VASc RS, and M-CHA2DS2-VASc RS were calculated in accordance with previous publications [17–19]. Also, the parameters that contribute to the scoring systems were analyzed individually. We additionally assessed levels of neutrophil-lymphocyte ratio (NLR), c-reactive protein (CRP), lactate dehydrogenase (LDH), cardiac troponin, and blood urea nitrogen (BUN) from the patients' records. Ischemic stroke was defined as an episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction [20]. These embolic events, the presence of clinical signs was confirmed by imaging modalities (magnetic resonance imaging with or without CT angiography). The clinical diagnosis of the stroke was made by a neurologist. Hypertension (HT) defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg measured in the supine position or use of antihypertensive medications [21], diabetes mellitus (DM) defined as fasting blood glucose level ≥ 126 mg/dl or HbA1c level ≥ 6.5% or use of hypoglycemic medications, congestive heart failure defined as recommended by the working group of the European Society of Cardiology [22].

CT image evaluation

Chest CT imaging was performed using a 64-detector CT scanner (Somatom Sensation 64 Eco; Siemens). All patients were examined in the supine position. CT images were then acquired during inspiratory and expiratory phases with or without contrast using. Our CT implication indications were; RT-PCR testing is not available, delayed RT-PCR testing; RT- PCR test is negative, but the patient with high clinical of suspicion of COVID-19; patients with high comorbidity burden who have a higher risk of disease progression; older age; physical exam with severe symptoms and sings; patients may have presentations that indicate COVID-19 complications such as pulmonary embolism, pulmonary fibrosis; cases are not responding to the treatment; case with acute clinical deterioration and patients have pre-existing chronic lung disease as WHO recommendations (23). We classified the CT data using the previously-mentioned the CT severity score CT-SS (3). The chest CT-SS uses the ground-glass opacity, interstitial opacity, and air trapping criteria. Air trapping was assessed with the inspiratory and expiratory scans. Chest CT-SS determines the 20 regions of the lung separately as point 0-1-2. Zero points describe no involvement; one point describes with less than 50% involvement; two points describe more than 50% involvement. It is worth mentioning that the maximum score for a patient is limited to 40 (3). Following the assignment of CT-SSs, the patients were divided into three CT-SS groups of 0–7, 8–15, and 16–40, classified as mild, moderate, and severe involvement, respectively (Fig. 1).

We also evaluated the patients according to the Radiological Society of North America Expert (RSNA) consensus statement category after CT-SS (24).
In addition to these radiological evaluations, the diameter of the ascending aorta and the cardiothoracic ratio (CR) were determined from CT's in all patients.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp. Armonk, NY, USA). Descriptive statistics were reported as mean ± standard deviation for continuous variables with normal distribution or median (25th-75th percentiles) values for continuous variables without normal distribution and as frequency with percentages for the categorical variables. The Shapiro-Wilk and Kolmogorov-Smirnov tests were used to test the normality of the distribution of continuous variables. Categorical variables were compared with Chi-square or Fisher exact tests as appropriate. Kruskal-Wallis and One-Way-ANOVA tests were used for comparisons of continuous variables as appropriate. When the variances were homogeneous in the post-hoc tests, Tukey test was performed and Tamhane's T2 test was performed in a homogeneous condition. After Kruskal Wallis test, Kruskal Wallis 1-way ANOVA (k samples) test was performed for post-hoc tests. Friedman test was used when Repeated Measures ANOVA test was not provided. In 2x2 comparisons between categorical variables, Pearson's Chi-square test was used if the expected value (> 5), chi-square yates test was used if the expected value was (3–5), and Fisher's Exact test was used if the expected value (< 3). In comparisons greater than 2x2 between categorical variables, the Pearson Chi-square test when the expected value is (> 5), and

the Fisher-Freeman-Halton test when the expected value is (< 5). Post-hoc tests after chi-square were done by the Bonferroni method. The significance level was accepted as $p < 0.05$ in all statistical analyses.

Results

The study cohort consisted of 348 patients (mean age: 66 (22–97) years; male:174) showing intermediate and typical involvement in the RSNA classification resulted in 148 patients (42.6%) with a score of 0–7 (mild), 104 patients (29.8%) with a score of 8–15 (moderate), and 96 patients (27.6%) with a score of 16–40 (severe). Demographic and clinical features as well as the laboratory parameters of the study group according to the CT-SS tertiles are shown in Table 1and 2. In categorical variables, the chest CT-SS tends to increase with higher CHA2DS2VASC RS ($p = 0.001$), M-CHA2DS2VASC RS ($p = 0.001$), and CHADS2 RS ($p = 0.003$). The data-driven tertiles of CHA(2)DS(2)-VASc RS, M-CHA(2)DS(2)-VASc RS, CHADS(2) RS total points were as follows T1: ≤1, T2: 2–3, T3: ≥4. HT and vascular disease, which are tertiles of CHADVASC RS and M-CHA2DS2VASC RS, are associated with higher chest CT-SS ($p < 0.001$, Table 1). Also, old age, CR, aortic diameter, white blood cell (WBC) count, neutrophil count, NLR, CRP, D-dimer, ferritin, fibrinogen, CRP, BUN, LDH ($p < 0.001$, for all), and AST levels ($p = 0.011$) tend to increase progressively from a lower CT-SS to a higher CT-SS score. On the other hand, lymphocyte count tends to decrease from a lower CT-SS to a higher chest CT-SS tertile ($p < 0.001$, Table 2).

The comparison of mild and moderate-severe chest CT-SS patients groups, using the Youden index, reveals that the high sensitivity parameters are neutrophil counts (77.0%), CR, (75.6%), BUN (71.9%), NLR (70.1%,), LDH (70.1%), corresponding to the 95% confidence interval (CI) for each. On the other hand, the results indicate the CHA2DS2VASC RS (73.0%), WBC count (72.0%), M-CHADVASC RS (69.3%), CHADS2 RS (65.7%), older age (65.0%), to be higher specificity parameters (95% CI for each). The areas under the curve (AUC) for CR, LDH, NLR, M-CHA2DS2-Vasc RS, CHA2DS2-Vasc RS, age, and CHADS2 RS were 0.72, 0.68, 0.67, 0.65, 0.648 0.63, and 0.62 respectively ($p < 0.001$, 95% CI for all). The AUC for BUN, CRP, D-dimer, neutrophil count, WBC count, AST, aortic diameter were 0.68, 0.67, 0.66, 0.65, 0.60 0.55, and 0.54 respectively ($p < 0.001$, 95% CI for all, Table 3). Receiver operating curves (ROC) are shown in Fig. 2. In linear regression analysis, we assessed CHA2DS2VASC RS, age, LDH, d-dimer, CRP, NLR, which are widely used in follow-up and at the time of admission in COVID-19 patients. We applied the regression analysis with three steps and excluded the variant with the lowest p-value in each step. In all stages, the CHA2DS2VASC RS was the only significant variable ($p = 0.001$), and its odds ratio was the highest in every stage (Table 4).

Discussion

The major finding of the current study is that the CHA2DS2VASC RS has a distinctive ability to predict chest CT-SS in patients with COVID-19. Previous COVID-19 radiology studies do not provide a thorough investigation of the association between the chest CT severity and patient's comorbidity conditions and laboratory findings. Statistically significant findings in this study can be well used as a guide to screen the patients and effectively identify the ones that may have severe CT involvement on admission in daily practice.

The COVID 19 is a disease that can progress with a severe immune response, as well as have a thrombus burden [25–27]. The mechanism of action of thrombosis has not been fully elucidated. It is thought that the development of coagulopathy adversely affects the prognosis of the patient. D dimer, platelet count, prothrombin time, fibrinogen level should be used to detect the coagulopathy [28]. Increased D-dimer and massive fibrin formation are associated with poor prognosis, prolonged mechanical ventilation, and death [29, 30]. D-dimer levels can also be used to administrate anticoagulants for COVID-19 patients [31]. The CHA2DS2VASC RS predicts the thromboembolic originated ischemic stroke in patients with or without atrial fibrillation (AF) [5]. It also predicts the risk stratification and death in patients with COVID-19 [6]. Recently, Cetinkal et al reported that M-CHA2DS2VASC RS score, derived from CHA2DS2VASC RS, well predicts the in-hospital mortality [12]. Our study indicated that the CT-SS score increases gradually with increasing CHA2DS2VASC RS and M-CHA2DS2VASC RS. Besides, analyses revealed that CHA2DS2VASC RS was more specific than other risk scores.

An irregular immune response is one of the leading causes of death in patients. This immune response progresses with leukocytosis, neutrophilia, monocytosis and lymphopenia. Recently, several investigators reported that NLR can facilitate in categorizing the disease severity and progression in patients, thereby enabling us to make appropriate and informed clinical decisions [32]. Hence, we compared leukocytosis and NLR with the chest CT-SS. Our results suggest that the NLR and leukocytosis correlate with high chest

CT-SS. The dysregulated immune response mentioned above may cause macrophage activation syndrome (MAS) in patients. The pathophysiology of MAS has not been fully identified. However, MAS has many different parameters revealed in various studies [33]; some of which are correlated with the high CT-SS, such as ferritin, LDH, CRP, AST. Therefore, in some studies, these parameters have been identified as a predictor of morbidity and mortality [13, 33].

The relationship between COVID-19 poor outcomes and CR or aortic diameter has not yet been investigated. However, in studies performed with non-covid patients, ascending aorta dilation and increased CR are associated with increased mortality [27, 31]. The current data suggests a statistically significant correlation between high CT-SS and ascending aortic diameter and CR elevation.

If the CT was not applicable, CR was obtained from the posterior-anterior lung film and may provided convenience in clinical practice.

Old age and HT are also associated with increased violence and mortality in COVID-19 patients [6, 10]. Coronary artery disease, one of the vascular diseases, shows that mortality increases in patients with COVID-19 [10]. In our study, patients with vascular diseases, including aortic atheroma plaques, carotid artery stenosis, coronary artery disease, and peripheral artery disease plaques, showed more severe CT involvement. Advanced age, vascular disease, and hypertension, which are elements of both scoring systems, predict an increasing chest CT-SS score. Moreover, CKD was previously reported to be associated with increased mortality in patients with COVID-19 [9]. However, in this study, no statistical relationship was found between CKD and chest CT-SS. Also, recently published studies have shown that a higher initial BUN indicate a higher in-hospital mortality rate. Similarly, in our result demostrated that the chest CT-SS gradually increases as the BUN gets higher, unlike creatinine.

Yang et al. designed the chest CT-SS for rapid and objective assessment in COVID-19 patients [3]. Colombi et al have recently demonstrated that the level of CT involvement shows clinical outcome and mortality [2]. However, there is no study investigating the parameters that predict the degree of involvement in CT using such a large sample and variable size.. In asymptomatic cases may have pneumonia, and clinical deterioration may occur rapidly (16). We think, even if the patient is clinically stable, CT plays a crucial role in decision-making for hospitalization. On the other hand, previous COVID-19 radiology studies do not provide a thorough investigation of the association between the chest CT severity and patient's comorbidity conditions, clinical scoring systems, and laboratory findings. Statistically significant findings in this study can be well used as a guide to screen the patients and effectively and accurately identify the ones that may have severe CT involvement on admission in daily practice. To the best of our knowledge, this is the first comprehensive analysis of comorbidity conditions or scales, radiological and biochemical characteristics that could aid in evaluating the CT involvement severity.

Limitations of the study

The present study has several limitations. First of all, this was a retrospective study and included a relatively small patient population. Second, the uncertainty of the time interval between onset of symptoms and hospitalization. Lastly, this analysis does not contain information about mortality and long-term follow-up of patients.

Conclusion

In conclusion, the CHA2DS2VASC RS can assist clinicians in predicting chest CT-SS in COVID-19 patients, even if they are asymptomatic. However, this finding should be confirmed by larger studies.

References

1. Li Y, Xia L. Coronavirus Disease 2019 (COVID-19): Role of Chest CT in Diagnosis and Management. American Journal of Roentgenology. 2020; 214:1280-1286.10.2214/AJR.20.22954
2. Davide Colombi FC, Bodini M, Petrini G, Maffi N, Morelli G, Milanese M, Silva N, Sverzellati E, Michieletti. Well-aerated Lung on Admitting Chest CT to Predict Adverse Outcome in COVID-19 Pneumonia. Radiology. Apr 17 2020, Vol. 296, No. 2
3. RanYang XiangLi, HuanLiu, YanlingZhen, XianxiangZhang, QiuxiaXiong, YongLuo, Gao C, Zeng W, MS. Chest CT Severity Score: An Imaging Tool for Assessing Severe COVID-19. Radiology: Cardiothoracic Imaging 2020; 2(2): e200047

4. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Carina Blomstro¨ m-Lundqvist, Boriani G, Castella M, Dan G-A, Dilaveris PE, Fauchier L, Filippatos G, Kalman JM, Mark La Meir. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC European Heart Journal. European Heart Journal (2020) 00, 1-126
5. Gaetano Ruocco, Peter A, McCullough, Kristen M, Tecson M, Mancone GMDe, Ferrari, Fabrizio D'Ascenzo, Francesco G, De Rosa A, Paggi G, Forleo GG, Secco, Gianfranco Pistis, Silvia Monticone, Marco Vicenzi, Irene Rota, Blasi F, Pugliese F, Francesco Fedele, and Alberto Palazzuoli. Mortality Risk Assessment Using CHA(2)DS(2)-VASc Scores in Patients Hospitalized With Coronavirus Disease 2019 Infection. The American Journal of Cardiology. Volume 137. 15 December 2020, Pages 111–117
6. Giuseppe Lippi J, Wong BM, Henry. Hypertension and its severity or mortality in Coronavirus Disease 2019 (COVID-19): a pooled analysis. Polish Archives of Internal MedicineVolume 130, Issue 4, 30 April 2020, Pages 304–309
7. Ian Huang MA, Lim, Raymond Pranata. Diabetes mellitus is associated with increased mortality and severity of disease COVID-19 pneumonia. A systematic review, meta-analysis, and meta-regression, Diabetes & Metabolic Syndrome: Clinical Research & Reviews, vol 14, 4, 2020, pp 395–403
8. Ssentongo P, Ssentongo AE, Heilbrunn ES, Ba DM, Chinchilli VM, Association of cardiovascular disease and 10 other pre-existing comorbidities with COVID-19 mortality: A systematic review and meta-analysis. PLoS ONE 15(8): e0238215
9. Mandeep R, Mehra SS, Desai, SreyRam Kuy TD, Henry (2020) and Amit N. Patel. Cardiovascular disease, drug therapy, and mortality in COVID-19. June 18, 2020. N Engl J Med 382:e102
10. Leonidas Palaiodimos DG, Kokkinidis W, Li D, Karamanis J, Ognibene S, Arora WN, Southern CS Mantzoros. Severe obesity, increasing age and male sex are independently associated with worse in-hospital outcomes, and higher in-hospital mortality, in a cohort of patients with COVID-19 in the Bronx, New York. Metabolism. 2020 Jul; 108: 154262
11. Gokhan Cetinkal BB, Kocas OS, Ser H, Kilci K, Keskin SN, Ozcan Y, Verdi, Mustafa Ismet Zeren, Tolga Demir, and Kadriye Kilickesmez. Assessment of the Modified CHA2DS2VASc Risk Score in Predicting Mortality in Patients Hospitalized With COVID-19. The American Journal of Cardiology. 2020 Nov 15;135:143–149
12. Tao Guo Y, Chen FM, Wu X, Zhang L, He T, Wang H, Wan J, Wang X, Lu Z (2020) Cardiovascular Implications of Fatal Outcomes of Patients With Coronavirus Disease 2019 (COVID-19). JAMA Cardiol 5(7):811–818. doi:10.1001/jamacardio.2020.1017
13. Yuwei Liu X, Du J, Chen Y, Jin L, Peng, Harry HX, Wang M, Luo L, Chen Y, Zhao (2020) Neutrophil-to-lymphocyte ratio as an independent risk factor for mortality in hospitalized patients with COVID-19. J Infect 81(1):e6–e12
14. Yuan Y, Sun C, Tang X, Cheng C, Mombaerts L, Wang M, Hu T, Sun C, Guo Y, Li X, Xu H, Ren T, Xiao Y, Xiao Y, Zhu H, Wu H, Li K, Chen C, Liu Y, Liang Z, Cao Z, Zhang HT, Ch Paschaldis I, Liu Q, Goncalves J, Zhong Q, Yan L. Development and Validation of a Prognostic Risk Score System for COVID-19 Inpatients: A Multi-Center Retrospective Study in China. Engineering (Beijing). 2020 Nov 28. doi: 10.1016/j.eng.2020.10.013. Epub ahead of print. PMID: 33282444; PMCID: PMC7695569
15. Anying Cheng, Liu Hu, Wang Y, Huang L et al. Diagnostic performance of initial blood urea nitrogen combined with D-dimer levels for predicting in-hospital mortality in COVID-19 patients. International Journal of Antimicrobial Agents, Volume 56, Issue 3, 2020
16. Cecconi M, Piovani D, Brunetta E et al (2020) Early Predictors of Clinical Deterioration in a Cohort of 239 Patients Hospitalized for Covid-19 Infection in Lombardy, Italy. J Clin Med. May 20;9(5):1548. doi: 10.3390/jcm9051548. PMID: 32443899; PMCID: PMC7290833
17. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ (2001) Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA 285(22):2864–2870
18. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ (2010) Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest 137(2):263–272
19. Nielsen PB, Overvad TF (2020) Female Sex as a Risk Modifier for Stroke Risk in Atrial Fibrillation: Using CHA2DS2-VASc versus CHA2DS2-VA for Stroke Risk Stratification in Atrial Fibrillation: A Note of Caution. Thromb Haemost 120(6):894–898
20. Powers WJ, Rabinstein AA, Ackerson T et al (2018) 2018 Guidelines for the Early Management of Patients with Acute Ischemic Stroke: A Guideline for Healthcare Professionals from the American Heart Association/American Stroke Association. Stroke

49:e46–e110

21. Williams B, Mancia G, Spiering W et al (2018) 2018 ESC/ESH Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension: the Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. J Hypertens 36:1953–2041
22. Ponikowski P, Voors AA, Anker SD et al (2016) 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)developed with the special contribution of the heart failure association (HFA) of the ESC. Eur Heart J 37:2129–2200
23. Chou R, Pappas M, Buckley D et al. Use of chest imaging in COVID-19: a rapid advice guide. WHO/2019-nCoV/Clinical/Radiology_imaging/2020.1
24. Scott Simpson DO, Fernando U. Kay MD, PhD, Suhny Abbara MD, Sanjeev Bhalla MD, Jonathan H. Chung MD, Michael Chung MD, Travis S. Henry MD, Jeffrey P. Kanne MD, Seth Kligerman MD, Jane P. Ko MD, Harold Litt MD PhD.Radiological Society of North America Expert Consensus Statement on Reporting Chest CT Findings Related to COVID-19. Endorsed by the Society of Thoracic.Radiology, the American College of Radiology, and RSNA. Sep 10 2020; Vol. 2, No.5
25. Klok FA, Kruip MJHA, van der Meer NJM et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19, Thrombosis Research, Volume 191, 2020, Pages 145–147
26. Sharon E, Fox A, Akmatbekov JL, Harbert G, Li J, Quincy Brown RS. Vander Heide. Pulmonary and Cardiac Pathology in Covid-19: The First Autopsy Series from New Orleans. medRxiv 2020.04.06.20050575
27. Iba T, Nisio MD, Levy JH, Kitamura N, Thachil J (2017) New criteria for sepsis-induced coagulopathy (SIC) following the revised sepsis definition: a retrospective analysis of a nationwide survey. BMJ Open 7:e017046
28. Makatsariya AD, Grigoreva KN, Mingalimov MA et al (2020) Coronavirus disease (COVID-19) and disseminated intravascular coagulation syndrome. Obstetrics Gynecology Reproduction 14(2):123–131
29. Chen S, Huang B, Luo DJ et al (2020 May) Pregnancy with new coronavirus infection: clinical characteristics and placental pathological analysis of three cases. Zhonghua Bing li xue za zhi = Chinese. J Pathol 49(5):418–423
30. Giuseppe Lippi, Emmanuel J, Favaloro. D-dimer is Associated with Severity of Coronavirus Disease 2019: A Pooled Analysis Thromb Haemost.2020 May; 120(5): 876–878
31. Paranjpe I, Fuster V, Lala A, Russak AJ et al (2020 Jul) Association of Treatment Dose Anticoagulation With In-Hospital Survival Among Hospitalized Patients With COVID-19. J Am Coll Cardiol 7(1):122–124 76(
32. Bg S, Gosavi S, Ananda Rao A et al (2021) Neutrophil-to-Lymphocyte, Lymphocyte-to-Monocyte, and Platelet-to-Lymphocyte Ratios: Prognostic Significance in COVID-19. Cureus 13:e12622
33. McGonagle D, Sharif K, O'Regan A, Bridgewood C. The Role of Cytokines including Interleukin-6 in COVID-19 induced Pneumonia and Macrophage Activation Syndrome-Like Disease. Autoimmun Rev. 2020 Jun;19(6)

Tables

Table 1: Clinical characteristics and demographic features of the patients according to chest CT-SS.

	Chest CT-SS Groups				
Variable	**All Patients (n:348)**	**0-7 (n:148)**	**8-15 (n:103)**	**16-40 (n:97)**	**P value**
Age	66 (22-97)	62 (22-87)	66 (34-97)	71 (22-92)	**<0.001**
Men	174 (50%)	69 (48%)	51 (49%)	54 (55%)	0.38
HTN	251 (72%)	90 (60%)	79 (73%)	82 (84%)	**<0.001**
DM	122 (35%)	44 (30%)	39 (37%)	39 (40%)	0.189
Stroke	30 (8%)	8 (5%)	11 (10%)	11 (11%)	0.182
CHF	25 (7%)	8 (5%)	6 (6%)	11 (11%)	0.174
Vascular Disease	183 (53%)	58 (39%)	64 (62%)	61 (63%)	**<0.001**
COPD	45 (12%)	19 (13%)	13 (13%)	13 (14%)	0.99
CKD	14 (4%)	9 (6%)	3 (2%)	2 (2%)	0.303
Atrial Fibrillation	18 (5%)	3 (2%)	7 (7%)	8 (8%)	0.067
RSNA Typical Category	283 (81%)	94 (64%)	92 (89%)	97 (100%)	**<0.001**
CHA(2)DS(2)-VASc RS					
0-1	58 (17%)	36 (24%)	13(12%)	9 (9%)	**0.001**
2-3	146(42%)	72 (49%)	43 (42%)	31 (32%)	
4<	144(41%)	40 (27%)	47 (46%)	57 (59%)	
M-CHA(2)DS(2)-VASc RS					
0-1	70 (20%)	46 (31%)	15 (14%)	9 (9%)	**0.001**
2-3	125 (36%)	58 (39%)	40 (39%)	27 (28%)	
4<	153 (44%)	44 (30%)	48 (47%)	61 (63%)	
CHADS(2) RS					
0-1	173 (50%)	89 (60%)	50 (48%)	34 (35%)	**0.001**
2-3	156 (45%)	55 (37%)	46 (45%)	55 (57%)	
4	19 (5%)	4 (3%)	7(%7)	8 (8%)	

HTN: Hypertension, DM: Diabetes Mellitus, CHF: Congestive Heart Failure, COPD: Chronic Obstructive Pulmonary Disease,

CKD: Chronic Kidney Disease, RSNA: Radiological Society of North America, CHA(2)DS(2)-VASc RS: CHA(2)DS(2)-VASc Risk Score, M-CHA(2)DS(2)-VASc RS: Modified-CHA(2)DS (2)-VASc Risk Score, CHADS(2)RS: CHADS(2) Risk Score.

Table 2: The biochemical and numeric radiological characteristics of the study population according to Chest CT-SS.

	Chest CT-SS Groups				
Variable	**0-7 (Group 1, n= 148)**	**8-15 (Group 2, n= 103)**	**16-40 (Group 3, n= 97)**	**P value**	**Post-hoc analysis***
Cardiothoracic Ratio	0,48 (0,32-0,66)	0,52 (0,34-0,68)	0,54 (0,43-0,63)	**<0,001**	Groups 1-2, 1-3
Aortic Diameter	34 (22-55)	35 (26-56)	36 (25-45)	0,039	Group 1-3
Hemoglobin (g/dl)	14,2 (5,6-36,80)	13,5 (7,6-18,7)	13,5 (9,2-18,7)	0,073	
White Blood Cell (mm3)	5,82 (2,22-19,80)	6,18 (2.9-20,84)	8,88 (2,6-35,86)	**<0,001**	Groups 1-3, 2-3
Neutrophil (/mm3)	3,5 (1,03-18,6)	4,62 (1,28-17,94)	7,13 (1,4-30,86)	**<0,001**	Groups 1-3, 2-3
Lymphocyte (/mm3)	1,37 (0,21-3,44)	1,12 (0,36-3,43)	0,98 (0,2-3,78)	**<0,001**	Groups 1-2, 1-3
NLR	2,61 (0,02-61)	3,99 (0,06-31,11)	7,19 (1,4-73,71)	**<0,001**	All
Platelet (/mm3)	217 (68-469)	196 (13-945)	207 (23-544)	0,138	
CRP (mg/dL)	17,2 (0,5-337,96)	33,85 (0,5-225)	54 (1,2-372)	**<0,001**	Groups 1-2, 1-3
ESR (mm/h)	20 (2-122)	24 (3-140)	29 (1-105)	0,293	
D-Dimer (ng/mL)	569 (19,25-13283)	733 (104-11049)	882 (190-18906)	**<0,001**	Groups 1-2, 1-3
Fibrinogen (mg/dL)	473,92 (171-797)	515,42 (218-1002)	560,29 (95-1128)	**0,001**	Group 1-3
Ferritin (ng/mL)	222,2 (11,6-1650)	289,6 (4-1650)	514,5 (21-3762)	**<0,001**	Groups 1-3, 2-3
Creatinine (mg/dL)	0,93 (0,3-4,2)	1 (0,5-14)	1 (0,36-4,8)	0,196	
BUN (mg/dL)	17 (6-81)	22 (0,88-131)	28 (12-98)	**<0,001**	All
Sodium (mmol/L)	139,15 (123-149)	138,97 (126-152)	137,84 (126-150)	0,057	
Potassium (mmol/L)	4,16 (3,2-5,49)	4,23 (2,9-5,44)	4,3 (2,99-5,72)	0,092	
ALT (U/L)	28 (9-187)	25,5 (6-140)	30 (9-319)	0,093	
AST (U/L)	33 (10-336)	34 (11-130)	39 (8-377)	**0,011**	Groups 1-3, 2-3
Triglyceride (mg/dL)	104,5 (55-358)	120 (45-529)	132 (65-394)	0,276	
pH	7,41 (7,25-7,52)	7,39 (7,25-7,52)	7,4 (7,16-7,49)	0,291	
LDH (U/L)	243 (108-2558)	295,5 (145-881)	383 (154-1105)	**<0,001**	All

NLR: Neutrophil-Lymphocyte Ratio, CRP: C-reactive Protein, ESR: Erythrocyte Sedimentation Rate, BUN: Blood Urea Nitrogen, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, LDH: Lactate Dehydrogenase.

* Kruskal Wallis test.

Table 3: ROC analysis comparing the mild with the moderate and severe chest CT-SS groups. The predictive accuracies of the significant parameters are shown below.

	Chest CT-SS 0-7		Chest CT-SS 8-40		Area Under the Curve (ROC)					
Variable	Mean ±std	Median (min-max)	Mean ±std	Median (min-max)	Cut-Off	Sensitivity	Specificity	AUC± Std. Error	CI 95% (Upper-Lower Bound)	P value
CHA(2)DS(2)-VASc RS	2,64± 1,59	3,00 (0-5)	3,55± 1,59	4 (0-8)	3,5	0,518	0,73	0,648± 0,03	0,588-0,707	**<0,001**
M-CHA(2)DS(2)-VASc RS	2,57± 1,65	3,00 (0-7)	3,61± 1,74	4 (0-8)	3,5	0,543	0,693	0,655± 0,03	0,596-0,714	**<0,001**
CHADS(2) RS	1,23± 1,06	1,00 (0-5)	1,79± 1,17	2 (0-5)	1,5	0,579	0,586	0,621± 0,03	0,561-0,681	**<0,001**
Age	62,43± 12,7	64 (22-92)	68,76± 10,6	70 (39-97)	68,5	0,563	0,657	0,633± 0,03	0,573-0,693	**<0,001**
Cardiothoracic Ratio	0,48± 0,07	0,48 (0,32-0,66)	0,53± 00,6	0,53 (0,34-0,68)	0,499	0,756	0,65	0,721± 0,02	0,665-0,778	**<0,001**
Aortic Diameter	34,44± 5,14	34 (22-55)	35,21± 4,66	35 (25-56)	34,75	0,583	0,533	0,535± 0,03	0,471-0,599	**<0,001**
White Blood Cell (mm3)	6,81± 3,20	5,82 (2,22-19,8)	8,72± 5,27	7,04 (2,6-35,86)	7,49	0,453	0,726	0,601± 0,03	0,539-0,662	**<0,001**
Neutrophil (/mm3)	4,67± 3,23	3,5 (1,03-18,6)	6,99± 5,17	5,08 (1,2-30,86)	3,42	0,771	0,489	0,647± 0,03	0,586-0,707	**<0,001**
NLR	5,02± 7,41	2,61 (0,02-61)	9,41± 11,71	4,81 (0,06-73,7)	3.03	0,701	0,579	0,674± 0,03	0,616-0,732	**<0,001**
CRP (mg/dL)	36,01± 52,2	17,20 (0,5-337,9)	61,14± 65,1	40,3 (0,5-372)	22,2	0,682	0,607	0,674± 0,03	0,615-0,734	**<0,001**
D-Dimer (ng/mL)	876± 1437	569 (19-13283)	1507± 2382	797,5 (99-18906)	600,5	0,698	0,57	0,659± 0,03	0,599-0,720	**<0,001**
BUN (mg/dL)	21,41±13,2	17 (6-81)	29,33± 17,9	25,22 (0,88-131)	19,5	0,719	0,607	0,681± 0,03	0,621-0,740	**<0,001**
AST (U/L)	41,04± 33,	33 (10-336)	44,54± 35,4	35 (8-377)	33,5	0,578	0,541	0,55± 0,032	0,487-0,614	**<0,001**
LDH (U/L)	292,7± 221	243	366,4± 161	324	308,5	0,569	0,721	0,684± 0,02	0,627-0,741	**<0,001**

	(108-2558)	(145-1105)		

AUC: Area Under the Curve, ROC:Receiver Operating Characteristic, CI: Confidence Interval.

Table 4

	Standart Error	Odds Ratio	CI 95% (Upper-Lower Bound)	P value
Model 1				
Age	0,014	1,008	0,98-1,037	0,570
NLR	0,017	1,028	0,995-1,063	0,099
D-dimer	-	1	1,000-1,000	0,256
LDH	0,001	1,002	1,000-1,004	0,087
CRP	0,003	1,005	1,000-1,010	0,064
CHA(2)DS(2)-VASc RS	0,100	1,244	1,022-1,514	**0,03**
Constant	0,819	0,144	-	0,018
Model 2				
NLR	0,017	1,03	0,996-1,064	0,082
D-dimer	-	1	1,000-1,000	0,217
LDH	0,001	1,002	1,000-1,004	0,087
CRP	0,003	1,005	1,000-1,010	0,064
CHA(2)DS(2)-VASc RS	0,081	1,287	1,099-1,507	**0,002**
Constant	0,387	0,217	-	-
Model 3				
NLR	0,017	1,029	0,995-1,063	0,092
LDH	0,001	1,002	1,000-1,004	0,054
CRP	0,003	1,005	1,000-1,010	0,053
CHA(2)DS(2)-VASc RS	0,079	1,315	1,126-1,536	**0,001**
Constant	0,389	0,213	-	-

CHA(2)DS(2)-VASc RS: CHA(2)DS(2)-VASc Risk Score; CRP: C-reactive Protein; LDH: Lactate Dehydrogenase; NLR: Neutrophil-Lymphocyte Ratio