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The Crazy-paving Pattern in Chest CT of Coronavirus Disease 2019 Patients; an Alarming Sign for Hospitalization

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Abstract

Background: The outbreak of coronavirus disease 2019 (COVID-19) becomes an enormous threat to all human beings. Via this retrospective study conducted on medical records of confirmed COVID-19 pneumonia patients on admission, we investigate the CT manifestation and clinical and laboratory risk factors associated with progression to severe COVID-19 pneumonia and assessed the association among clinical and laboratory records, CT findings, and epidemiological features. The medical records and radiological CT Features of 236 confirmed COVID-19 patients were reviewed at one public hospital and one respiratory clinic in Quom, from 1 August to 30 September 2020.

Results: Among a total of 236 confirmed Covid-19 cases, 62 were infected with moderate to severe COVID-19 disease and required hospital admission, and 174 were followed up on outpatient bases. A significant difference was verified in the mean age between outpatients and hospitalized groups. The incidences of bilateral lung involvement, consolidation, linear opacities, crazy-paving pattern, air bronchogram sign, and the number of lobe involvement were significantly higher in hospitalized groups. However, only the crazy-paving pattern was significantly associated with an SpO2 level lower than 90%, with clinical sign of cough severity. Our data indicate that this pattern is also significantly associated with inflammatory levels and the presence of this pattern along with SpO2 level lower than 90%, older age, diabetes, on admission are independent risk factors for COVID-19 progression to severe level.

Conclusions: The crazy-paving pattern can predict the severity of COVID-19, which is of great significance for the management and follow-up of COVID-19 pneumonia patients. The clinical factors of aging, male gender, and diabetes, may be risk factors for the crazy-paving pattern, whereas severe coughing is considered to be the most important clinical symptom related to this pattern, and SpO2 level lower than 90%, which is a matter of more severity.

Background

Since December 2019 that the first official human cases of coronavirus disease 2019 (COVID-19), was reported in Wuhan City, China, its global spread has become an enormous threat to all human beings and the lives of millions of people around the world are still in danger(1). Iran has been dealing with theCOVID-19 crisis since 19th February 2020, and Quom was among one of the first metropolitan areas that reported the disease. Interestingly respiratory tract infections caused by novel coronavirus SARS-CoV-2 (2019-nCoV) can range from mild infection with good prognosis to severe form that progress to acute respiratory distress syndrome (ARDS) in the early stages, and consequently requiring hospitalization. The probability of progression to severe cases was estimated at around 15.7 to 26.1% all COVID-19 patients (2–4). Primary management of patients at risk of progression may facilitate treatment strategies and optimized utilization of the medical resource, especially now that clinicians are facing a serious shortage of beds and hospital facilities.

Computed tomography (CT) examination plays an important role in both the initial screening and the auxiliary diagnosis of COVID-19 (5). Although nucleic acid amplification test (NAAT) of the respiratory tract or sometimes blood specimens is still the gold standard method to confirm the disease (6), both American and Chinese researchers strongly recommend CT imaging as the main basis for the diagnosis of COVID-19 in the current situation (7–10). A previous study conducted on a series of 51 patients with chest CT and RT-PCR assay performed within 3 days showed that the sensitivity of CT for COVID-19 infection was 98% compared to RT-PCR sensitivity of 71% ($p < .001$)(11). Meanwhile, the close relationship between the extents of lung lesions and the clinical symptoms makes it an irreplaceable method for the preliminary screening of COVID-19(7). Some clinicians also believe that the severity of COVID-19 and its progression can be judged best by CT imaging as well (7, 12, 13).

Via this retrospective study conducted on medical records of confirmed COVID-19 pneumonia patients on admission, we investigate the CT manifestation and clinical and laboratory risk factors associated with progression to severe COVID-19 pneumonia and assessed the association among clinical and laboratory records, CT findings, epidemiological features, and inflammation.

Results

Among a total of 236 confirmed Covid-19 cases (mean age (SD), 51.08 (13.80); range, 18–84 years; 53.3% male), 62 (mean age (SD), 54.86 (14.88); range, 29–83 years; 57.1% male) were infected with moderate to severe COVID-19 disease and required hospital admission and 174 mild cases with a mean age of 49.8 years (SD,13.24; range, 18–84 years; 52.1% male) were followed up on outpatient bases. The ground-glass opacity (GGO) was the common chest CT features in both outpatients and hospitalized groups with no significant differences (96.0% of outpatients and 100% hospitalized groups) (Table 1). Bilateral Lung Involvement which was present in 80.5% of patients, was significantly higher among the hospitalized group than outpatients (93.5% vs. 75.9%) (Table 1). The incidences of consolidation, linear opacities, crazy-paving pattern, air bronchogram sign, and the number of lobe involvement were also significantly higher among hospitalized groups (Table 1). However, only the crazy-paving pattern was significantly associated with inflammatory levels and hypoxemia ($SpO2 < 90\%$ in room air at rest; OR 4.506; 95% CI, 1.530–13.270).

Table 1
Radiological computed tomography (CT) features of the COVID-19 patients, based on the disease severity.

Characteristics		All Patients (N = 236)	Disease Severity		P-value
			Outpatients (N = 174)	Hospitalized patients (N = 62)	
Side of involved lung	Unilateral	19.5	24.1	6.5	0.003*
	Bilateral	80.5	75.9	93.5	
Number of Lobe	1	13.1	16.1	4.8	0.000*
	2	14.8	19.5	1.6	
	3	17.8	19.5	12.9	
	4	20.3	21.8	16.1	
	5	33.9	23.0	64.5	
Lung Involvement	Peripheral	98.3	98.3	98.4	1.000
	Both Peripheral and Central	51.3	40.8	80.6	0.000*
	Central	53.8	43.9	82.0	0.000*
Prominent	Peripheral	94.0	93.6	95.1	1.000
	Central	6.0	6.4	4.9	
Pulmonary lesion type	The ground glass opacity (GGO)	97.0	96.0	100	0.195
	Crazy-paving	23.6	16.3	44.3	0.000*
	Consolidation	32.5	26.0	50.8	0.000*
	Nodule	0.4	0.6	-	1.000
	Air Broncho Gram	42.3	36.4	59.0	0.002*
	Linear Morphology	40.6	31.8	65.6	0.000*
	Round Morphology	93.1	95.3	86.9	0.037*
	Pleural Effusion (P.E)	1.7	1.2	3.3	0.281
	Lymphadenopathy (LAP)	0.4	0.6	-	1.000

Each categorical variables data are reported as percentage and significant level of a two-sided α (p Value) less than 0.05 is marked by “*”.

Cavitation	0.9	1.2	-	1.000
Fibrosis	0.9	1.2	-	1.000
Emphysema	0.4	0.6	-	1.000

Each categorical variables data are reported as percentage and significant level of a two-sided α (p Value) less than 0.05 is marked by “*”.

Although no difference was observed in the ratio of men and women between outpatients and hospitalized groups, the crazy-paving pattern was higher among men with a significant difference by the chi-square test ($P < 0.05$; OR 0.408; 95% CI, 0.211–0.788) (Table 2). Interestingly, we also found that this pattern is significantly higher among older (OR for age above 50 years old = 2.684; 95% CI, 1.408–5.117) and patients with underlying diabetes (OR 2.102; 95% CI, 1.015–4.352) (Table 2). Most clinical symptoms were similar between COVID-19 patients with a crazy-paving pattern and those without the mentioned pattern, except for severe cough (OR 2.529; 95% CI, 1.008–6.344) and palpitation (Table 3). Regarding the laboratory findings, the increased values of C-reactive protein (CRP), neutrophil ratio, and erythrocyte sedimentation rate (ESR) were significantly higher among patients who indicated the crazy-paving pattern in their chest CT-imaging (Table 4). Lymphocytes decreased was present among 41.7% of patients indicating the crazy-paving pattern in chest CT.

Table 2
Demographic data, and comorbidities along with related medications of the COVID-19 patients, based on the presence of the crazy-paving pattern in patients CT scan.

Characteristics		All Patients (N = 236)	Patients		P-value
			with Crazy-paving (N = 55)	without Crazy-paving (N = 181)	
Age Mean (SD)		51.08 (13.805)	56.79 (13.759)	49.17 (13.396)	0.000*
Age Range		18–90	31–84	18–83	
Gender	Male	53.3	69.8	48.5	0.007*
	Female	46.7	30.2	51.5	
Hospitalized		26.3	49.1	19.1	0.000*
BMI Group	Normal	26.3	33.3	24.8	0.514
	Overweight	47.4	42.2	49.1	
	Obese	26.3	24.4	26.1	
Contact with Infected Person		31.4	22.6	34.7	0.100
Comorbidities	Hypertension	25.2	25.0	24.6	0.948
	Diabetes	18.9	28.8	16.2	0.043*
	Hypothyroidism	7.2	3.8	8.4	0.370
	Rheumatoid arthritis	5.9	1.9	7.2	0.310
	Asthma	6.3	3.8	7.2	0.527
	COPD	4.5	2	5.4	0.459
	Kidney disease	5.0	3.8	5.4	1.0000
	Open heart surgery	3.2	-	4.2	0.202
	Cancer	1.8	-	1.8	1.0000
Smoking		16.4	9.1	18.2	0.143
Chemotherapy		1.8	-	1.8	1.0000

Each categorical variables data are reported as percentage and significant level of a two-sided α (p Value) less than 0.05 is marked by “*”. 1: Angiotensin-converting enzyme (ACE)-inhibitors such as Captopril (Capoten), Enalapril (Epaned or Vasotec) and Lisinopril (Zestril or Prinivil). 2: Recalls of Angiotensin II Receptor Blockers (ARBs) including Valsartan, Losartan and Irbesartan

Characteristics	All Patients (N = 236)	Patients		P-value
		with Crazy-paving (N = 55)	without Crazy-paving (N = 181)	
Corticosteroid Oral Spray	17.0	21.6	15.2	0.291
Corticosteroid Nasal Spray	2.3	2.0	1.8	1.0000
Systematic Corticosteroid	10.1	11.8	9.1	0.789
Total Corticosteroid Consumption History	21.7	27.5	19.6	0.235
Chloroquine Consumption History	10.6	19.6	7.4	0.012*
ACEI[1] Consumption History	2.8	4.0	2.5	0.628
ARB[2] Consumption History	21.8	24.0	20.2	0.569
Metformin Consumption History	13.8	21.6	11.7	0.075
Influenza Vaccination in Recent Year	7.7	10.9	6.3	0.335
Pneumococcal Vaccination in Recent Year	1.4	2.2	1.3	0.533

Each categorical variables data are reported as percentage and significant level of a two-sided α (p Value) less than 0.05 is marked by “*”. 1: Angiotensin-converting enzyme (ACE)-inhibitors such as Captopril (Capoten), Enalapril (Epaned or Vasotec) and Lisinopril (Zestril or Prinivil). 2: Recalls of Angiotensin II Receptor Blockers (ARBs) including Valsartan, Losartan and Irbesartan

Table 3
Clinical signs and symptoms of COVID-19 based on presence of the crazy-paving pattern in patients CT scan.

Clinical signs and symptoms	All Patients (N = 236	Patients		P-value
		with Crazy-paving (N = 55)	without Crazy-paving (N = 181)	
Weakness	82.1	79.2	82.7	0.565
Cough	79.0	88.7	75.6	0.042*
Breath shortness	72.6	78.8	70.2	0.226
Anorexia	74.1	83.0	70.8	0.079
Fatigue	76.4	73.3	76.8	0.634
Body pain	71.0	79.2	32.1	0.113
Fever	63.8	70.0	62.5	0.641
Headache	63.1	54.9	64.9	0.197
Sweating	69.1	63.5	70.2	0.357
Shiver	58.9	60.4	56.5	0.637
Nausea	44.2	37.7	45.2	0.337
Palpitations	40.7	28.8	47.0	0.021*
Loss of taste	37.3	27.5	39.2	0.129
Loss of smell	35.3	26.9	36.7	0.193
Stomach problem	35.7	30.8	36.1	0.478
Sputum	30.3	34.6	28.9	0.435
Diarrhea	28.6	25.5	29.5	0.578
Sore throat	29.4	25.0	31.3	0.384
Bruises	23.8	26.7	22.8	0.589
Vomiting	19.5	19.2	18.8	0.943
Blurred vision	19.5	23.1	17.5	0.416
Coughing up blood	2.1	1.9	2.4	1.0000

Each categorical variables data are reported as percentage and significant level of a two-sided α (p Value) less than 0.05 is marked by "*".

Table 4
Clinical and laboratory findings of the COVID-19 patients, based on the presence of the crazy-paving pattern in patients CT scan.

Characteristics			All Patients (N = 236)	Patients		P-value
				with Crazy-paving (N = 55)	without Crazy-paving (N = 181)	
Clinical findings	Pulse Rate Range	60–100 signals per minute	68.1	68.9	68.5	1.000
		> 100	31.4	31.1	30.8	
		< 60	0.5	-	0.7	
	Spo2	≥ 90	92.1	81.4	95.2	0.007*
		< 90	7.9	18.6	4.8	
	Respiratory Rate	12–30	100	100	100	0.200
		> 30	-	-	-	
	Blood Pressure	Normal	90.3	92.9	88.2	1.000
		> 14	9.7	7.1	11.8	
Laboratory findings	WBC	4000–11000	76.0	79.3	74.2	0.280
		< 4000	14.6	6.9	18.2	
		> 11000	9.4	13.8	7.6	
	LYMPH	1000–4800	68.4	58.3	72.5	0.218
		< 1000	31.6	41.7	27.5	
	NEUT	1500–8000	83.3	73.3	90.5	0.210
		> 8000	16.7	26.7	9.5	
	RBC	4.7–6.1 in Male 4.2–5.4 in female	46.7	28.6	62.5	0.063
		Low	53.3	71.4	37.5	

Each categorical variables data are reported as percentage and significant level of a two-sided α (p Value) less than 0.05 is marked by "*".

	HGB	13.5–17.5 in Male 12-15.5 in female	75.8	75.9	75.4	1.000
		Low	22.1	24.1	21.5	
		High	2.1	-	3.1	
	PLT	150.000-450.000	78.1	79.3	77.3	1.000
		< 150.000	19.8	20.7	19.7	
		> 450.000	2.1	-	3.0	
	CRP	-	31.3	13.6	40.0	0.017*
		+	20.9	13.6	24.4	
		++	17.9	18.2	17.8	
		+++	28.4	50.0	17.8	
		++++	1.5	4.5	-	
	ESR	Normal	10.2	11.1	53.7	0.002*
		High	15.3	88.9	46.3	
	LDH	140–280	10.5	-	18.2	0.485
		> 280	89.5	100	81.8	
	BUN	7–20	16.1	14.3	17.6	1.000
		> 20	83.9	85.7	82.4	
	CR	0.7–1.2 in Male 0.5-1 in female	56.7	61.5	52.9	0.638
		High	43.3	38.5	47.1	
	MCV	80–96	88.2	85.7	90.0	1.000
		> 96	11.8	14.3	10.0	
	MCH	27–33	93.8	100	90.0	1.000
		< 27	6.3	-	10.0	

Each categorical variables data are reported as percentage and significant level of a two-sided α (p Value) less than 0.05 is marked by "*".

Discussion

Our data indicated that the crazy-paving pattern in a radiological Chest CT can predict the severity of COVID-19. The crazy-paving pattern is a radiological sign which is characterized by the presence of scattered or diffuse ground-glass attenuation with a linear pattern superimposed on chest CT imaging, resembling irregularly shaped paving stones (Fig. 1) (14). The linear pattern is associated with interlobular septal thickening and intralobular lines and can also be caused by the presence of intralobular fibrosis, or a linear deposition of material within the airspaces (14). Although the crazy-paving pattern was initially described as a pathognomonic sign of alveolar proteinosis, nowadays it counts as a non-specific pattern that reported later in a variety of diffuse acute and chronic lung diseases including bacterial or viral pulmonary infection and adult (acute) respiratory distress syndrome (ARDS) (14, 15). The overall distribution of COVID-19 patients with the crazy-paving pattern in different studies is around 5–36% (12). In this study we noticed a significantly higher incidence of the crazy-paving pattern among hospitalized patients (OR 4.084; 95% CI, 2.138–7.803), suggesting that this manifestation could serve as an alert in the management of patients. This is in concordance with a recently published study from china (13). Based on the pathological knowledge of SARS, the crazy-paving pattern in COVID-19 may be also caused by the alveolar edema and interstitial inflammatory of acute lung injury (16, 17). Therefore, as previously mentioned, it can be the signal of COVID-19 entering progressive or peak stage (18). 18.6% of patients with the crazy-paving pattern presented with hypoxemia ($SpO2 < 90\%$ in room air at rest), while hypoxemia occurred in only 4.8% of patients with no sign of this pattern. It is well known that hypoxemia is an alarming symptom and matter of concern for both the patients and the physicians, especially in the decision-making strategies for managing patients on a hospitalization basis.

The clinical factors of aging, male gender, and diabetes, may be risk factors for the crazy-paving pattern, which may be the result of their weakened immune function and comorbid with other kinds of infections, especially among diabetes patients. Sever cough seems to be the most important clinical symptom related to the crazy-paving pattern that may cause by the inflammatory affection of the pleura. Based on the previous hypothesis the sever dry cough in COVID-19 patients with the crazy-paving pattern may be explained by the high viscosity of mucus and the damage of dilated bronchioles that causes insufficient sputum motility (12).

41.7% of patients indicating the crazy-paving pattern in chest CT were also suffered from the lymphocytes decrease, indicating immune function inhabitation due to consuming a large number of immune cells. Damage to lymphocytes have been associated with disease exacerbations in subjects with COVID-19 and introduced as an important index in the evaluation of disease severity (19, 20). The increased values of the neutrophil ratio and CRP in patients with the crazy-paving pattern may be also related to cytokine storm induced by virus invasion, which was mentioned by the various studies (19, 21).

GGO was the most common CT finding among COVID-19 pneumonia patients with no significant difference between hospitalized and outpatients groups. Bilateral distribution of GGO with or without consolidation in posterior and peripheral lungs was initially described as the cardinal hallmark of COVID-19 (3, 22). Consolidation on the other hand was significantly more frequent in severe cases, probably due

to the inflammatory exudation in the alveoli. In a review study on the chest CT manifestations of COVID-19, the consolidation has been introduced as an indication of disease progression (12).

Conclusions

In conclusion, our data indicate that the crazy-paving pattern is significantly associated with inflammatory levels and the presence of this pattern along with SpO2 level lower than 90%, older age, diabetes, on admission are independent risk factors for severity and progression of COVID-19. Therefore we believe this pattern has the potential to predict the risk of progression, therefore can be used as a guide for designing a model for decision-making of hospital admission.

Methods

A retrospective review of the medical and radiological computed tomography records of confirmed COVID-19 patients was performed at one public hospital and one respiratory clinic in Quom, from 1 August to 30 September 2020. The exclusion criteria were negative CT findings or chest CT image quality insufficient for image analysis and history of other lung infectious diseases. The clinical symptoms, recent exposure history, patient demographic information, comorbidities along with related medications, CT examinations on admission were recorded from the clinical history. The laboratory results including complete blood count, blood chemical analysis, coagulation testing, C-reactive protein, lactate dehydrogenase, and creatine kinase were also obtained from the clinical history. CT scans have been uniformly obtained by one operator in one radiological center and interpreted once more by an independent expert chest radiologist blinded to the clinical history and primary interpretation of the original radiological center, based on the Fleischner Society Nomenclature recommendations and similar studies 14. In the case of any inconsistency, a third radiologist (25 years of experience in pulmonary imaging diagnosis) reviewed the case for confirmation.

Statistical analyses were performed using SPSS statistical software (version 22.0, IBM, Armonk, NY, USA). Categorical variables were described as frequency rates and percentages, and compared by Pearson’s chi-square test or Fisher’s exact test, as appropriate, with the statistically significant level of a two-sided α (p-Value) less than 0.05. Quantitative variables were described as mean (SD) since they were normally distributed (Kolmogorov–Smirnov D test, $P \geq 0.05$), and compared by parametric t-test. P values less than 0.05 were considered statistically significant.

List Of Abbreviations

COVID-19: Coronavirus disease 2019; ARDS: Acute respiratory distress syndrome; CT: Computed tomography; NAAT: Nucleic acid amplification test; SD: Standard deviation; ACE: Angiotensin-converting enzyme; ARBs: Angiotensin II Receptor Blockers

Declarations

Ethics approval and consent to participate

This study was approved by the ethics committee of the Digestive Diseases Research Institute, Tehran University of Medical Sciences, Iran, and all ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been totally considered by all authors.

Consent for publication

All authors concur with the submission and have seen a draft copy of the manuscript and agree with its publication.

Availability of data and material

The full SPSS datasets can be uploaded if it is desired.

Competing interests

All authors had access to study data and none has any conflict of interest to declare.

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Authors'contributions

MRM was the key contributor in conceptualization, methodology, investigation, data curation, writing, and project administration.

MGB was a major contributor in imaging methodology and interpretation.

AM was a major contributor in resources, conceptualization, methodology, review, and supervision.

FM was a major contributor in resources, methodology, review, editing, and supervision.

MY was a major contributor in conceptualization, methodology, validation, review, and editing.

AS, was a major contributor in formal analysis, data curation, analysis, and interpretation.

MA was a major contributor in project administration, data curation, analysis, and interpretation writing, original draft preparation.

The final version of the manuscript was reviewed by all authors for accuracy and completeness.

All authors concur with the submission and have seen a draft copy of the manuscript and agree with its publication.

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Figures

Figure 1

The crazy-paving pattern. The crazy-paving pattern can be observed in left upper lobe.

Figure 1

The crazy-paving pattern. The crazy-paving pattern can be observed in left upper lobe.