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RESEARCH ARTICLE

Classification Of Post COVID-19 Pulmonary Findings Evaluated By Computed Tomography

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Abstract

Introduction: The COVID-19 pandemic has affected millions of people worldwide. Some patients with COVID-19 pneumonia have residual Computed Tomography (CT) findings in the lungs due to lingering symptoms for weeks after infection. Given the widespread impact of the COVID-19 pandemic, it is crucial to recognize and classify these findings. The aims of study is to identify and classify patients post COVID-19 chest CT findings according to a pattern.
Methods: : We examined 74 patients over the age of 18 who tested positive for COVID-19 using Polymerase Chain Reaction (PCR) and underwent multiple chest CT scans at intervals after their first diagnosis. Patients were classified as having non-specific interstitial pneumonia (NSIP), possible usual interstitial pneumonia (UIP), organizing pneumonia (OP), or no distinctive pattern. We also evaluated demographic data of the patients.
Results: A total of 74 patients were included in the study, with 57 (77%) males and 17 (23%) females. The median age of the participants was 64 years. Of these, 47 (63.5%) had NSIP, 6 (8.1%) had possible UIP, 3 (4.1%) had OP pattern, and 18 (24.3%) patients had no distinctive pattern.
Conclusion: Studies using control chest CT examinations 3-12 months after COVID-19 infection have shown residual lung findings at varying rates. In our study, most patients exhibited NSIP pattern, with fewer OP and possible UIP pattern findings. One fourth of the patients had no distinctive pattern.

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Introduction

The COVID-19 (Coronavirus Disease 2019) pandemic began in China in 2019 and swiftly became a part of our lives in 2020, infecting millions of people and resulting in numerous deaths.[1] Although the infection rate has significantly decreased in recent times due to vaccinations and natural immunity, the disease has not been entirely eradicated. Furthermore, there is a possibility of a resurgence with new variants. Recent studies indicate that approximately 20% of cases have a severe profile requiring hospitalization, with acute viral pneumonia and associated acute respiratory distress syndrome (ARDS) being the most common causes of morbidity and mortality.[2] Some patients with COVID-19 pneumonia experience weakness, fatigue, shortness of breath, exertional dyspnea, and a persistent cough that lasts for weeks, prompting them to seek care at COVID follow-up outpatient clinics.[3] The estimated rate of these complaints during a one-year follow-up is approximately 40%.[4] According to some studies, post-infectious complications are observed in about 70% of cases, especially following severe COVID-19 infection, with pulmonary fibrosis being one of the most significant complications.[5] The British Medical Journal guideline defines prolonged COVID if an infection lasts longer than 4 weeks and post-COVID syndrome if it lasts longer than 12 weeks.[6-7]

It is known that SARS-CoV-2 causes pulmonary damage through multiple mechanisms, and lung CT findings during the acute phase of the disease have been clearly defined.[8] The pulmonary pathology in the acute phase of the disease is diffuse alveolar damage, which is considered to be a factor in the development of post-COVID-19 fibrosis, as the final stage of diffuse alveolar damage leads to fibrosis.[9-10] Organized pneumonia may emerge as a long-term sequelae of acute COVID-19 infection.[11] In some severe cases, histopathologic alterations associated with fibrosis have been reported,[12] and other studies have shown the occurrence of usual interstitial pneumonia, desquamative interstitial pneumonia, and acute organized pneumonia patterns in the patient group with residual findings after COVID-19 pneumonia.[13-14] According to another study, there is a stronger association between Post-COVID-19 pulmonary fibrosis and the progression of the disease, particularly involving factors like the presence of pneumonia and the persistence of positive PCR tests for more than four weeks.[15]

The issue to be addressed pertains to the timing and extent of regression in pulmonary findings, if any, within the context of post-COVID-19 recovery. Questions arise regarding the persistence of residual lung alterations upon completion of the recovery process. Should such alterations endure, what specific manifestations can we anticipate? Furthermore, we must investigate the clinical relevance of these pulmonary changes as opposed to their status as purely radiological observations. Additionally, when conducting long-term follow-up chest CT examinations in these patients, there is a legitimate concern that these residual findings may introduce diagnostic challenges, particularly in cases where comprehensive patient medical histories are unavailable. Despite the existence of numerous publications on this subject, a definitive consensus remains elusive.

Previous experiences with the SARS-CoV-1 and MERS outbreaks indicated that very few patients with these diseases developed chronic pulmonary alterations. However, it's crucial to note that the scale of patients affected during those outbreaks was considerably smaller when compared to the SARS-CoV-2 pandemic. While the 3% rate of chronic pulmonary alterations for SARS-CoV-1 may appear low, it becomes a matter of significance when considering the enormous number of individuals infected by SARS-CoV-2. Furthermore, there is currently no universally accepted consensus regarding the rate of such alterations for SARS-CoV-2.[16-17]

Our purpose in this study is to identify the pulmonary parenchymal alterations that may develop after COVID-19 pneumonia, identify fibrosis symptoms that may have clinical significance for the patient, and reveal a possible post-COVID lung disease pattern by comparing it with the findings in previously recognized interstitial pneumonia with fibrosis. This will enable us to establish a classification and make it easier to recognize thorax CT examinations of these patients in the following years.

Material and Methods

Study Approval and Participants

This study obtained approval from the ethics committee, and the institutional review board waived the requirement for written informed consent, thereby confirming the retrospective nature of the research. The study comprised individuals aged 18 and above who had positive COVID-19 PCR test and sub-

sequently received follow-up care at COVID outpatient clinics during the period spanning July 2020 to May 2021. Eligible participants were those presenting ongoing complaints of chest pain, shortness of breath, fatigue, and persistent cough. A substantial portion of these individuals had undergone multiple chest CT examinations subsequent to receiving a positive PCR test result for COVID-19. A total of 200 patients were enrolled in the study. These participants were classified into two groups based on their chest CT findings: those with normal findings and those with abnormal findings. Among the initial 200 patients, 122 individuals displaying normal chest CT findings were excluded from the study. Consequently, the primary focus of the analysis was directed toward the remaining 78 patients who exhibited abnormal chest CT findings, with the objective of discerning patterns indicative of fibrosis or possible fibrosis. An additional four patients were subsequently excluded from the study due to findings that appeared to be associated with non-COVID-related factors, such as lung masses, suspected metastases, or potential asbestos exposure.

CT Indication

In the post-COVID-19 era, the indications for chest CT scans exhibit variability, albeit with a predominant focus on the presence of persistent or newly emergent respiratory symptoms. These symptoms encompass phenomena such as dyspnea, chest pain, or recurrent infections. Furthermore, the decision to undertake a chest CT scan was subject to influence from preliminary assessments conducted in primary care or emergency care settings. In these contexts, suspicions regarding potential abnormalities were grounded in initial clinical evaluations and radiological appraisals. Several follow-up CT studies were conducted as an integral component of the patients' routine clinical surveillance, notably following the initial CT scan that had delineated the presence of sequela lesions. These ensuing studies were subsequently incorporated into our data compilation efforts. It is crucial to underscore that the determination of these indications was guided by the prevailing standard clinical guidelines and protocols in force during the patients' assessments.

CT Imaging Procedure

A standardized non-contrast chest CT scan was conducted using equipment from GE Healthcare in Chicago, Illinois, USA. The scans were performed with patients in the supine position during the inspiratory phase. The scan parameters included a tube voltage of 100kV, a range of 50-399 milliampere-seconds (mAs), and a section thickness of 1.3 millimeters.

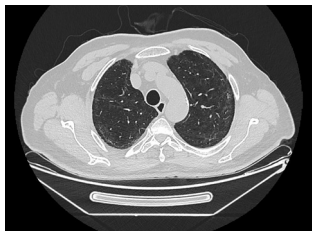
CT Examination and Analysis

The CT scans were carefully examined, encompassing a wide range of features such as ground-glass opacity (GGO), consolidation, irregular subpleural patterns, traction bronchiectasis, the presence of a honeycombing sign, volume loss, involvement of perilobular regions, nodules, parenchymal bands, subpleural striations, subpleural preservation, and subsegmental atelectasis. We also conducted a comprehensive analysis of the distribution patterns of these findings. The selection of these specific features for analysis during chest CT examinations was based on our extensive experience with interstitial lung diseases and the standardized terminology provided by the Fleischner Society for chest scanning.

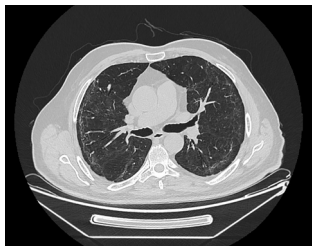
Classification of Patients

Patients underwent classification into distinct categories, which encompassed non-specific interstitial pneumonia (NSIP), possible usual interstitial pneumonia (UIP), organized pneumonia (OP), or the absence of a distinctive pattern. The criteria employed for classification included the presence of lower lobe and peripheral/peribronchovascular predominant ground glass opacities, irregular reticulations, subpleural preservation, and bronchiectasis/bronchioloectasis for NSIP (figures 1a,1b and 1c).

1a



1b



1c

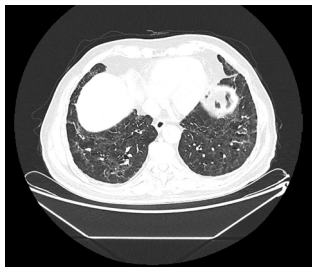
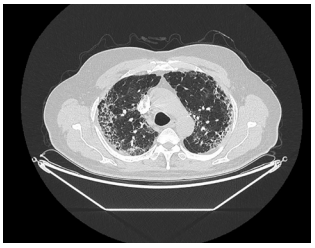


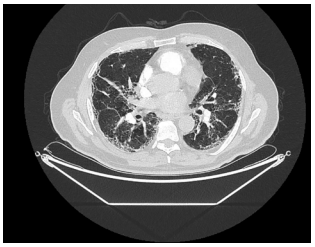
Figure 1: Images of a post-COVID-19 patient's upper zone (a), middle zone (b), and lower zone (c) at 5 months, showing subpleural sparing, subpleural reticular opacities, and peripheral GGO in the upper lobes, as well as GGO, subpleural reticular opacities, and parenchymal bands in the lower lobes. The patient was evaluated as having a non-specific interstitial pneumonia (NSIP) pattern.

UIP was identified by the predominance of irregular reticulations, honeycombing cysts, and volume loss, primarily in the lower lobes and peripheral regions (figures 2a,2b and 2c).

2a



2b



2c

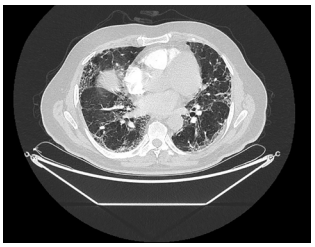
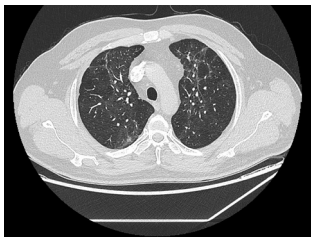


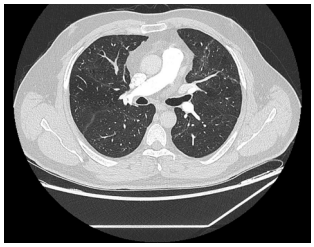
Figure 2: Images of a post-COVID-19 patient's upper zone (a), middle zone (b), and lower zone (c) at 5 months, showing peripheral reticular opacities and honeycombing in all lobes, as well as architectural distortion in the lower lobes. The patient was evaluated as having a usual interstitial pneumonia (UIP) pattern.

OP was characterized by lower lobe predominant consolidation/ground glass opacities and perilobular opacities displaying peripheral and peribronchovascular distribution. Findings that defied classification within these established categories were designated as "no distinctive pattern" (figures 3a,3b and 3c).

3a



3b



3c

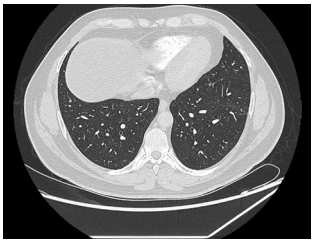


Figure 3: Images of a post-COVID-19 patient's upper zone (a), middle zone (b), and lower zone (c) at 7 months, showing bilateral upper lobe parenchymal bands, traction bronchiectasis, and peripheral ground-glass opacities (GGO). Note that the lower lobes appear normal. The patient was evaluated as having no distinctive pattern.

Demographic and Clinical Data

Demographic data, including smoking history, comorbid conditions, hospitalization, intensive care unit admissions, mechanical ventilation, steroid usage, and antiviral treatments, underwent meticulous analysis.

Radiological Assessment

Chest CT examinations were performed by two radiologists, each possessing over a decade of experience in chest CT imaging. In instances where conflicting findings emerged, a third radiologist, specialized in chest radiology, was consulted to facilitate consensus.

Statistical Analysis

Data were subjected to statistical analysis utilizing the IBM SPSS Statistics Standard Concurrent User V26 software package, developed by IBM Corporation in Armonk, New York, USA. Descriptive statistics were presented in terms of both the numerical count (n) and percentage (%) values. Relationships between categorical variables were assessed employing the Fisher's Exact Test and Chi-Square test, with statistical significance being determined by a p-value of less than 0.05.

Results

Study Population and Demographics

The study enrolled a total of 74 patients, comprising 57 (77%) males and 17 (23%) females. The median age of the patient cohort was 64 years, with a mean age of 64.15 ± 9.22 years. The median interval between the patients' initial COVID-19 infection and their subsequent CT examinations was determined to be 7 months (Table 1).

Table 1. Descriptive Statistics on Patient Information

	Mean ± SD	*Median (Min-Max)*
Age (year)	64,15±9,22	64 (47-83)
Evaluated CT Time (month)	7,64±2,84	7 (4-12)

SD: Standard Deviation, CT: Computed Tomography

Prevalence of Comorbidities and Medical Interventions

A noteworthy proportion of patients reported comorbidities, including hypertension (48.6%), diabetes mellitus (17.6%), and heart disease (23.0%).

Additionally, the majority of patients had no history of smoking (54.1%), chronic kidney disease (94.6%), cancer (98.6%), or Chronic Obstructive Pulmonary Disease (COPD) (90.5%).

Concerning medical interventions, a substantial number of patients underwent hospitalization (94.6%) during the course of their illness, and a smaller percentage necessitated mechanical ventilation (6.8%). Corticosteroid treatment was administered to the majority of patients (87.8%), while antiviral treatment was almost universally employed (98.6%) among the study cohort (Table 2).

Table 2. Descriptive Statistics on Patient Characteristics

		N	*%*
Smoking	No	40	54,1
	Yes	34	45,9
Hypertension	No	38	51,4
	Yes	36	48,6
Diabetes Mellitus	No	61	82,4
	Yes	13	17,6
Chronic Kidney Disease	No	70	94,6
	Yes	4	5,4
Cancer	No	73	98,6
	Yes	1	1,4
COPD	No	67	90,5
	Yes	7	9,5
Heart Disease	No	57	77,0
	Yes	17	23,0
Hospitalization	No	4	5,4
	Yes	70	94,6
Intensive Care Unit Stay	No	40	54,1
	Yes	34	45,9

N: Number, COPD: Chronic Obstructive Pulmonary Disease

Distribution of CT Findings

As all of our patients were drawn from a population exhibiting pathological alterations in lung parenchyma, the majority presented with multiple CT findings, including ground-glass opacities, subpleural reticulation, traction bronchiectasis, and perilobular involvement. Ground-glass opacities (GGO) were the most prevalent CT finding (89%), followed by subpleural reticulation (64%), traction bronchiectasis (44%), perilobular involvement (31%), and subpleural sparing (18%). Nodules (2%), consolidation (4%), and honeycombing (7%) were the least frequently encountered findings.

Moreover, we scrutinized the distribution of these findings within the lung to establish a discernible pattern. GGO was predominantly located peripherally (55%), followed by an axial plane distribution (31%), and central localization (2.7%). In terms of craniocaudal distribution, GGO within the lung zones exhibited the following patterns: 55% distributed throughout all lung zones, 24% displayed predominant involvement in the middle and lower zones, and 9.5% exhibited predominant involvement in the upper zones. Subpleural reticulations were most commonly observed in the middle-lower zone (41%), while traction bronchiectasis predominated in the middle-lower zone (32%) (Table 3).

Predominant CT Findings

The most frequently observed pattern among our patients entailed irregular reticulation, perilobular opacities, and ground-glass opacities, primarily situated subpleurally. However, in some instances, these findings exhibited peribronchovascular distribution in the lower lobe levels and occasionally extended to involve the upper lobes, albeit with a slightly greater predilection for the lower lobes. These features were sometimes accompanied by predominant traction bronchiectasis in the peripheral and lower lobe regions. Honeycombing, consolidation, volume loss, and parenchymal bands were infrequently identified. The CT characteristics of the disease predominantly suggested a non-specific interstitial pneumonia (NSIP) pattern. Additionally, perilobular involvement and isolated areas of consolidation contributed to the organized pneumonia component. The usual interstitial pneumonia (UIP) or UIP-like pattern was exceedingly rare. In this study, we categorized 63.5% of the patients under the classification of fibrotic NSIP (Table 3).

Table 3. Descriptive Statistics on Clinical Findings

		N	*%*
Ground-Glass Opacity (GGO)	No	8	10,8
	Yes	66	89,2
Ground-Glass Opacity (GGO) Distribution	None	8	10,8
	Peripheral	41	55,4
	Central	2	2,7
	Random	23	31,1
Ground-Glass Opacity (GGO) Zone	None	8	10,8
	Upper Zone	7	9,5
	Middle-Lower Zone	18	24,3
	All Zone	41	55,4
Consolidation	No	70	94,6
	Yes	4	5,4
Subpleural Irregular Reticulation	No	10	13,5
	Yes	64	86,5
Subpleural Irregular Reticulation Distribution	None	10	13,5
	Upper Zone	10	13,5
	Middle-Lower Zone	31	41,9
	All Zone	23	31,1
Traction Bronchiectasis	No	30	40,5
	Yes	44	59,5
Traction Bronchiectasis Distribution	None	30	40,5
	Upper Zone	8	10,8
	Middle-Lower Zone	24	32,4
	All Zone	12	16,2
Honeycomb	No	67	90,5
	Yes	7	9,5
Volume Loss	No	72	97,3
	Yes	2	2,7
Perilobular Opacity	No	43	58,1
	Yes	31	41,9
Nodule	No	72	97,3
	Yes	2	2,7
Parenchymal Bands	No	60	81,1
	Yes	14	18,9
Subpleural Lines	No	46	62,2
	Yes	28	37,8
Subpleural Sparing	No	56	75,7
	Yes	18	24,3
Subsegmental Atelectasis	No	59	79,7
	Yes	15	20,3
Pattern	No Distinctive Pattern	18	24,3
	Fibrotic Nonspecific Interstitial Pneumonia (NSIP)	47	63,5
	Possible Usual Interstitial Pneumonia (UIP)	6	8,1
	Organising Pneumonia (OP)	3	4,1

N: Number, GGO: Ground Glass Opacities, NSIP: Nonspecific Interstitial Pneumonia, UIP: Usual Interstitial Pneumonia, OP: Organising Pneumonia

Patients exhibiting a "no distinctive pattern" displayed irregular reticulation and ground-glass opacities, with a more pronounced presence in the upper lobes and peripheral zones.

Discussion

Thorax CT findings related to COVID-19 infection have now been described in detail, and current research is focused on post-COVID pulmonary alterations. Studies on this subject are being conducted with CT findings and pulmonary function tests obtained at various times after COVID-19 infection, and our knowledge is growing. The most critical question in this regard is when and how much the findings will improve after COVID-19 infection. Studies have shown that most of these findings regress or even completely resolve, especially on follow-up CT examinations after one year. However, residual abnormalities persist in some patient groups. Considering the millions of people infected with COVID-19, this group of patients is not a minority. Therefore, the following questions arise: are these residual abnormalities true fibrotic alterations affecting pulmonary function, or are they insignificant sequelae? Another important question is, just like tuberculosis infection, which was once widely distributed and whose sequelae are now seen on thorax CT examinations, will these alterations be observed on thorax CT examinations for years to come, and will they cause confusion from time to time? Certainly, such questions will be answered in time and through detailed studies. It is the latter question that we try to answer and outline in the present study. It is an effort to look for a possible pattern for pulmonary alterations after COVID-19 infection.

Consistent with previous studies, most of the patients in the study were elderly (mean age 65), and the majority of them were male (77%). The patients were analyzed with CT examinations taken an average of 7 months after they had COVID-19 infection.[18-19]

In various studies, residual lung anomalies after COVID-19 infection have been reported, ranging from a minimum of 9-23% to a maximum of 72-84% .[19-20]

In a study by Bocchinio et al., the CT findings of 84 patients at 3, 6, and 12 months after COVID-19 infection were compared. The study recorded monthly alterations in imaging features such as ground-glass opacity (GGO), consolidation, pleural-parenchymal bands, linear atelectasis, bronchiectasis/bronchiole-

ctasis, reticulation, and honeycombing. While 100% of patients had GGO at baseline, the rate decreased over the months, reaching 20% at month 6. In the 12th month, it decreased to 2%. Consolidation was not observed in any patient after 6 months. GGO and consolidation were mostly diffuse, whereas, in those with focal distribution, the findings were predominant in the lower lobe. In the same study, fibrosis/fibrosis-like findings were found in 50% of the patients in the first 3 months and 42% in the 6th month. The findings were predominant in the lower lobe and periphery. Residual fibrotic alterations were detected in 5% of patients at the end of the 12th month (19). As in our study, the predominant finding in the aforementioned study was GGO with lower lobe peripheral predominance. In our study, we found 89% GGO, 5% consolidation, 86% reticulation, 59% traction bronchiectasis, and 18% parenchymal bands. The reason for such high values is that our patient group was selected from those with pathologic chest CT findings. However, in this study, we aimed to emphasize the possibility of residual thorax CT findings following COVID-19 and to fit them into a pattern.

In a meta-analysis of 15 studies and 3134 cases including thorax CT findings observed approximately 12 months after COVID-19 pneumonia by Watanabe et al., residual lung abnormalities were found in approximately 33% of patients. The most common finding was GGO and fibrosis-like alteration (21%). The other findings were bronchiectasis (10%), interlobular septal thickening (8%), reticulation (6%), and consolidation (3%). The residual findings were similar to our study, but no clear pattern was reported in these studies.[21]

In a study by Besutti G. et al., 6-7 months follow-up thorax CT examinations of 405 patients were analyzed. They classified CT findings as resorbed anomalies, residual non-fibrotic anomalies, and residual fibrotic anomalies. Complete or near complete resolution of lung anomalies was present in 55.6% of patients. Residual non-fibrotic anomalies were 37.5%. The most common finding was GGO with 35.1%, followed by bronchiectasis with a periferal predominant distribution in 12.8% of patients, perilobular opacities in 7.9%, and other anomalies (such as parenchymal band, consolidation) in less than 3%. Researchers classified 67.7% of patients as non-fibrotic NSIP and 32.3% as mixed NSIP-OP patterns in the no-fibrotic group.[18] Residual fibrotic anomalies were found in 6.9% and most of them were classified as fibrotic NSIP as a pattern and very few of them were identified as possible UIP and UIP patterns.[18] In our study, similar findings to the above study were observed and we conclude that the most common pattern is the NSIP-like pattern. Additionally, there was an unclassifiable group that did not resemble the patterns we know in our study, and upper lobe predominance or diffuse lung involvement was mainly observed.

The limitations of our study are that it is a single-center, retrospective study and has a relatively small number of patients. Moreover, the examination of residual anomalies and possible fibrosis in the lung following COVID-19 infection was conducted only with CT, and we did not have data on pulmonary function tests and the 6-minute walk test. Another challenge is the definition of pulmonary fibrosis. The issue may include some individual differences. Although various studies have emphasized similar features with slight differences, there is no common consensus yet. Another challenge is whether these findings will be permanent or not. At later stages, the findings may regress, remain stable or progress to progressive fibrosis. In this case, we may need a new nomenclature and classification, time will tell.

Conclusion

In conclusion, In studies conducted with control thorax CT examinations between 3-12 months following COVID-19 infection, it was detected that there were residual findings in the lung at various rates. Naturally, not all of these can be classified as fibrosis. However, there are certainly some long-term or permanent alterations in the lung, especially after severe COVID-19 infection, and this is manifested in the patient's clinic. Considering that millions of people worldwide are affected by this infection, it is likely that post-COVID lung findings will be common in the years to come. Our purpose when we started this study was to see if there was a method to identify these patients in a pattern similar to tuberculosis infection. In our study, we found that most of the patients had NSIP-like findings in the first year, while OP and UIP pattern findings were less common. A quarter of the patients had findings that did not match.

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