

Radiographic Features and Prognosis of Early- and Late-onset Non-small Cell Lung Cancer Immune Checkpoint Inhibitor-related Pneumonitis

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Research Article

Keywords: immunotherapy, NSCLC, checkpoint inhibitor-associated pneumonia, prognosis, radiographic patterns

Posted Date: March 1st, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-171264/v2>

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Abstract

Background: Immunotherapy is becoming a standard of care for non-small cell lung cancer (NSCLC). Checkpoint inhibitor-associated pneumonia (CIP) is a rare and potentially life-threatening event that can occur at any time during tumor immunotherapy. However, there may be differences in the radiological patterns and prognosis of CIP during different periods. This study aimed to investigate the radiographic features and prognosis of early- and late-onset immune-related pneumonitis.

Methods: We retrospectively analyzed the clinical data of 677 NSCLC patients receiving immunotherapy to identify 32 patients with CIP who were being effectively treated by immunotherapy, analyzed the clinical and radiographic data, and summarized the radiological features and prognosis of early- and late-onset CIP.

Results: CIP had an incidence of 4.7%, a median onset time of 2.4 months, and a mortality of 28.1%. Among these, CIP included 14 early-onset cases, where grade ≥ 3 CIP accounted for 92.9%, main radiographic pattern was organizing pneumonia (OP)-like pattern, and mortality was 50.0%. We also identified 18 late-onset CIPs, where grade ≥ 3 CIP accounted for 50.0%, main radiographic pattern was nonspecific interstitial pneumonia (NSIP)-like pattern, and mortality was 11.1%. The overall survival rate of the early-onset group was significantly lower than that of the late-onset group ($P < 0.05$).

Conclusion: Early-onset CIP cases were higher in the National Comprehensive Cancer Network (NCCN) grade and mainly presented with an OP-like radiographic pattern; whereas, late-onset CIP cases were lower in NCCN grade and mainly presented with an NSIP-like radiographic pattern. Finally, the prognosis of the early-onset CIP group was poorer than that of the late-onset CIP group. We believe that this study will be helpful for clinicians for making early diagnosis and deciding treatment modalities for patients with CIP.

Background

In the last decade, immune checkpoint inhibitors (ICIs) have played an increasingly important role in the treatment of advanced non-small cell lung cancer (NSCLC), malignant melanoma, and other malignancies.^{1,2} However, with the continuously expanding indications of ICIs and their widespread application in clinical front-line treatment, many immune-related adverse reactions associated with ICIs have been observed, for instance, in the skin, pituitary gland, thyroid gland, liver, kidney, lung, and other organs; these reactions can even be life-threatening.^{3,4}

Checkpoint inhibitor-associated pneumonia (CIP) is a rare fatal immune-related adverse event (irAE), which has an incidence rate of 2–5%.⁵ Nishino et al. found that the incidence of CIP is higher in NSCLC than in melanoma.⁶ Further, compared with patients with other malignant tumors, NSCLC patients had a higher mortality rate associated with ICI treatment.^{7,8} CIP could occur at any time during tumor immunotherapy⁹, and typically varies from 2 to 24 months.¹⁰ Nakahama et al.¹¹, Erwin et al.¹², and Costa

et al.¹³ have found that CIP can occur within a few days after ICI application; however, the clinical manifestations of these patients were inconsistent. For instance, some patients developed respiratory failure quickly; whereas, other patients showed no obvious discomfort, even though their chest computed tomography (CT) showed an obvious exudation shadow. Additionally, Erwin et al. found that patients with early CIP have severe clinical symptoms.¹² However, there is no report that investigates the relationship between the occurrence period and prognosis of CIP.

In this study, we found that the occurrence period of CIP was significantly associated with its prognosis and proposed the concept of early- and late-onset CIP accordingly. Furthermore, the radiographic pattern of CIP is complicated. In addition to the typical cryptogenic organizing pneumonia (COP)-like, nonspecific interstitial pneumonia (NSIP)-like, hypersensitivity pneumonia (HP)-like, and acute interstitial pneumonia (AIP)-like interstitial patterns, there are some uncommon radiographic patterns such as sarcoid-like granulomatosis¹⁴ and pleural effusion.¹⁵ However, there are no reports that evaluate the radiographic difference between early- and late-onset CIP. Thus, in this study, we retrospectively analyzed 32 patients with CIP and summarized the differences in the radiographic features and prognosis between early- and late-onset CIP. We believe that this study will be helpful for clinicians to make early diagnosis and decide treatment modalities for patients with CIP.

Methods

Subjects

We retrospectively analyzed the clinical data of 677 NSCLC patients who received ICI treatment (anti-programmed death 1/programmed death ligand 1) at two Grade III Level A hospitals in Beijing, China from January, 2017 to September, 2020. A total of 32 patients with CIP were identified, and patients with infection or tumor progression were excluded. Further, patients who had received epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) were also excluded to rule out EGFR-TKI-induced interstitial lung disease (ILD). Postoperative histopathology, CT-guided lung puncture biopsy, or tracheoscopic bronchial mucosa biopsy was used to identify the 677 patients with NSCLC. Clinical data of the patients included sex, age, smoking history, underlying diseases, allergy history, tumor location, pathological pattern, degrees of differentiation, clinical stages, clinical symptoms, treatment methods, and overall survival. All patients were followed up from the time of initiation of ICI therapy to death or last research phone call by a member of the research team. The study was approved by the ethics committee of the hospital.

CIP, Peritumoral Infiltration (PTI), and Criteria for CIP Classification

The diagnosis of CIP was determined by the treating oncologist (Mei Xie) and confirmed by a multidisciplinary irAE team consisting of a pulmonologist (Aiben Huang), radiologist (Xiaoli Sun) and a second oncologist (Chongchong Wu). For identifying CIP patients, we considered patients who developed dyspnea or other respiratory symptoms (including cough, shortness of breath, etc.) after treatment with

ICIs, along with the presence of new radiographic infiltration and lack of evidence of pulmonary infection or other alternative etiologies (tumor progression, radiation pneumonitis, diffuse alveolar hemorrhage, heart failure, etc.). Briefly, using a combination of clinical (history and examination, arterial blood gas analysis, and pulmonary function testing), radiographic (presence or absence of tumor progression and pattern of parenchymal infiltrates), and biologic parameters (white blood cell count, sputum and/or bronchoalveolar lavage cultures, respiratory viral cultures, and cytopathologic testing), we excluded alternative etiologies such as heart failure, infection, and tumor progression. Improvement was defined as a decrease in oxygen requirement, increase in exercise capacity, or improvement in radiographic infiltrates after commencement of CIP treatment. Conversely, worsening was defined as lack of improvement in oxygen requirement and exercise capacity after 72 hours of steroid therapy.¹⁶ CIP that occurred after 1–2 cycles of ICI treatment and after >2 cycles of ICI treatment were considered early- and late-onset CIP, respectively. Further, PTI was defined as ground glass opacity (GGO) confined to the area around the tumor.¹⁷ We considered the guidelines of National Comprehensive Cancer Network (NCCN) to classify CIP. According to NCCN,¹⁸ CIP is classified based on the clinical and radiographic features as follows: grade 1: no symptoms, lesions confined to a single lung lobe or <25% lung parenchyma; grade 2: emerging respiratory symptoms or aggravation of original symptoms such as shortness of breath, cough, chest pain, and fever as well as increased oxygen inhalation demand; grade 3: severe symptoms, lesions involve all lobes or >50% lung parenchyma as well as limited daily activities; and grade 4: life-threatening respiratory impairment.⁷

Chest CT

All patients included in this study underwent a non-contrast CT of the chest performed with a GE LightSpeed 16-Slice CT scanner (GE Healthcare, Beijing, China) or a Siemens SOMATOM Sensation 64-Slice CT Scanner (Siemens, Forchheim, Germany). CT was performed with the following parameters: routine section thickness: 1.0, 1.25, or 1.5 mm; section thickness after reconstruction: 0.625–1.25 mm; filtered back-projection reconstruction method; 80–120 kV; 200–280 mAs; and a B70f kernel. We considered the initial chest CT studies as the first observation and the last chest CT studies just before histopathologic diagnosis as the last observation. The chest CT data of the 677 patients were obtained from picture archiving and communication system (PACS).

Chest CT Interpretation

A thoracic radiologist (J.W., with 24 years of experience in cardiopulmonary imaging) and a medical student (Y.T., with 2 years of experience in pulmonary imaging diagnosis) reviewed the CT images, in consensus, from each institution by using PACS (AGFA Healthcare, Mortsel, Belgium; lung window width, 1500 HU; level, 2500 HU) and labeled the chest CT images that were suspected to be CIP. Afterwards, the studies in these patients were reviewed to confirm the presence of CIP by a radiologist in pulmonary imaging (S.Z., with 17 years of experience in pulmonary imaging diagnosis) and a pulmonary radiologist (C.W., with 15 years of experience in pulmonary imaging diagnosis). These two readings were performed for the same patient independently on the same day, and if there were any differences, the radiologists

resolved them through consensus. All radiologists were unaware of the pathologic diagnoses of the patients. The following parameters were recorded for each lesion on the CT images: presence and distribution of GGO, consolidation, nodularity, reticulation, traction bronchiectasis, and pleural effusion, and determination of the validity of ILD in new diffuse infiltration. CT patterns of ILD were classified according to the American Thoracic Society/European Respiratory Society (ATS/ERS) international multidisciplinary classification of IP as AIP/DAD-like pattern, HP-like pattern, COP-like pattern, NSIP-like pattern, and others.

Statistical Methods

Excel (Microsoft) was used for data collection, and SPSS version 26.0 (IBM Statistics, Armonk, NY, USA) was used for statistical analysis. Numerical data are expressed as mean \pm standard deviation. Chi-square or Fisher's exact test was used for categorical data. Patient survival was estimated by Kaplan-Meier method and compared with the log-rank test. $P < 0.05$ was considered significant.

Results

Clinical Features

Figure 1 shows the flowchart of screening the patients. A total of 32 (4.7%) patients with CIP (mean age: 64.1 ± 10.3 years; age range: 43–82 years) were included in this study, including 26 (81.2%) males (mean age: 64.0 ± 10.3 years; age range: 43–82 years) and 6 (18.8%) females (mean age: 64.5 ± 11.3 years; age range: 45–78 years). Among these patients, 25 (78.1%) had a history of smoking, with an average of 40.4 ± 31.5 pack-years (range: 22.2–58.6 pack-years). Of the 32 patients, 21 (65.6%) patients were administered pembrolizumab, 6 (18.8%) were administered nivolumab, 2 (6.3%) were administered sintilimab, 2 (6.3%) were administered durvalumab, and 1 (3.1%) was administered nivolumab and ipilimumab. 32 CIP patients received steroid treatment, after which, 23 (71.9%) patients survived, including 17 patients' condition improved (Figure 2), 6 patients' condition worsened. In addition, 9 (28.1%) patients died. Clinical features are detailed in Table 1.

Table 1. Baseline Characteristics of 32 CIP Patients

Characteristics	Datum
age of all 32 patients (y), mean±SD	64.1 ± 10.3
age of 26 male patients (y), mean±SD	64.0 ± 10.3
age of 6 female patients (y), mean±SD	64.5 ± 11.3
No. of current smokers, n (%)	25 (78.1)
No. of nonsmokers, n (%)	7 (21.9)
No. of pack-years in the 21 patients who smoked□mean ± SD	40.4 ± 31.5
Symptoms, n (%)	
Cough	17 (53.1)
Dyspnea	29 (90.6)
Fever/Fatigue/Chest pain/No symptom	11 (11.3)
Tumor location, n (%)	
Left lung	13 (40.6)
Right lung	19 (59.4)
Tumor histology, n (%)	
squamous	9 (28.1)
adenocarcinoma	19 (59.4)
others	4 (12.5)
Initial tumor stage, n (%)	
I-II	1 (3.1)
III--V	31 (96.9)
Tumor differentiation, n (%)	
High-high to medium-medium	5 (15.6)
Medium to low-low	22 (68.8)
Other	5 (15.6)
ICI agents, n (%)	
pembrolizumab	21 (65.6)
Nivolumab	6 (18.8)
sintilimab/durvalumab/nivolumab+ipilimumab	5 (15.6)
Surgery, n (%)	7 (21.9)
Chemotherapy, n (%)	20 (62.5)
Radiotherapy, n (%)	8 (25.0)
Radiation pneumonitis, n (%)	2 (6.3)
Prognosis, n (%)	
Survival	23 (71.9)
Death	9 (28.1)

Radiographic Patterns of CIP

The chest CT patterns of the 32 patients with CIP included GGO (29 patients, 90.6%; Figure 3A), reticulation (14 patients, 43.8%; Figure 3B), consolidation (12 patients, 37.5%; Figure 3C), nodularity (8 patients, 25.0%; Figure 3D), bronchitis (7 patients, 21.9%; Figure 3E), pleural effusion (2 patients; 6.3%), and among which 5 (15.6%; Figure 3F) patients showed PTI features. The radiographic patterns of CIP included OP-like pattern (11 patients, 34.4%; Figure 4A), NSIP-like pattern (11 patients, 34.4%; Figure 4B), HP-like pattern (2 patients, 6.3%; Figure 4C), and AIP-like pattern (1 patient, 3.1%; Figure 4D).

Difference in Radiographic Patterns of Early-onset and Late-onset CIP

According to the occurrence time of CIP after ICI treatment, the patients were categorized into early-onset and late-onset CIP groups. In the early-onset CIP group, the chest CT patterns included GGO (13 patients, 92.9%), consolidation (7 patients, 50.0%), reticulation (5 patients, 35.7%), nodularity (5 patients, 35.7%), and bronchitis (3 patients, 21.4%); whereas, in the late-onset CIP group, the chest CT patterns included GGO (16 patients, 88.9%), reticulation (9 patients, 50.0%), consolidation (5 patients, 27.8%), nodularity (3 patients, 16.7%), bronchitis (4 patients, 22.2%), and pleural effusion (2 patients, 11.1%), indicating that there was no statistical difference in the radiographic patterns between both the groups ($P > 0.05$).

The radiographic patterns of early-onset CIP included OP-like pattern (7 patients, 50.0%), NSIP-like pattern (2 patients, 14.3%), HP-like pattern (1 patient, 7.1%), AIP-like pattern (one patient, 7.1%), and others (3 patients, 21.4%); whereas, the radiographic patterns of late-onset CIP included OP-like pattern (4 patients, 22.2%), NSIP-like pattern (9 patients, 50.0%), HP-like pattern (1 patient, 5.6%), and others (4 patients, 22.2%), thereby indicating that there was no statistical difference in the radiographic patterns between both the groups ($P > 0.05$).

According to the grading system of NCCN, there was one patient with grades 1–2 CIP (7.1%) and 13 patients with grades 3–4 CIP (92.9%) in the early-onset group. Whereas, in the late-onset group, 9 patients had grades 1–2 CIP (50.0%) and 9 patients had grades 3–4 (50.0%), Here as well, no statistical difference was observed in the CIP grading between both the groups ($P < 0.05$). In the early-onset group, 7 patients (50.0%) survived and 7 patients (50.0%) died; whereas, in the late-onset group, 16 patients (88.9%) survived and 2 patients (11.1%) died, indicating a statistical difference in the overall survival (OS) between both the groups ($P < 0.05$; Table 2 and Figure 5).

Table 2. Radiographic patterns of 14 early-onset CIPs and 18 late-onset CIPs

	Overall N=32	Early-onset CIP N=14	Late-onset CIP N=18	<i>P</i>
CIP location, n (%)				
Bilateral	25 (78.1)	10 (71.4)	15 (83.3)	0.459*
Left	4 (12.5)	3 (21.4)	1 (5.6)	
Right	3 (9.4)	1 (7.2)	2 (11.1)	
Number of lobes involved, n (%)				
1-3	10 (31.3)	5 (35.7)	5 (27.8)	0.712*
4-5	22 (68.7)	9 (64.3)	13 (77.2)	
CT findings at onset of CIP, n (%)				0.598*
Ground glass opacity	29 (90.6)	13 (92.9)	16 (88.9)	
Consolidation	12 (37.5)	7 (50.0)	5 (27.8)	
Reticulation	14 (43.8)	5 (35.7)	9 (50.0)	
Bronchitis/Nodularity	15 (46.9)	8 (57.1)	7 (38.9)	
Pleural effusion	2 (6.3)	0 (0)	2 (11.1)	
Overall pattern of ILD, n (%)				0.096*
OP-like pattern	11 (34.4)	7 (50.0)	4 (22.2)	
NSIP-like pattern	11 (34.4)	2 (14.3)	9 (50.0)	
AIP/HP/Others-like pattern	10 (31.3)	5 (35.7)	5 (27.8)	
Grades of CIP, n (%)				
1-2	10 (31.3)	1 (7.1)	9 (50.0)	0.019*
3-4	22 (68.7)	13 (92.9)	9 (50.0)	
Prognosis, n (%)				
Survival	23 (71.9)	7 (50.0)	16 (88.9)	0.022*
Dead	9 (28.1)	7 (50.0)	2 (11.1)	

* Fisher exact test

Discussion

ICIs have played an increasingly important role in the treatment of advanced malignant neoplasms in various systems.¹⁹ However, with the expansion of clinical application, irAEs, especially fatal ones such as CIP, have drawn increasing attention. Despite its infrequency, CIP shows no specificity in clinical findings but has complex radiographic patterns, which makes early diagnosis difficult. For some patients, a missed early diagnosis of CIP may have fatal consequences. Furthermore, CIP can occur at any time during the course of tumor immunotherapy. However, there is no report that determines the relationship between the occurrence time of CIP and prognosis. In this study, we found that there was a significant difference in the prognosis of early- and late-onset CIP patients. Accordingly, we proposed the concept of early-onset and late-onset CIP.

In multiple clinical trials, 3–7% of patients had CIP after treatment with ICIs for solid tumors,^{20,21} among which approximately 0.8% were grade ≥ 3 CIP.⁶ In this study, we found that 4.7% of the patients had CIP, and grade ≥ 3 CIP accounted for 68.8%, which was significantly higher than the results of previous clinical trials. This difference may be associated with the patient selection in the abovementioned clinical trials, where some patients with CIP high-risk factors (advanced age, complicating interstitial pneumonia,

or radiation pneumonitis) were rejected. The median onset time of CIP is reportedly 2.8 months,²² and the median onset time in our study was 2.4 months (0.7–16.8 months), and early-onset and late-onset CIP accounted for 43.8% and 56.2%, respectively. In early-onset CIP, 59.1% were grade ≥ 3 CIP, indicating that severe patients often had CIP in the early stage of ICI treatment despite the low incidence of CIP.

Tomohisa et al.¹⁷ found that the mortality rate of nivolumab-related interstitial pulmonary diseases was 17.4%. In this study, the mortality rate of CIP was 28.1%. After group assignment, it was found that the mortality of the early-onset CIP group (50.0%) was significantly higher than that of the late-onset CIP group (11.1%). The results of the log-rank test suggested that the median survival time of the early-onset CIP group was only 7 months, and the OS rate of the early-onset CIP group was significantly lower than that of the late-onset CIP group. Thus, physicians should identify high-risk patients during the early stages and perform regular follow-ups to ensure an early diagnosis and treatment.

CIP has various radiographic patterns characterized by nodularity, PTI, reticulation, consolidation, GGO, interlobular septal thickening, and funicular opacity (Figure 6). According to the ATS/ERS international multidisciplinary classification of IP,²³ the radiographic patterns of CIP are characterized by NSIP-, OP-, GGO-, and AIP-like patterns. This study found that CIP was often involved in multiple lobes and segments of both lungs, and radiographic patterns were consistent with those reported in the literature, where the most common pattern was GGO, followed by OP-like, NSIP-like, bronchitis-like, nodularity, and AIP-like patterns. Meghan Shea et al. reported that one patient had fatal CIP after treatment with pembrolizumab, and the post-onset chest CT suggested an OP-like change.²⁴ Mizuki Nishino et al. reported that two patients receiving nivolumab treatment for advanced NSCLC had CIP in the early stages after treatment, and their chest CT suggested GGO and OP-like changes.¹⁰ Mizuki Nishino et al. also reported the chest CT findings and radiographic patterns of 20 patients with malignant tumors (10 with malignant melanoma, 6 with lymphoma, and 4 with pulmonary malignancy) who had developed CIP after treatment with immune checkpoint blockade.²⁵ Out of 20 patients, 7 had developed CIP in early stages (CIP onset time since treatment: 0.5–1.4 months). Their chest CT were mainly characterized by GGO, reticular opacity, and consolidation; whereas, 6 patients (85.7%) showed an OP-like pattern, 1 patient (14.3%) showed an HP-like pattern, and no patients presented with an NSIP-like pattern. Thirteen patients developed CIP in the late stage (CIP onset time since treatment: 1.6–11.5 months). Moreover, in addition to GGO, reticular opacity, and consolidation patterns, bronchodilation and centrilobular nodularity were also observed. In terms of radiographic patterns, 7 patients (53.8%) had an OP-like pattern, 3 (23.1%) patients had an NSIP-like pattern, two (15.4%) patients had an AIP-like pattern, and one (7.7%) patient had an HP-like pattern. Therefore, the main radiographic patterns in early-onset CIP is an OP-like pattern, while the NSIP-like pattern is seen more frequently in late-onset CIP patients. The results of this study were consistent with those reported in the literature, where we identified 7 (50.0%) patients with an OP-like pattern and 3 (21.4%) patients with NSIP-like pattern in the early-onset group, compared to 9 (50.0%) patients with an NSIP-like pattern and five (27.8%) patients with an OP-like pattern in the late-onset group.

At present, there are only a few markers for the early prediction of CIP. Schoenfeld et al. found that the increase of C-X-C motif chemokine ligand 2, IL1ra, and IL2ra was consistent with the development of

CIP.²⁶ Recently, Jing et al. reported that the combination of lymphocyte cytosolic protein 1 and adenosine diphosphate dependent glucokinase is a promising biomarker for irAEs.²⁷ However, biomarkers for predicting early- and late-onset CIP have not been reported.

Conclusion

Our cohort provides a new insight into the difference of radiographic pattern and prognosis between early and late CIP. We have shown that early-onset CIP patients often have more severe symptoms and poorer prognosis, with an OP-like pattern as the dominant radiographic pattern. Late-onset CIP patients often have fewer symptoms and better prognosis, with NSIP-like pattern as the dominant radiographic pattern. When CIP develops in clinical settings, attention should be paid to the onset time, grading, and radiographic pattern of CIP; consequently, immediate diagnosis must be performed and treatment should be provided to improve the prognosis. The current study has several limitations, including its retrospective design, small sample size, and lack of histopathological and bronchoscopic findings. Thus, additional studies with larger sample sizes are required to confirm our results.

Abbreviations

ICI: Immune checkpoint inhibitors

NSCLC: Non-small cell lung cancer

CIP: Checkpoint inhibitor-associated pneumonia

irAE: Immune-related adverse event

CT: Computed tomography

COP: Cryptogenic organizing pneumonia

NSIP: Nonspecific interstitial pneumonia

AIP: Acute interstitial pneumonia

EGFR-TKI: Epidermal growth factor receptor-tyrosine kinase inhibitor

PTI: Peritumoral Infiltration

GGO: Ground glass opacity

NCCN: National Comprehensive Cancer Network

PACS: Picture archiving and communication system

ATS/ERS: American Thoracic Society/European Respiratory Society

Declarations

Ethical Approval and Consent to participate

This study was approved by the Clinical Trial Ethics Committee of Beijing Shijitan Hospital.

Consent for publication

This manuscript has been read and its submission approved by all the coauthors.

Availability of supporting data

All the data generated and analyzed during this study are included in this published article.

Competing interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Funding

National Natural Science Fund Youth Project (81700007); National Natural Science Foundation of China (81772798, 62041602); Research and innovation fund of the Ministry of Education (2018A03026); Beijing Natural Science Foundation (2019A10); "Qingmiao" plan of Beijing Municipal Hospital Administration (2018QM4); Outstanding top talent (2019YXBJ1); Capital health development scientific research unit matching fund (2020-2Z-2086).

Author Contributions

A.H., Y.X., S.L., G.Z., and X.X. conceptualized the article. A.H., Y.X., X.Z., C.W., J.G., X.L., M.X., X.M., H.D., J.S., F.R., L.P., J.Q., Z.Y., S.W., Y.C., L.P., and X.X. analyzed the data. A.H., Y.X., X.Z., and X.X. wrote the initial draft. G.Z., S.L., and X.X. are the guarantors.

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Figures

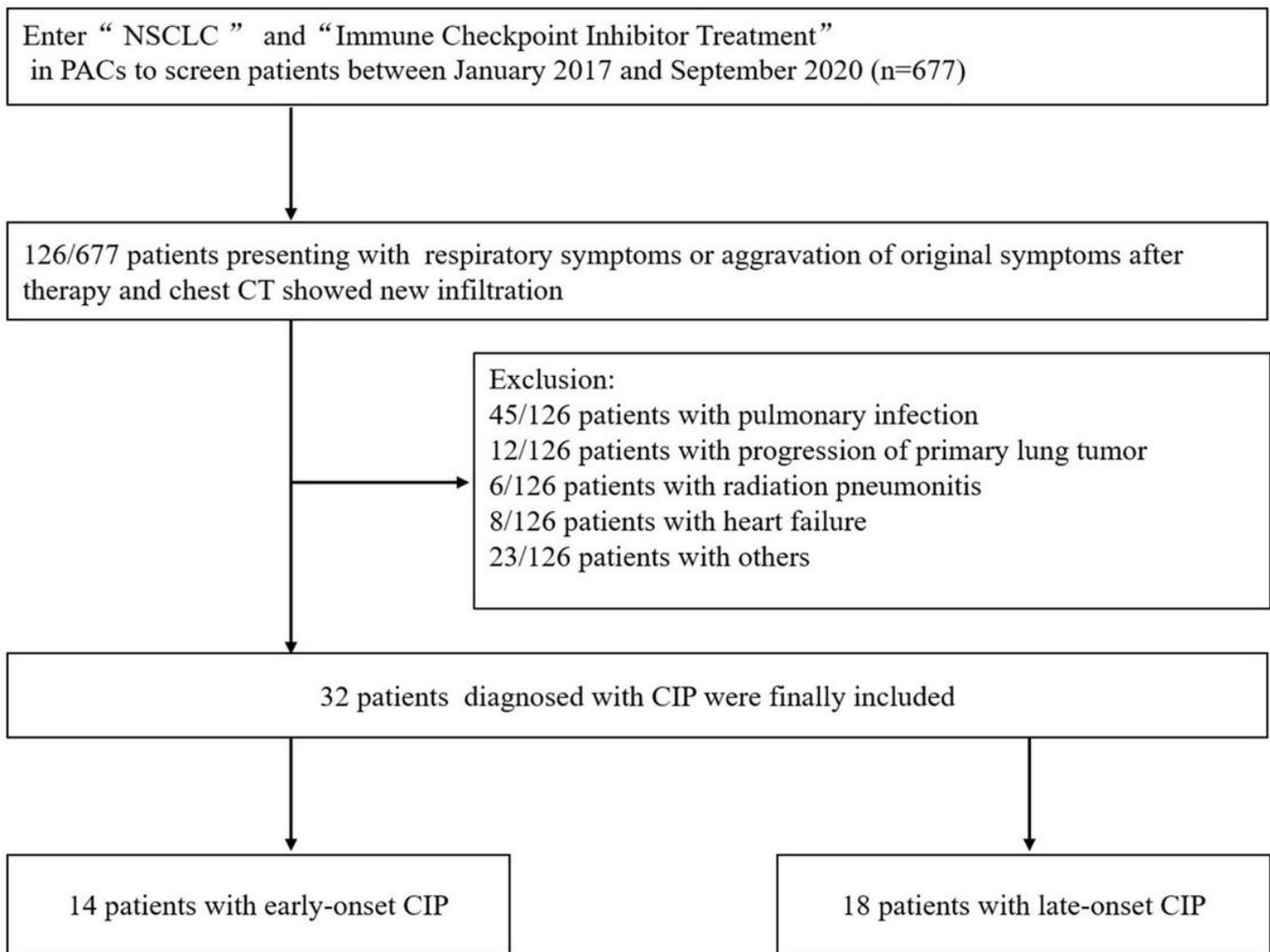


Figure 1

Flowchart of Screening CIP Patients

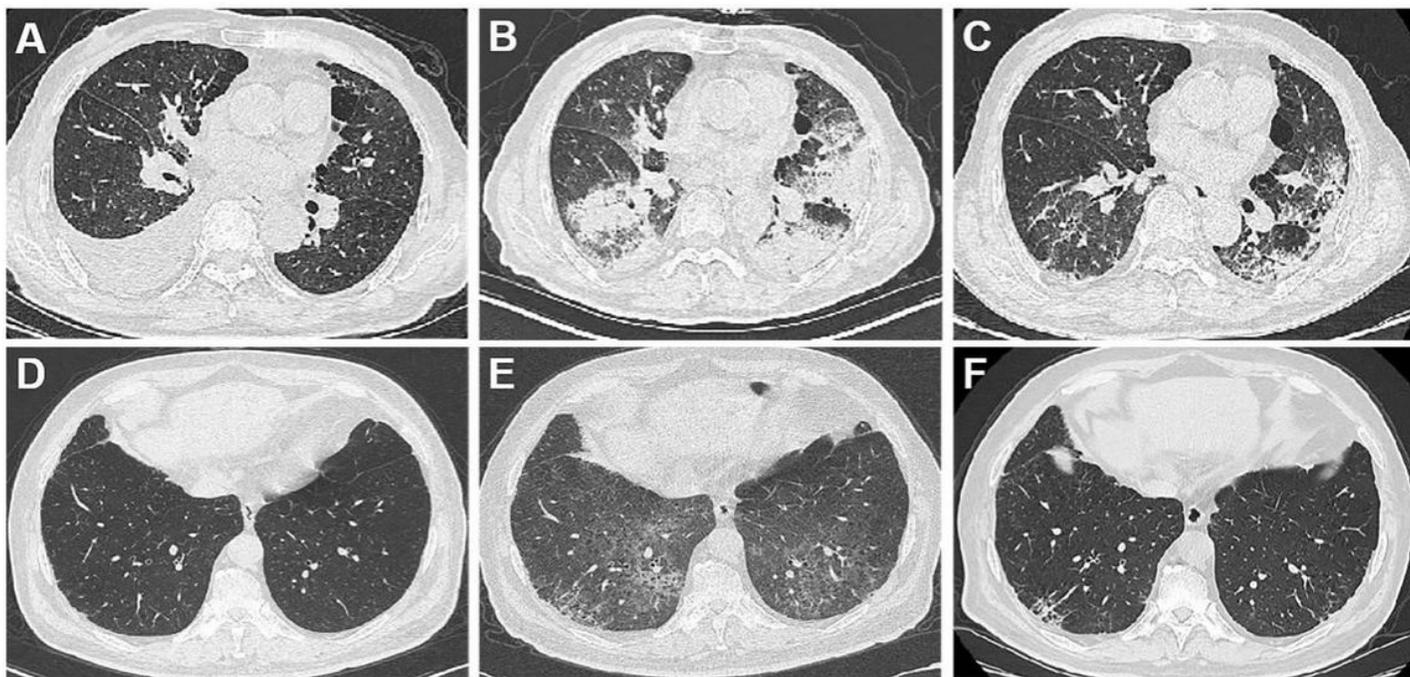


Figure 2

Representative radiological manifestations of CIP. CIP.(A), (D) are CT images before ICI treatment. (B), (E) are CT images at the onset of CIP. (C), (F) are CT images after hormone therapy. (A), (B) and (C) are early onset CIP with OP like pattern in an 81 year old male with adenocarcinoma. Consolidation appeared in the subpleural field of the left lung and right lower lung after the first dose of pembrolizumab. (D), (E) and (F) are late onset CIP with NSIP like pattern in a 69 year old male with squamous lung cell carcinoma. Ground glass opacities and reticulation appeared in both lower lung fields. After hormone treatment, the above lesions were absorbed.

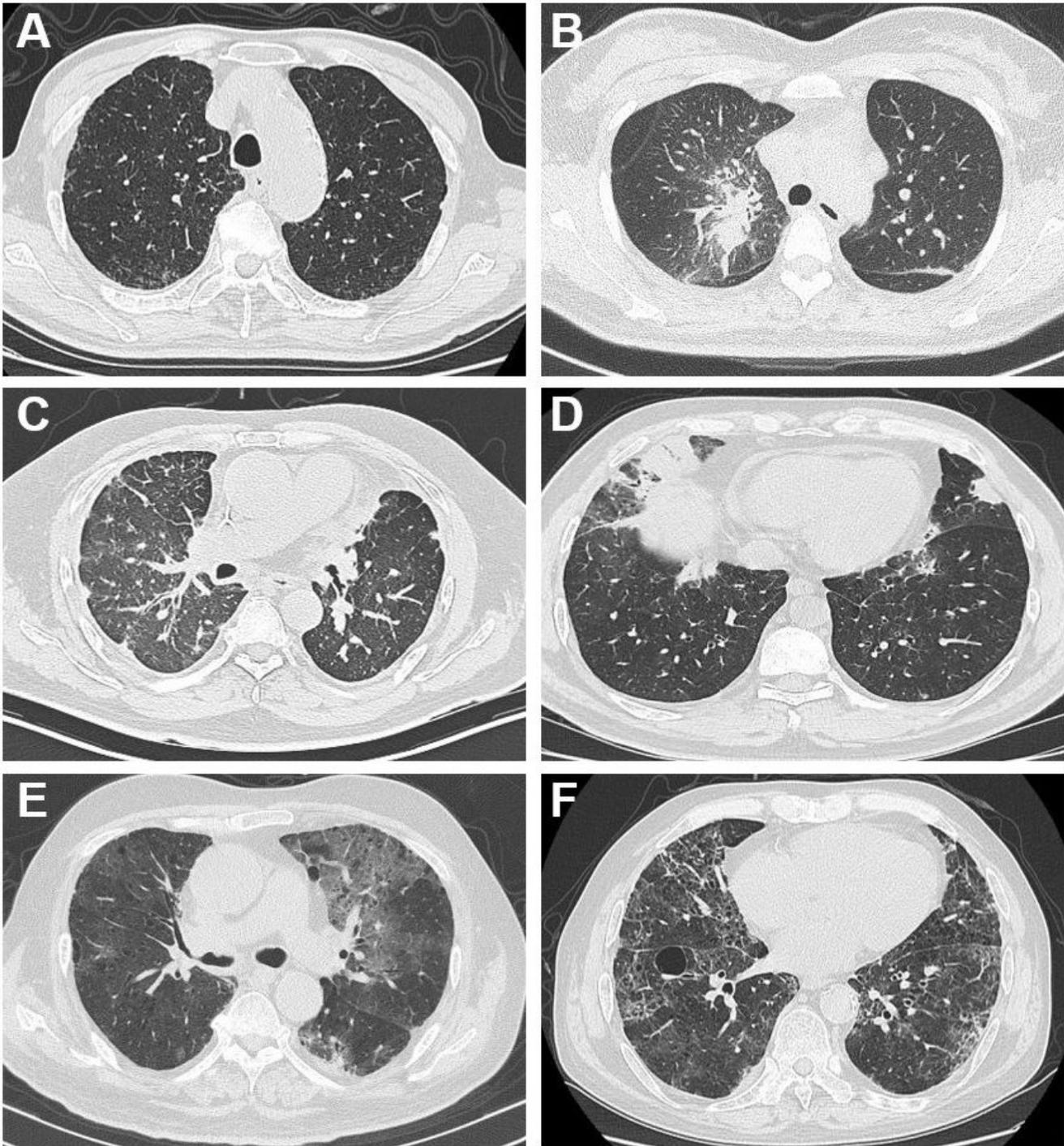


Figure 3

Thoracic computed tomography (CT) findings in patients with checkpoint inhibitor related pneumonitis .. (A) Nodularity: Multiple nodules observed at bilateral upper lung and right lower lobe dorsal segment. (B) PTI: Ground glass opacity around the tumor observed at right upper lobe.(C) Bronchitis pattern: Bronchial thickening observed at bilateral lower lungs and right middle lobe, exudation and nodules observed around bronchi.(D) Consolidation: Consolidation shadow observed at left upper lobe inferior lingular

segment and right subpleural middle lobe. (E) GGO: GGO observed at bilateral superior lobes and left lower lobe dorsal segment.(F) Reticulation: GGO and reticulation shadows observed at left lung and right middle and lower lobes.

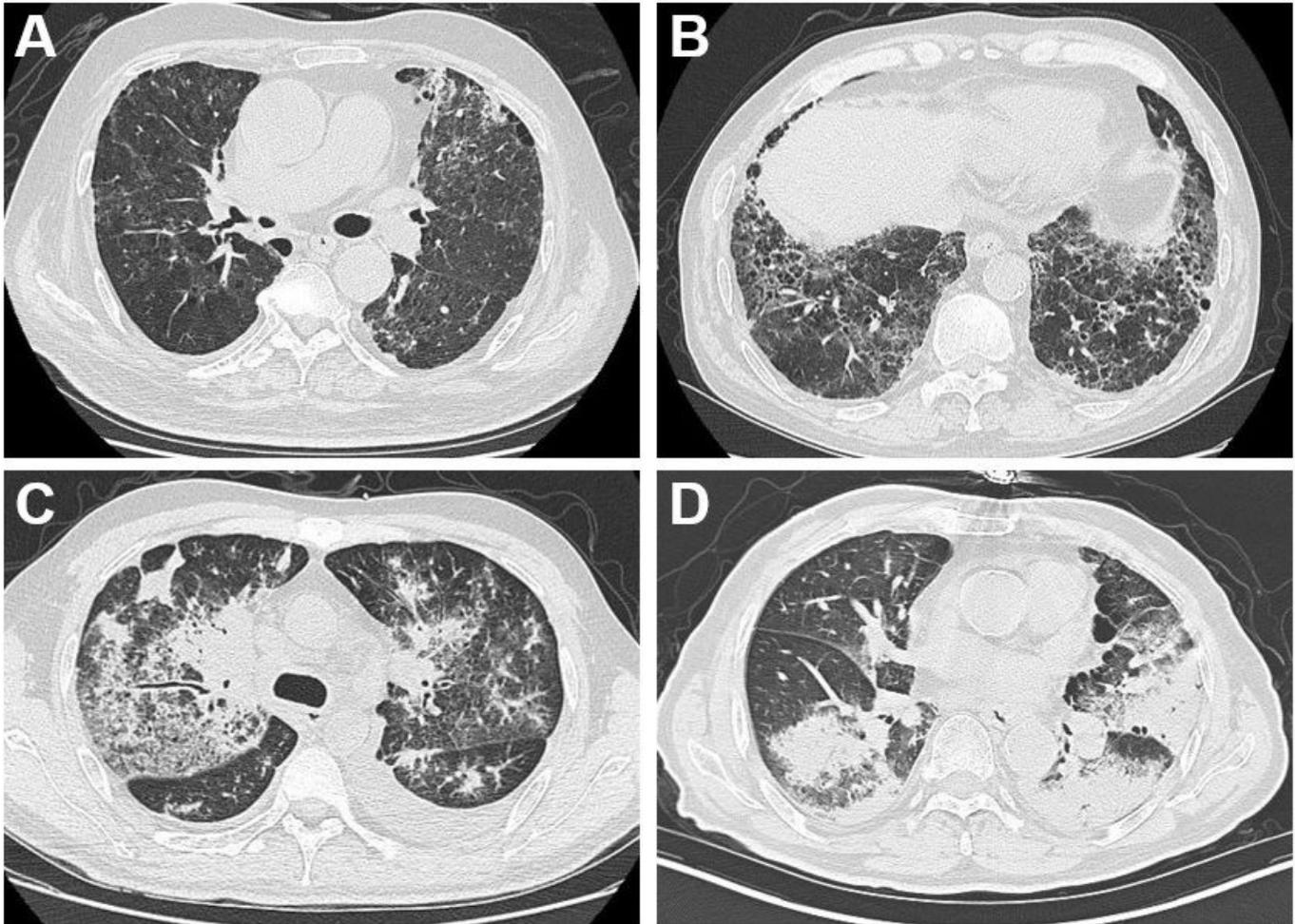


Figure 4

Radiographic patterns of CIP. CIP.(A) HP like pattern: GGO and nodules observed at left lung and right upper lung.(B) NSIP like pattern: GGO and reticulation shadows observed at bilateral lungs.(C) AIP like pattern: Diffuse GGO observed at bilateral upper lung and bilateral lower lobe dorsal segment, accompanied by consolidation and reticulation shadows.(D) OP like pattern: Consolidation shadow and scattered GGO observed at left lung and right subpleural lower lung.

Overall Survival

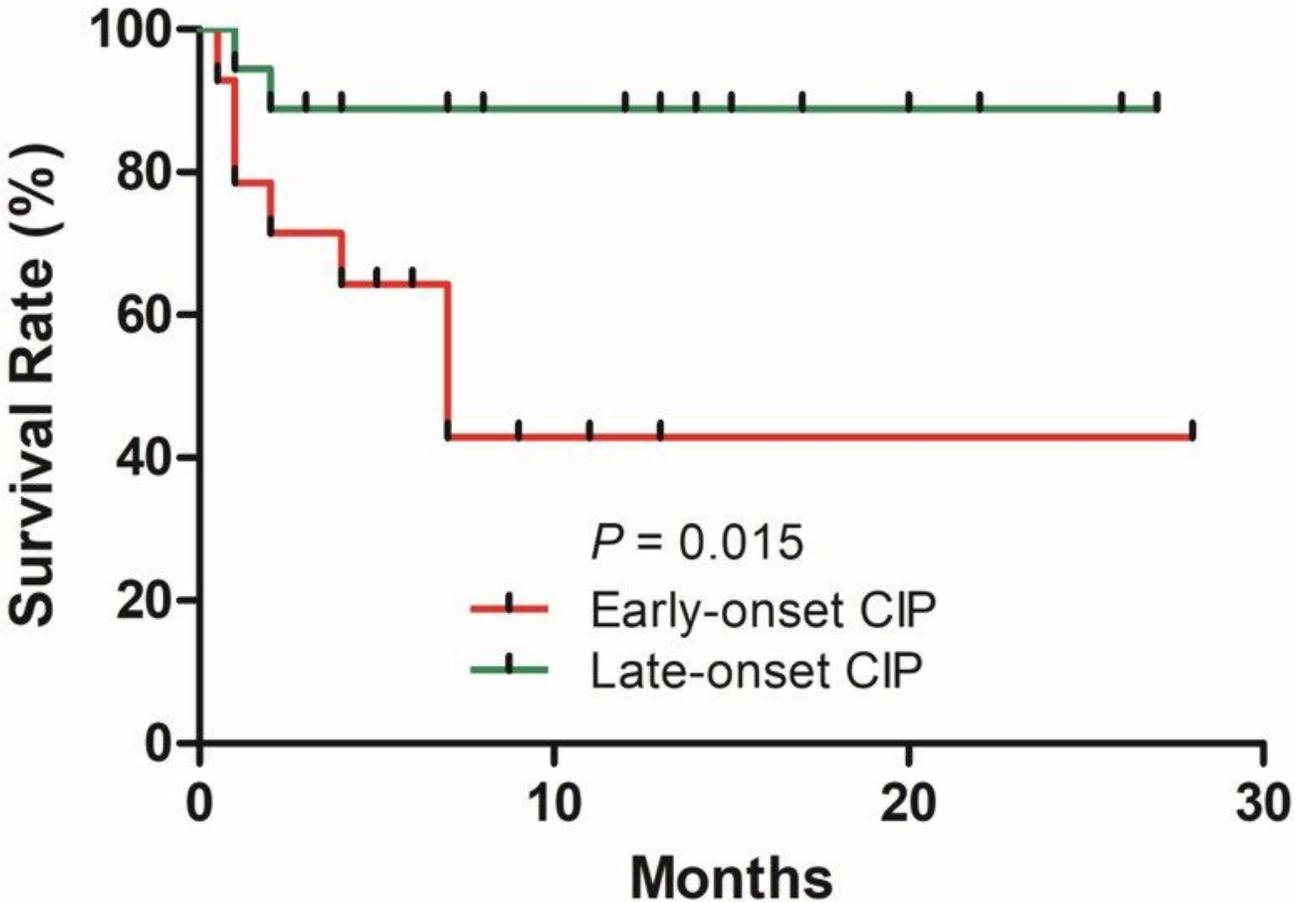


Figure 5

Difference in OS between early onset and late onset CIP groups

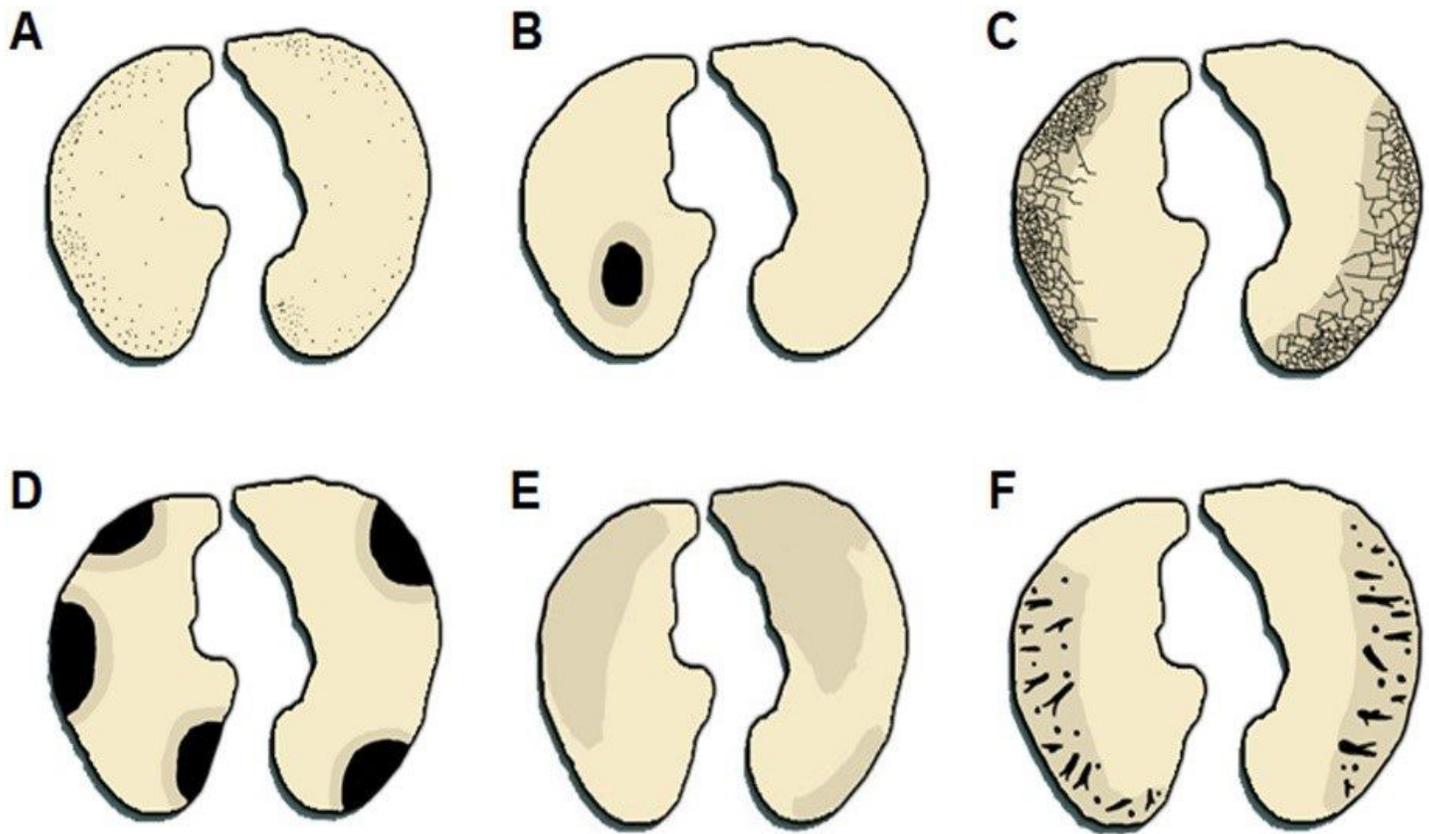


Figure 6

Chest CT patterns of CIP. (A) Nodularity. (B) PTI. (C) Reticulation. (D) Consolidation. (E) Ground glass opacity. (F) Bronchitis.