Possible Alterations of Imaging Patterns in Computed Tomography for Delta-VOC of SARS-CoV-2

Mögliche Abweichungen der bildmorphologischen Charakteristika der SARS-CoV-2 Delta-Variante in der Computertomografie

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ABSTRACT

Background So far, typical findings for COVID-19 in computed tomography (CT) have been described as bilateral, multifocal ground glass opacities (GGOs) and consolidations, as well as intralobular and interlobular septal thickening. On the contrary, round consolidations with the halo sign are considered uncommon and are typically found in fungal infections, such as invasive pulmonary aspergillosis. The authors recently observed several patients with COVID-19 pneumonia presenting with round, multifocal consolidations accompanied by a halo sign. As this may indicate alterations of CT morphology based on the virus variant, the aim of this study was to investigate this matter in more detail.

Methods 161 CT scans of patients with confirmed SARS-CoV-2 infection (RT-PCR within 2 days of CT) examined between January 2021 and September 15, 2021 were included. Follow-up examinations, patients with invasive ventilation at the time of CT, and patients with insufficient virus typing for variants of concern (VOC) were excluded. CT scans were assessed for vertical and axial distribution of pulmonary patterns, degree of involvement, uni- vs. bilaterality, reticulations, and other common findings. The mean density of representative lesions was assessed in Hounsfield units. Results were compared using Mann-Whitney U-tests, Student's t-rests, descriptive statistics, and Fisher's exact tests.

Results 75 patients did not meet the inclusion criteria. Therefore, 86/161 CT scans of unique patients were analyzed. PCR VOC testing confirmed manifestation of the Delta-VOC SARS-CoV-2 in 22 patients, 39 patients with Alpha-VOC and the remaining 25 patients with Non-VOC SARS-CoV-2 infections. Three patients with the Delta-VOC demonstrated multiple pulmonary masses or nodules with surrounding halo sign, whereas no patients with either Alpha-VOC ($p = 0.043$) or non-VOC ($p = 0.095$) demonstrated these findings. All three patients were admitted to normal wards and had no suspicion of a pulmonary co-infection. Patients with Delta-VOC were less likely to have ground glass opacities compared to Alpha-VOC (7/22 or 31.8 % vs. 4/39 or 10.3 %; $p < 0.001$), whereas a significant difference has not been observed between Delta-VOC and non-VOC (5/25 or 20 %; $p = 0.348$). The mean representative density of lesions did not show significant differences between the studied cohorts.

Conclusion In this study 3 out of 22 patients (13.6 %) with Delta-VOC presented with bilateral round pulmonary masses or nodules with surrounding halo signs, which has not been established as a notable imaging pattern in COVID-19 pneumonia yet. Compared to the other cohorts, a lesser percentage of patients with Delta-VOC presented with ground glass opacities. Based on these results Delta-VOC might cause a divergence in CT-morphologic phenotype.

Key Points:

- Until recently, CT-morphologic signs of COVID-19 pneumonia have been presumed to be uncontroversially understood. Yet, recently the authors observed diverging pulmonary alterations in patients infected with Delta-VOC.
- These imaging alterations included round pulmonary masses or nodules with surrounding halo sign.
- These imaging alterations have not yet been established as typical for COVID-19 pneumonia, yet.
- Based on these results, Delta-VOC could impose a divergence of CT-morphologic phenotype.

Citation Format

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ZUSAMMENFASSUNG

Hintergrund Bisher wurden typische Zeichen für eine COVID-19-Pneumonie in der Computertomografie (CT) als bilaterale, multifokale Milchglastrübungen und Konsolidierungen sowie Verdickung der intralobulären als auch interlobulären Septen beschrieben. Demgegenüber werden rundliche Konsolidierungen mit umgebendem Halo-Zeichen bisher als ungewöhnlich angesehen und sind typischerweise in pulmonalen Pilzinfektionen, wie der angioinvasiven pulmonalen Aspergillose beschrieben. Die Autoren beobachteten in jüngster Zeit mehrere Patienten mit COVID-19-Pneumonien, welche in der CT multifokale, runde Konsolidierungen mit umgebendem Halo-Zeichen aufwiesen. Da diese Beobachtung auf eine Veränderung der CT-grafischen Morphologie abhängig von der Virusvariante hinweisen kann, war das Ziel der Studie, diesen Zusammenhang detailliert zu untersuchen.

Methoden 161 CTs von Patienten mit bestätigter SARS-CoV-2-Infektion (RT-PCR innerhalb von 2 Tagen um die CT) wurden zwischen Januar 2021 und dem 15. September 2021 eingeschlossen. Verlaufskontrollen, Patienten mit invasiver Beatmung zum Zeitpunkt der CT sowie Patienten mit insuffizienter Virustypisierung für variants of concern (VOC) wurden ausgeschlossen. Die CTs wurden nach vertikaler und axialer Verteilung pulmonaler Veränderungen, dem Grad der Lungenbeteiligung, Uni- vs. Bilaterilarität, Retikulationen und anderen bekannten pulmonalen Veränderungen ausgewertet. Die durchschnittliche Dichte repräsentativer Läsionen wurde in Houndsfield-Units gemessen. Die Resultate wurden mittels Mann-Whitney-U-Tests, Student's t-Tests, deskriptiver Statistik sowie Fisher-Exact-Tests verglichen.

Ergebnisse 75 Patienten erfüllten die Einschlusskriterien nicht. Deswegen wurden 86/161 CTs von individuellen Patienten analysiert. PCR-Virustypisierung nach VOC bestätigte die Infektion mit der SARS-CoV-2 Delta-VOC von 22 Patienten, von 39 Patienten mit der Alpha-VOC und von den 25 übrigen Patienten mit keiner SARS-CoV-2-VOC. 3 Patienten mit der Delta-VOC wiesen multiple Rundherde oder Raumforderungen mit umgebendem Halo-Zeichen auf, während weder Patienten mit der Alpha-VOC ($p = 0.043$) oder ohne VOC ($p = 0.095$) diesen Befund zeigten. Alle 3 Patienten wurden anschließend auf Normalstation versorgt und es bestand kein Verdacht auf eine pulmonale Koinfektion. Patienten mit Delta-VOC im Vergleich zu Alpha-VOC hatten eine geringere Wahrscheinlichkeit, Milchglastrübungen aufzuweisen (7/22 oder 31.8 % vs. 4/39 oder 10.3 %, $p < 0.001$), während kein signifikanter Unterschied zwischen Patienten mit Delta-VOC und ohne VOC bestand (5/25 oder 20 %; $p = 0.348$). Die mittlere Dichte der Läsionen wies keinen signifikanten Unterschied zwischen den Kohorten auf.

Zusammenfassung In dieser Studie zeigten 3 von 22 Patienten (13.6 %) mit der Delta-VOC beidseitige Rundherde oder Raumforderungen mit umgebendem Halo-Zeichen. Diese Beobachtung ist bislang nicht als relevantes Bildmuster der COVID-19-Pneumonie etabliert. Verglichen mit den anderen Kohorten präsentierte ein geringerer Anteil von Patienten mit der Delta-VOC Milchglastrübungen. Basierend auf diesen Ergebnissen könnte die Delta-VOC eine Divergenz des CT-morphologischen Phänotyps bedingen.

Kernaussagen:

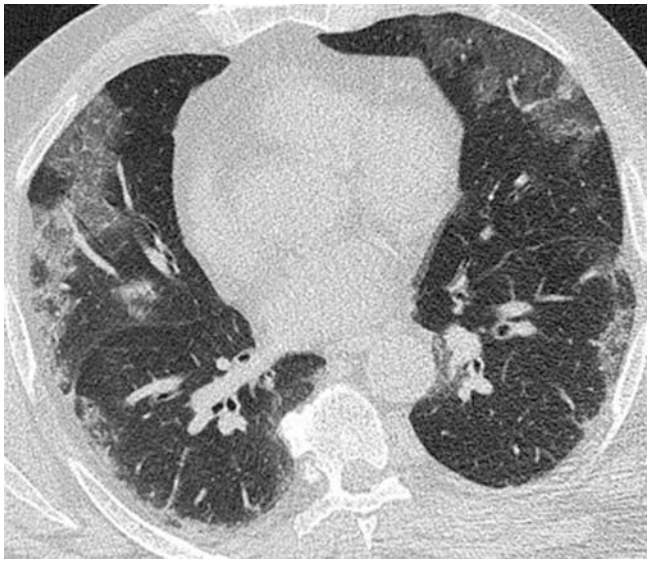
- Bisher wurde angenommen, dass CT-morphologische Zeichen einer COVID-19-Pneumonie unkontrovers etabliert sind. Demgegenüber beobachteten die Autoren eine Divergenz der Lungenveränderungen bei Patienten infiziert mit der Delta-VOC.
- Diese Veränderungen in der Bildgebung beinhalteten pulmonale Raumforderungen oder Rundherde mit umgebendem Halo-Zeichen.
- Diese Veränderungen in der Bildgebung wurden bislang nicht als typisch für eine COVID-19-Pneumonie etabliert.
- Basierend auf diesen Ergebnissen könnte die Delta-VOC eine Divergenz des CT-morphologischen Phänotyps bedingen.

Introduction

Since the outbreak of SARS-CoV-2 in December 2019, imaging morphologic signs of COVID-19 pneumonia on imaging have been studied extensively. Typical signs of SARS-CoV-2 on computed tomography (CT) have been described as bilateral ground glass opacification (GGOs) and consolidations with peripheral emphasis and multifocality as well as interlobular and intralobular septal thickening, depending on disease progression [1–5]. An exemplary CT slice with typical imaging findings in COVID-19 pneumonia is provided in ▶ **Fig. 1**. Until now, these findings have been considered well understood and present in the vast majority of patients with confirmed SARS-CoV-2 pneumonia [6–10].

In contrast to the imaging features mentioned above, nodules or round pulmonary masses with surrounding halo sign have so far been described as uncommon for COVID-19, with only a few publications even mentioning this kind of pattern on CT scans of COVID-19 patients [11–13]. Interestingly, several publications focusing on pediatric chest CT imaging for COVID-19 mention

nodules and round pulmonary masses with surrounding halo signs as possible findings [14, 15]. Aside from COVID-19, these signs are predominantly found in pulmonary fungal infections, such as pulmonary aspergillosis [12, 16]. While there are a few publications linking pulmonary aspergillosis and COVID-19 as possible coinfections (COVID-19-associated pulmonary aspergillosis, CAPA) [17–19], CAPA has been reported primarily in ICU patients and not in otherwise healthy adults.



▶ **Fig. 1** Typical morphological signs of COVID-19 pneumonia on CT with bilateral peripheral GGOs and beginning consolidations.

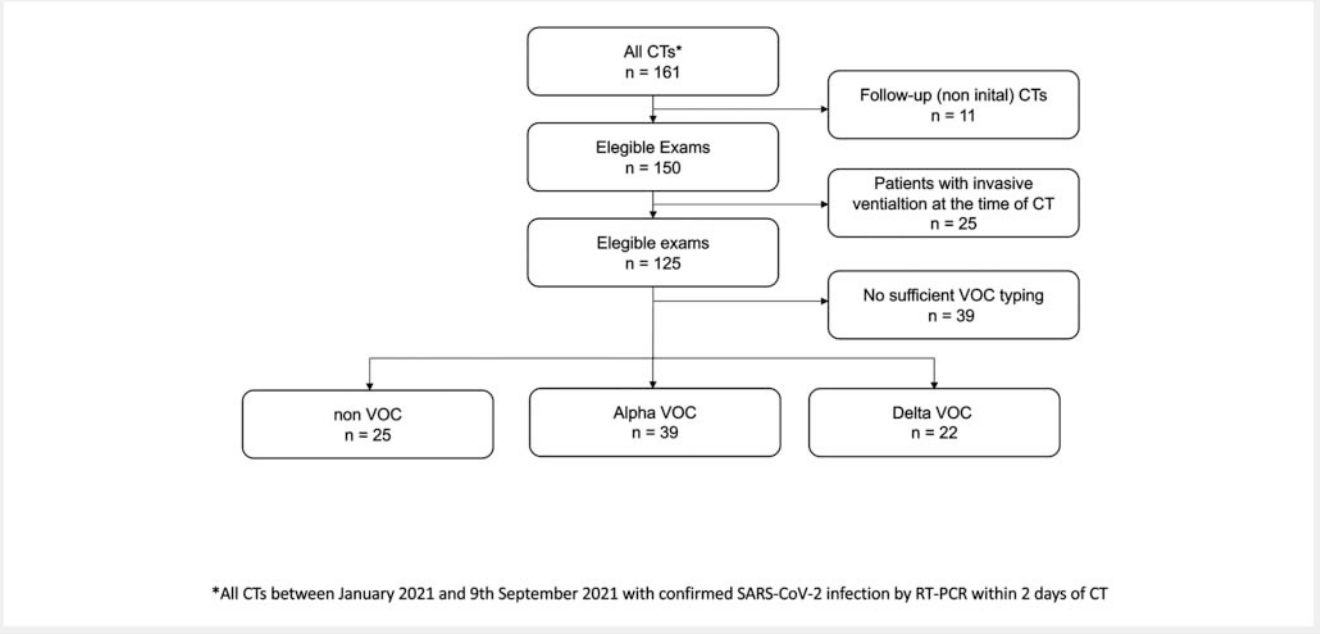
▶ **Abb. 1** COVID-19-Pneumonie-typische Zeichen in der Computertomografie mit bilateralen, peripher betonten Milchglastrübungen sowie beginnenden Konsolidierungen.

During routine clinical practice between the summer and fall of 2021, the authors observed several symptomatic, young, non-ICU COVID-19 patients who presented with multifocal nodules or round pulmonary masses with halo sign, which would otherwise have been consistent with pulmonary fungal infections, while at the same time the Delta-VOC of SARS-CoV-2 took hold (and meanwhile dominates) in the authors' geographic location. Furthermore, a higher number of patients seemed to present with lesser pulmonary alterations of the lung parenchyma on CT scans, as time progressed towards the autumn of 2021.

Our recent anecdotal findings suggest potential differences in the morphological features of COVID-19 with respect to different viral subtypes. Therefore, the aim of the study was to compare the imaging patterns of patients suffering from Delta-VOC-, Alpha-VOC and non-VOC SARS-CoV-2 pneumonia.

Material and Methods

This retrospective single-center study of a tertiary academic medical center in Germany was conducted according to the Declaration of Helsinki and the Standards for Reporting of Diagnostic Accuracy Studies (STARD) reporting guidelines for Diagnostic Accuracy Studies of the Equator Network [20]. It was approved by the local ethics committee EK 488/21. The need for informed consent was waived.



▶ **Fig. 2** STARD compliant diagram of the final cohort consisting of 86 patients after excluding follow-up CT scans (n = 11), CT scans of patients with invasive ventilation (n = 25), and CT scans of patients without sufficient VOC-typing (n = 39).

▶ **Abb. 2** STARD-konformes Diagramm der finalen Kohorte bestehend aus 86 Patienten, nachdem CT-Verlaufskontrollen (n = 11), CTs von Patienten mit invasiver Beatmung (n = 25) und CTs von Patienten mit insuffizienter Virustypisierung (n = 39) ausgeschlossen wurden.

A standardized query in the hospital database was conducted to identify all chest CT examinations of patients with positive RT-PCR within two days of CT. The time period was set from January of 2021 to September 15, 2021. The exclusion criteria were follow-up examinations of the same patient, patients under invasive ventilation at the time of CT and insufficient VOC typing (e. g., not enough specimen for sufficient viral typing). ▶ **Fig. 2** shows a flowchart of the declared inclusion and exclusion criteria. All diagnoses of SARS-CoV-2 infection for the purpose of this study have been established through reverse transcriptase polymerase chain reaction (RT-PCR) testing from nasopharyngeal or oral swabs using test kits e. g., by Altona diagnostics (Hamburg, Germany). Viral typing was performed in house.

All CT studies had been acquired with one of three CT systems (Somatom X.cite, Somatom Definition AS-40, and Definition FLASH, Siemens Medical Systems, Forchheim, Germany). Depending on the clinical condition and possible differential diagnoses at the time of examination, chest CT examinations were conducted using standardized examination protocols using either the low-dose technique (tube voltage: 80 kV) without i. v. administration of contrast agent or the full-dose technique (tube voltage: 120–140 kV) with i. v. administration of contrast agent. The tube current was automatically modulated (CareDose4 D). CT images were reconstructed with a 1-mm and 3- or 5-mm slice thickness (increment of 0.7 mm, 2 mm, and 4 mm, respectively). Patient files were reviewed for vaccination status and demographic data. All CT scans were retrospectively reviewed by a board-certified radiologist with 8 years of experience in thoracic imaging for the following criteria (▶ **Table 2–4**):

- Distribution emphasis and configuration of GGOs and consolidations, as well as mean density of representative lesions (both GGO and consolidations),
- Degree of involvement for GGOs and consolidations, documented on ordinal scales ranging from 0 (no lesions) to 3 (high involvement),
- Multifocality was assessed on ordinal scales ranging from 0 (no lesions) to 4 (predominantly confluent lesions),
- Other CT morphological signs known to be associated with atypical pneumonia, e. g.: Halo sign, vacuolar sign, intralobular reticulation, inverse halo sign, cavities, tree-in-bud sign, pulmonary noduli, pleural effusion, and nodules or round pulmonary masses with associated halo sign as a distinct category

For the purpose of this study, horizontal distribution discriminated between emphasis that was centrally located, peripherally located, and located in between. Vertical distribution discriminated between emphasis located apically, basally, and in between, corresponding to pulmonary fields in chest X-ray examinations.

The distribution of pulmonary lesions was compared between Delta-VOC, Alpha-VOC, and Non-VOC using Fisher's exact tests, Mann-Whitney U-tests (degree of involvement and degree of multifocality) and unpaired t-tests (mean density of representative GGOs and/or consolidations). All test results represent two-tailed p-values. A p-value of ≤ 0.05 was considered statistically significant.

▶ **Table 1** Detailed analysis of other CT morphological signs known to be associated with atypical pneumonia in CT of the three Delta-VOC patients with pulmonary nodules or masses with associated halo sign. This table only contains imaging alterations present in these three patients. Exemplary images are provided in ▶ **Fig. 3–5**.

▶ **Tab. 1** Detaillierte Analyse der pulmonalen Veränderungen assoziiert mit atypischen Pneumonien in der Computertomografie der 3 Patienten der Delta-VOC-Kohorte mit pulmonalen Rundherden oder Raumforderungen mit assoziiertem Halo-Zeichen. Diese Tabelle enthält nur Veränderungen, die bei diesen 3 Patienten abgrenzbar waren. Beispielbilder finden sich in ▶ **Abb. 3–5**.

Patient	1	2	3
GGOs	None	Yes	Yes
Apical emphasis	None	No	No
Basal emphasis	None	No	Yes
Vertical emphasis in between	None	Yes	No
Peripheral emphasis	None	Yes	Yes
Central	None	No	No
Horizontal emphasis in between	None	No	No
Unilateral	None	No	Yes
Bilateral	None	Yes	No
Degree of involvement	None	1	1
Degree of multifocality	None	1	1
Lobular confinement	No	Yes	Yes
Mean density (HU)		–530	–372
Consolidations	Yes	Yes	Yes
Apical emphasis	No	No	No
Basal emphasis	No	Yes	Yes
Vertical emphasis in between	No	No	No
Peripheral emphasis	Yes	Yes	Yes
Central	No	No	No
Horizontal emphasis in between	Yes	No	No
Unilateral	No	No	No
Bilateral	Yes	Yes	Yes
Degree of involvement	1	3	2
Degree of multifocality	3	4	1
Wedge-shaped	No	Yes	No
Round	Yes	Yes	Yes
Curvilinear	No	No	No
Halo sign	Yes	Yes	Yes
Round with halo sign	Yes	Yes	Yes
Mean density (HU)	–21	50	–23
Other signs			
Vacuolar sign	No	No	Yes

▶ **Table 2** Detailed analysis of GGOs stratified by viral typing. Note, that lesion distribution emphasis can occupy up to two areas.

▶ **Tab. 2** Detaillierte Analyse der Ausprägung und Verteilung der Milchglastrübungen stratifiziert nach Virustypisierung. Die Betonung der Läsionsverteilung kann bis zu 2 Regionen pro Kriterium einnehmen.

Signs in CT	DELTA-VOC		ALPHA-VOC		Non-VOC		Delta vs. Alpha p-value	Delta vs. non-VOC p-value	Alpha vs. non-VOC p-value
Sum	22		39		25				
Bland:	7/22	31.8 %	4/39	10.3 %	5/25	20.0 %	0.079	0.505	0.296
GGO	13/22	59.1 %	35/39	89.7 %	19/25	76.0 %	0.008	0.348	0.170
Apical emphasis	0/13	0.0 %	2/35	5.7 %	4/19	21.1 %	1	0.128	0.169
Basal emphasis	7/13	53.8 %	12/35	34.3 %	5/19	26.2 %	1	0.150	0.760
Vertical emphasis in between	4/13	30.8 %	16/35	45.7 %	9/19	47.4 %	1	0.471	1
Peripheral emphasis	11/13	84.6 %	28/35	80.0 %	14/19	73.7 %	1	0.667	0.730
Central	0/13	0.0 %	2/35	5.7 %	3/19	15.8 %	1	0.245	0.332
Horizontal emphasis in between	2/13	15.4 %	6/35	17.1 %	2/19	10.5 %	1	1	0.701
Unilateral	2/13	15.4 %	6/35	17.1 %	1/19	5.3 %	1	0.552	0.401
Bilateral	11/13	84.6 %	29/35	82.9 %	18/19	94.7 %	1	0.552	0.401
Degree of involvement							0.024	0.127	0.688
0	9/22	40.9 %	4/39	10.3 %	6/25	24 %			
1	4/22	18.2 %	11/39	28.2 %	5/25	20 %			
2	5/22	22.7 %	10/39	25.6 %	4/25	16 %			
3	4/22	18.2 %	14/39	35.9 %	10/25	40 %			
Degree of multifocality							0.020	0.067	0.863
0	9/22	40.9 %	6/39	15.4 %	6/25	24.0 %			
1	6/22	27.3 %	11/39	28.2 %	5/25	20.0 %			
2	1/22	4.5 %	5/39	12.8 %	2/25	8.0 %			
3	3/22	13.6 %	2/39	5.1 %	2/25	8.0 %			
4 (Confluent)	3/22	13.6 %	15/39	38.5 %	10/25	40.0 %			
Lobular confinement	10/13	76.9 %	17/35	43.6 %	10/19	40.0 %	0.107	0.267	1
Mean density (HU)	–431.5		–416.1		–488.2		0.736	0.225	0.072
SD (HU)	127.2		142.8		127.3				

▶ **Table 3** Detailed analysis of consolidations stratified by viral typing. Note, that lesion distribution emphasis can occupy up to two areas.

▶ **Tab. 3** Detaillierte Analyse der Ausprägung und Verteilung der Konsolidierungen stratifiziert nach Virustypisierung. Die Betonung der Läsionsverteilung kann bis zu 2 Regionen pro Kriterium einnehmen.

Signs in CT	DELTA-VOC		ALPHA-VOC		Non-VOC		Delta vs. Alpha p =	Delta vs. non-VOC p =	Alpha vs. non-VOC p =
Sum	22		39		25				
Bland:	7/22	31.8 %	4/39	10.3 %	5/25	20.0 %	0.079	0.50	0.296
Consolidations	13/22	59.1 %	24/39	61.5 %	14/25	56.0 %	1	1	0.795
Apical emphasis	1/13	7.7 %	0/24	0.0 %	2/14	14.3 %	0.351	1	0.129
Basal emphasis	10/13	76.9 %	20/24	83.3 %	6/14	42.9 %	0.678	0.120	0.014
Vertical emphasis in between	0/13	0.0 %	4/24	16.7 %	6/14	42.9 %	0.276	0.016	0.127
Peripheral emphasis	12/13	92.3 %	23/24	95.8 %	13/14	92.9 %	1	1	1
Central	1/13	7.7 %	0/24	0.0 %	1/14	7.1 %	0.351	1	0.368
Horizontal emphasis in between	1/13	7.7 %	3/24	12.5 %	0/14	0.0 %	1	0.480	0.283
Unilateral	2/13	15.4 %	7/24	29.2 %	3/14	21.4 %	0.446	1	0.715
Bilateral	11/13	84.6 %	17/24	70.8 %	11/14	78.6 %	0.446	1	0.715
Degree of involvement							0.942	0.973	0.965
0	9/22	40.9 %	15/39	38.5 %	11/25	44.0 %			
1	9/22	40.9 %	18/39	46.2 %	8/25	32.0 %			
2	3/22	13.6 %	3/39	7.7 %	4/25	20.0 %			
3	1/22	4.5 %	3/39	7.7 %	1/25	4.0 %			
Degree of multifocality							0.994	0.737	0.704
0	10/22	45.5 %	18/39	46.2 %	13/25	52.0 %			
1	8/22	36.4 %	14/39	35.9 %	7/25	28.0 %			
2	2/22	9.1 %	2/39	5.1 %	4/25	16.0 %			
3	1/22	4.5 %	3/39	7.7 %	0/25	0,0 %			
4 (confluent)	1/22	4.5 %	2/39	5.1 %	1/25	4.0 %			
Wedge-shaped	9/13	69.2 %	14/24	58.3 %	12/14	85.7 %	0.724	0.385	0.147
Curvilinear	4/13	30.8 %	14/24	58.3 %	6/14	42.9 %	0.170	0.695	0.503
Round	4/13	30.8 %	4/24	16.7 %	0/14	0.0 %	0.413	0.041	0.276
Halo sign	3/13	23.1 %	10/24	41.7 %	6/14	42.9 %	0.305	0.420	1
Mean density (HU)	−8.9		−0.3		−4.07		0.776	0.887	0.881
SD (HU)	104.6		76.1		69.1				

▶ **Table 4** Detailed analysis of other CT morphological signs known to be associated with atypical pneumonia in CT stratified by viral typing.

▶ **Tab. 4** Detaillierte Analyse der Ausprägung der übrigen pulmonalen Veränderungen assoziiert mit atypischen Pneumonien in der Computertomografie stratifiziert nach Virustypisierung.

Signs in CT	DELTA-VOC		ALPHA-VOC		Non-VOC		Delta vs. Alpha p =	Delta vs. non-VOC p =	Alpha vs. non-VOC p =
Sum	22		39		25				
Bland:	7/22	31.8 %	4/39	10.3 %	5/25	20.0 %	0.079	0.505	0.296
Consolidations exclusively	2/22	9.1 %	0/39	0.0 %	1/25	4.0 %	0.126	0.593	0.391
GGOs exclusively	2/22	9.1 %	11/39	28.5 %	6/25	24.0 %	0.109	0.253	0.778
Predominantly GGOs	11/22	50.0 %	21/39	53.8 %	16/25	64.0 %	0.796	0.386	0.450
Intralobular reticulation	7/22	31.8 %	22/39	56.4 %	15/25	60.0 %	0.108	0.080	0.801
Inverse halo	0/22	0.0 %	0/39	0.0 %	0/25	0.0 %	1	1	1
Cavity	0/22	0.0 %	0/39	0.0 %	0/25	0.0 %	1	1	1
Tree in bud	0/22	0.0 %	0/39	0.0 %	0/25	0.0 %	1	1	1
Nodules	0/22	0.0 %	3/39	7.7 %	1/25	4.0 %	0.547	1	1
Pleural effusion	2/22	9.1 %	10/39	25.6 %	8/25	32.0 %	0.182	0.079	0.584
Vacuolar sign	9/22	40.9 %	20/39	51.3 %	12/25	48.0 %	0.594	0.770	1
Round consolidations with surrounding halo sign	3/22	13.6 %	0/39	0.0 %	0/25	0.0 %	0.043	0.095	1

Results

161 CT scans of 150 patients met the inclusion criteria of the standardized query. Of these, 11 follow-up examinations, 25 CT scans of patients under invasive ventilation, and 39 CT scans of patients without sufficient viral typing were excluded due to the aforementioned criteria. Therefore, the final cohort consisted of 86 patients. Hereof, 22/86 (26 %) were infected with the Delta-VOC, 39/86 (45 %) were infected with the Alpha-VOC, and 24/86 (28 %) had SARS-COV-2 infections inconsistent with any known VOC (Non-VOC SARS-CoV-2). The mean age in the Delta-VOC cohort was 49.1 (± 13.6) years, whereas the mean age in the Alpha-VOC and Non-VOC cohorts was significantly older, with 60.8 years (± 17.5) and 68.0 years (± 15.6), respectively (Delta-VOC vs. Alpha-VOC cohorts: $p = 0.016$, Delta-VOC vs. non-VOC cohorts: $p < 0.001$, Alpha-VOC vs. Non-VOC cohorts: $p = 0.048$). As ICU patients had been excluded from this study, all patients were either admitted to the emergency department or normal wards at the time of CT.

Nodules or round pulmonary masses with associated halo signs in Delta-VOC patients

3 of 22 patients (13.6 %) with the Delta-VOC presented with multiple nodules and or round pulmonary masses with associated halo signs. This pattern was found neither in patients with the Alpha-VOC (0/39) nor in the non-VOC cohort (0/25). While this difference was statistically significant when the Delta-VOC cohort was compared to the Alpha-VOC cohort ($p = 0.043$), no significant difference could be observed for Delta-VOC vs. non-VOC ($p = 0.095$) and Alpha-VOC vs. Non-VOC ($p = 1$). Representative CT slices of all three patients are provided in ▶ **Fig. 3–5** (note that two of these patients did not display any of the aforementioned pulmonary findings commonly found in COVID-19 patients). While four patients in the Alpha-VOC cohort demonstrated somewhat round-shaped pulmonary alterations, these were either GGOs or consolidations without associated halo signs. All of the three respective Delta-VOC patients were not documented to be under any kind of immune suppression and were otherwise healthy with no underlying conditions conducive to pulmonary fungal infections. These patients were younger than 30 years (24, 27, 28). None of these patients were admitted to an ICU but were discharged after a few days of observation. A detailed descriptive analysis of their pulmonary lesions is provided in ▶ **Table 1**.

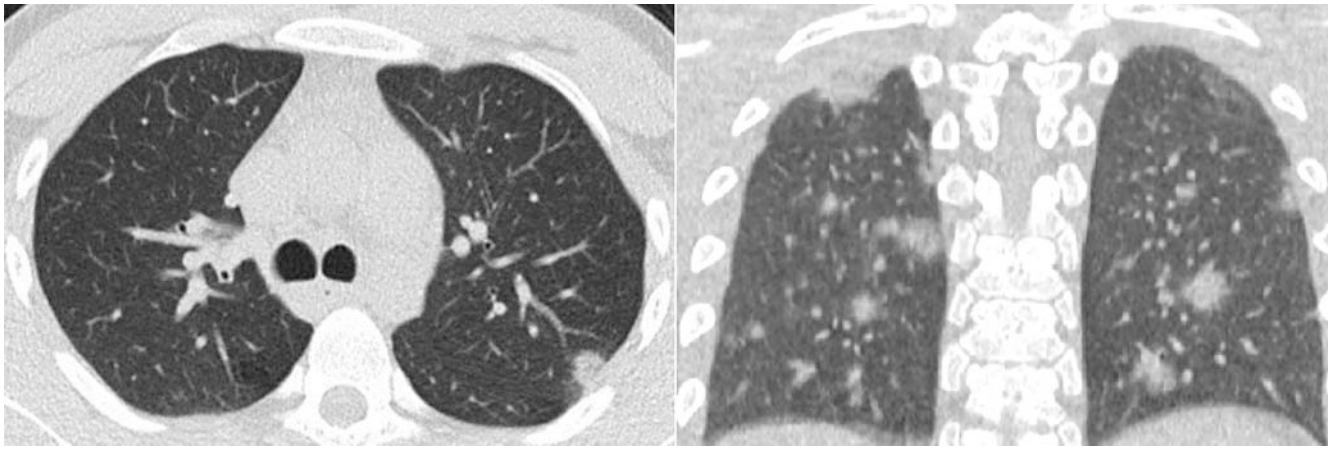
Under disregard of a possible halo sign, the proportion of patients with nodules or round pulmonary masses (as a subgroup of consolidations) was 4/13 in the Delta-VOC group, 4/24 in the Alpha-VOC group and 0/14 in the non-VOC group. This amounted to a statistically significant difference between the Delta-VOC and non-VOC cohort ($p = 0.041$). No statistically significant difference had been observed between the Alpha-VOC vs. Delta-VOC cohort ($p = 0.413$) or Alpha-VOC vs. non-VOC cohort ($p = 0.276$). Detailed results are provided in ▶ **Table 2–4**.

Delta-VOC patients presented with a lesser degree of pulmonary findings

Compared with Alpha-VOC, patients with Delta-VOC were more likely to have no depictable ground glass opacities on CT scans (Delta-VOC: 9/22 or 41.9 % vs. Alpha-VOC: 4/39 or 10.3 %; $p = 0.008$). While a higher proportion of patients without GGOs in the Delta-VOC cohort compared to the non-VOC cohort were observed, this was not statistically significant (9/22 or 41.9 % vs. 6/25 or 24 %; $p = 0.348$). Delta-VOC patients showed significantly fewer GGOs as well as fewer multifocal lesions when compared to the Alpha-VOC cohort ($p = 0.024$ and $p = 0.002$, respectively).

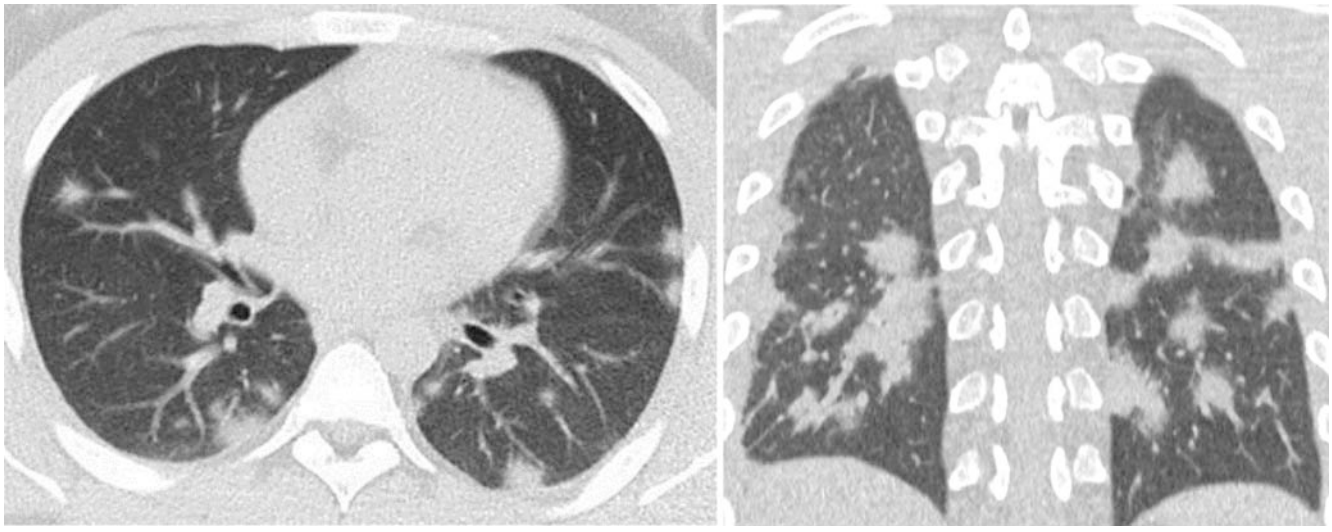
Differences in lesion distribution

Alpha-VOC consolidations manifested more often with basal emphasis when compared to non-VOC (20/24 or 83.3 % vs. 5/13 or 38.5 %; $p = 0.014$). In the Delta-VOC cohort consolidations presented more often with vertical emphasis in between basal and



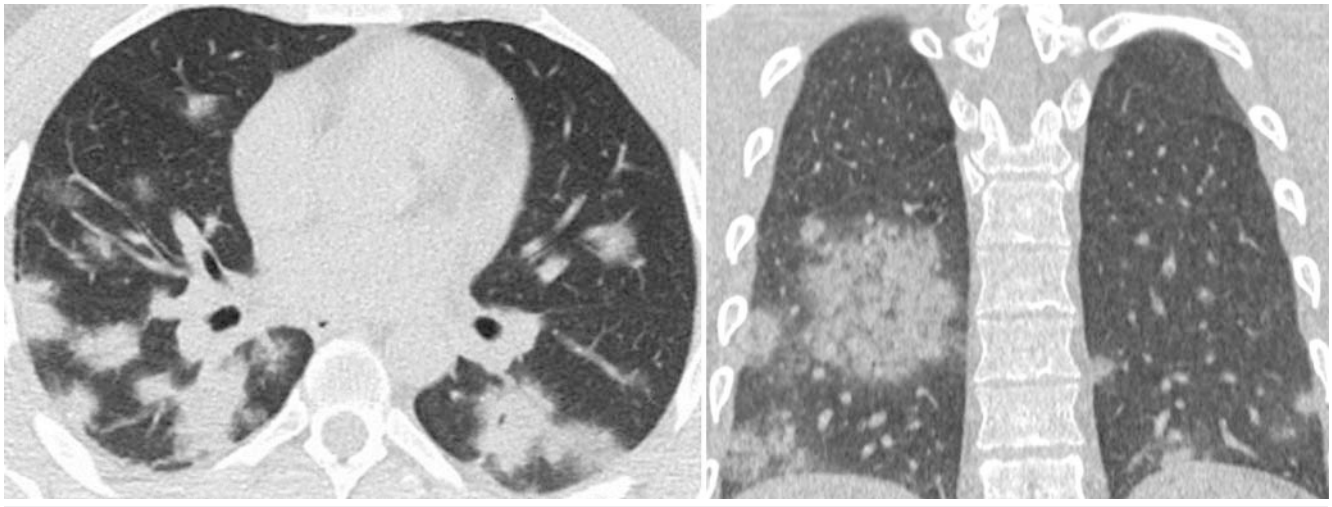
▶ **Fig. 3** First Delta-VOC SARS-CoV-2 patient presenting with multiple nodules or round pulmonary masses with surrounding halo sign. These findings were bilateral and of varying diameter (not depicted in this slice).

▶ **Abb. 3** CT des ersten Patienten mit der SARS-CoV-2 Delta-Variante mit multiplen rundlichen Konsolidierungen und umgebendem Halo-Zeichen. Diese Veränderungen waren bilateral und in unterschiedlicher Größenausdehnung nachweisbar (nicht in diesem axialen Schnitt abgebildet).



▶ **Fig. 4** Multiple bilateral nodules or round pulmonary masses with surrounding halo sign of varying diameter in the second Delta-VOC SARS-CoV-2-positive patient.

▶ **Abb. 4** Multiple, bilaterale, rundliche Konsolidierungen mit umgebenden Halo-Zeichen unterschiedlicher Größenausdehnung in der CT des zweiten Patienten mit der SARS-CoV-2 Delta-Variante.



▶ **Fig. 5** Third Delta-VOC SARS-CoV-2 patient presenting with multiple bilateral and unambiguous nodules or round pulmonary masses with surrounding halo sign, varying greatly in diameter.

▶ **Abb. 5** CT des dritten Patienten mit der SARS-CoV-2 Delta-Variante mit multiplen, bilateralen und eindeutig runden Konsolidierungen mit umgebendem Halo-Zeichen, welche deutlich in ihrem Durchmesser variierten.

apical when compared to non-VOC consolidations (0/13 or 0 % vs. 6/14, respectively p = 0.016). Furthermore, consolidations in the Delta-VOC cohort were less often centrally emphasized than in the non-VOC cohort (0/13 or 0 % vs. 6/13 or 46.2 %; p = 0.016). Detailed results are provided in ▶ **Table 2–4**.

Density of pulmonary findings is comparable across all cohorts

Mean Hounsfield-Units (HU) in representative lesions were comparable in all three groups: The mean density of GGOs in the Delta-VOC was -416.1 HU [± 142.8], –431.5 HU [± 127.2] in Alpha-VOC and –488.2 HU [± 127.3] in non-VOC patients (Alpha-VOC vs. Delta-VOC p = 0.736; Delta-VOC vs. non-VOC p = 0.225; Alpha-VOC vs. non-VOC p = 0.072). The mean density of representative consolidations was -0.3 HU [± 76.1] in the Alpha-VOC cohort, –8.9 HU [± 105.0] in the Delta-VOC cohort, and –4.1 HU [± 69.1] in non-VOC (Alpha-VOC vs. Delta-VOC p = 0.776.; Delta-VOC vs. non-VOC p = 0.887; Alpha-VOC vs. non-VOC p = 0.881). Detailed results are provided in ▶ **Table 2–4**.

Vaccination status across the cohorts

In general, a relatively small proportion of patients were partially or fully vaccinated (10 out of 86 patients or 11.6 %).

Delta-VOC cohort

Three patients (3/22 or 13,6 %) of the Delta-VOC cohort were fully vaccinated (as determined by the initial vaccination protocol of European Medical Agency approved SARS-CoV-2 vaccines), with two of them displaying no pathological lung changes on CT. One patient (1/22 or 4.5 %) was partially vaccinated and displayed pathological lung changes. None of these patients displayed nodules or pulmonary masses with associated halo sign. 18 patients (18/22 or 81.8 %) were not vaccinated or had no documented status of vaccination. Five of these patients (5/22 or 22.7 %) did not show any pathological lung changes on CT.

Alpha-VOC cohort

One patient in the Alpha-VOC cohort was fully vaccinated (1/39 or 2.6 %) but displayed pathological lung changes on CT. Three patients (3/39 or 7.7 %) of the Alpha-VOC cohort were partially vaccinated, with three patients demonstrating pathological lung changes. 35 patients (35/39 or 89.7 %) were not vaccinated or had no documented status of vaccination. Four of these patients did not show any pathological lung changes on CT.

Non-VOC cohort

23 patients (23/25 or 92.0 %) of the non-VOC cohort had no documented status of vaccination or were not vaccinated. Five of these patients (5/25 or 20 %) had no pathological lung changes on CT. No patient was documented to be partially vaccinated. Two patients (2/25 or 8.0 %) were fully vaccinated, with one of them demonstrating no pathological lung changes. Details for the vaccinated patients are provided in ▶ **Table 5**.

Overall, despite increasing vaccination rates over the course of the pandemic, there were no relevant differences in the vaccination rates of the patients between these cohorts.

Discussion

In this observational study, the imaging phenotypes in cohorts of different virus types of SARS-CoV-2, namely Delta-VOC, Alpha-VOC, and non-VOC, were investigated. Especially nodules or round pulmonary masses with surrounding halo sign were found in a subset of patients in the Delta-VOC cohort, whereas other SARS-CoV-2 genotypes did not show this imaging pattern.

These findings have previously been reported to be uncommon in patients with SARS-CoV-2 infections and are predominantly found in invasive pulmonary aspergillosis [12, 16]. The only noteworthy records are recent publications on ICU patients with COVID-19 pneumonia and co-infections of invasive aspergillosis (CAPA). Contrary to the otherwise healthy patients of our study, patients with CAPA mostly suffer from a critically ill condition or have a compromised immune status [9–11]. Although fungal co-infections have not been ruled-out, manifestation of invasive aspergillosis seems rather unlikely in the otherwise healthy and immune-competent Delta-VOC patients of this study. Until now, no reported cases of aspergillosis and SARS-CoV-2 co-infection in mild to medium cases in adults have been described. Interestingly, there have been reports of series of cases with similar findings in pediatric chest CT scans of patients with confirmed SARS-CoV-2 infection [11, 14, 15]. In addition to this, predominantly round-shaped consolidations (with or without associated halo sign) became generally more common as VOC predominance shifted from Non-VOC (0 %) to Alpha-VOC (16.7 %) and finally to Delta-VOC (30.8 %). The results of our study, therefore, suggest that there may be ongoing alterations in the morphological features of Delta-VOC on CT.

In addition to the discussed alterations, it has also become apparent that there was an overall lesser extent of pulmonary changes in the Delta-VOC cohort compared to the Alpha-VOC and Non-VOC cohorts. A higher proportion of patients with no depictable GGOs was found in the Delta-VOC vs. Alpha-VOC cohort (31.8 % vs. 10.3 %; $p = 0.008$). Furthermore, Delta-VOC patients had a lower mean degree of involvement and multifocality of pulmonary findings compared to patients of the Alpha-VOC cohort ($p = 0.024$ and $p = 0.020$, respectively). While these findings seem intriguing, there are few likely explanations for this. On the one hand, it might be explained by a slightly increased number of fully vaccinated patients. However, the vaccination rate was rather low in all of the examined cohorts (Delta-VOC: 13.6 % vs. Alpha-VOC: 2.6 % vs. non-VOC 8 %). On the other hand, patients with Delta-VOC infections were significantly younger compared to the other two groups with a mean age of 49.1 (± 13.6) years in the Delta-VOC cohort versus 60.8 years (± 17.5) in the Alpha-VOC cohort, and 68.0 years (± 15.6) in the non-VOC cohort. This might influence the observed findings. Older patients, who are more susceptible to a severe disease progression, were prioritized for vaccination in Germany [21]. This may have led to a lower hospitalization rate of such patients, reducing the average age of hospitalized patients. The fact that younger patients generally exhibit a more benign clinical course of SARS-CoV-2 infections has already been established in a variety of studies [11, 22]. This suggests that the lesser pulmonary involvement may be caused by a selection bias. Nevertheless, based on the present study, it cannot be excluded that patients with Delta-VOC infection may reveal less depictable pulmonary changes on CT, which thus could have impact on the relevance of CT for certain clinical indications. Of course, further studies with higher patient numbers are required to resolve this issue.

When vertical consolidation distribution was compared, consolidations in the Delta-VOC cohort manifested less often in locations that correspond to the pulmonary middle field than non-VOC patients ($p = 0.016$). Also, patients in the Alpha-VOC presented more often with basally emphasized consolidations, when compared to non-VOC patients ($p = 0.014$).

This study has several limitations that need to be mentioned. Firstly, due to the strict exclusion criteria and narrow time windows for the (transiently) predominant SARS-CoV-2 variants, the number of patients enrolled in this study is relatively low. Therefore, statistical considerations must be interpreted with care. This might have contributed to the fact that no statistically significant difference between the Delta-VOC and Non-VOC cohort

▶ **Table 5** Detailed analysis of other CT morphological signs known to be associated with atypical pneumonia on CT of patients vaccinated against SARS-CoV-2.

▶ **Tab. 5** Detaillierte Analyse der pulmonalen Veränderungen assoziiert mit atypischen Pneumonien in der Computertomografie der gegen SARS-CoV-2 geimpften Patienten.

Vaccinated patients										
Patient	**Delta-VOC 1**	**Delta-VOC 2**	**Delta-VOC 3**	**Delta-VOC 4**	**Alpha-VOC 1**	**Alpha-VOC 2**	**Alpha-VOC 3**	**Alpha-VOC 4**	**Non-VOC 1**	**Non-VOC 2**
Vaccination status	Complete	Complete	Complete	Partial	Complete	Partial	Partial	Partial	Complete	Complete
GGOs	None	None	None	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Apical emphasis		None	None	No	No	No	No	No	Yes	No
Basal emphasis	None	None	None	No	No	No	No	No	No	No
Vertical emphasis in between	None	None	None	No	Yes	Yes		Yes	No	Yes
Peripheral emphasis	None	None	None	Yes	Yes	No	No	Yes	No	No
Central	None	None	None	No	No	Yes	No	No	Yes	Yes
Horizontal emphasis in between	None	None	None	No	No	No	Yes	No	No	No
Unilateral	None	None	None	No	No	No	No	No	No	No
Bilateral	None	None	None	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Degree of involvement	None	None	None	2	2	1	1	3	2	1
Degree of multifocality	None	None	None	4	4	None	1	4	3	None
Lobular confinement	None	None	None	Yes	No	No	Yes	No	No	Yes
Mean density (HU)	None	None	None	−565	−595	−398	−634	−272	−415	−664
Consolidations	None	None	Yes	Yes	None	None	None	Yes	Yes	None
Apical emphasis	None	None	Yes		None	None	None	Yes		None
Basal emphasis	None	None	No	Yes	None	None	None	No	Yes	None
Vertical emphasis in between	None	None	No	No	None	None	None	No	Yes	None
Peripheral emphasis	None	None	Yes	Yes	None	None	None	Yes	Yes	None
Central	None	None	No	No	None	None	None	No	No	None
Horizontal emphasis in between	None	None	No	No	None	None	None	No	No	None
Unilateral	None	None	No	No	None	None	None	No	No	None
Bilateral	None	None	Yes	Yes	None	None	None	Yes	Yes	None
Degree of involvement	None	None	2	1	None	None	None	3	1	None
Degree of multifocality	None	None	1	None	None	None	None	4	1	None
Wedged-shaped	None	None	Yes	No	None	None	None	No	Yes	None
Round	None	None	No	No	None	None	None	No	No	None

▲ **Table 5** (Continuation)

Vaccinated patients									
Patient	**Delta-VOC 1**	**Delta-VOC 2**	**Delta-VOC 3**	**Delta-VOC 4**	**Alpha-VOC 1**	**Alpha-VOC 2**	**Alpha-VOC 3**	**Alpha-VOC 4**	**Non-VOC 1**	**Non-VOC 2**
Curvilinear	None	None	No	Yes	None	None	None	No	Yes	None
Halo sign	None	None	No	No	None	None	None	Yes	No	None
Round with Halo sign	None	None	No	No	None	None	None	No	No	None
Mean density (HU)	None	None	60	-230	None	None	None	80	15	None
Predominantly GGOs	None	None	No	Yes	Yes	No	Yes	No	Yes	None
Intralobular reticulation	None	None	No	Yes	Yes	None	Yes	Yes	Yes	None
GGOs exclusively	None	None	Yes	No	Yes	No	No	Yes	Yes	None
Nodules	None	None	None	None	None	None	Yes	Yes	None	None
Pleural effusion	None	None	Yes	None	None	None	None	Yes	Yes	None
Vacuolar sign	None	None	None	Yes	Yes	None	Yes	Yes	None	None

regarding the presence of pulmonary nodules or masses with surrounding halo sign had been observed, even though this pattern was exclusively found in the Delta-VOC cohort (p = 0.095). Since only non-VOC patients with available viral typing were to be included (which was established as additional diagnostics at the time of transition between Non-VOC SARS-CoV-2 and SARS-CoV-2 Alpha-VOC), a relatively low number of patients met the inclusion criteria in the Non-VOC cohort. Secondly, as already mentioned, the mean age of patients included in the study decreased steadily during the transition from Non-VOC to Alpha-VOC and finally to Delta-VOC predominance in the authors' geographic location, probably caused by an underlying selection bias. Finally, Delta-VOC patients presenting with nodules or round pulmonary masses and surrounding halo sign were not tested for fungal infection. While, to the knowledge of the authors, CAPA has not been reported in non-ICU cases, it remains a possible differential diagnosis, yet seems unlikely in this cohort.

Conclusion

During the course of the pandemic, mutations in the SARS-CoV-2 virus may have led to potential alterations in the CT imaging patterns. This first-of-its-kind observational study detected a pattern in a relevant number of patients with Delta-VOC that had not been observed in Alpha-VOC and non-VOC. This appearance with nodules or round pulmonary masses with halo resembles patterns seen in invasive aspergillosis and should not be misinterpreted as such. Larger studies are needed to confirm these changes.

Conflict of Interest

The authors declare that they have no conflict of interest.

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