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Article - Version of Record

Suggested Citation:
Steuwe, A., Ljimani, A., Andrée, M., Wienemann, T. H. G., Lübke, N., Walker, A., Jensen, B.-E., The Racoon Study Group, Radke, K. L., Antoch, G., & Valentin, B. (2024). Disease Course and Pulmonary Involvement of COVID-19 during the Delta Variant Period in Germany: A Comparative Study of Vaccinated and Unvaccinated Patients at a Tertiary Hospital. Current Medical Imaging, 20, Article e15734056282920. https://doi.org/10.2174/0115734056282920231212104602

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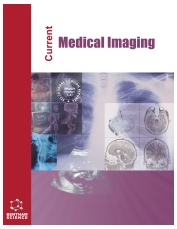

RESEARCH ARTICLE

Disease Course and Pulmonary Involvement of COVID-19 during the Delta Variant Period in Germany: A Comparative Study of Vaccinated and Unvaccinated Patients at a Tertiary Hospital

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Abstract:

Background:

Despite the availability of vaccines, there is an increasing number of SARS-CoV-2-breakthrough-infections.

Objective:

The aim of this study was to determine whether there is a radiological difference in lung parenchymal involvement between infected vaccinated and unvaccinated patients. Additionally, we aimed to investigate whether vaccination has an impact on the course of illness and the need for intensive care.

Methods:

This study includes all patients undergoing chest computed tomography (CT) or x-ray imaging in case of a proven SARS-CoV-2 infection between September and November 2021. Anonymized CT and x-ray images were reviewed retrospectively and in consensus by two radiologists, applying an internal severity score scheme for CT and x-ray as well as CARE and BRIXIA scores for x-ray. Radiological findings were compared to vaccination status, comorbidities, inpatient course of the patient's illness and the subjective onset of symptoms.

Results:

In total, 38 patients with acute SARS-CoV-2 infection underwent a CT scan, and 168 patients underwent an x-ray examination during the study period. Of these, 32% were vaccinated in the CT group, and 45% in the x-ray group. For the latter, vaccinated patients exhibited significantly more comorbidities (cardiovascular ($p=0.002$), haemato-oncological diseases ($p=0.016$), immunosuppression ($p=0.004$)), and a higher age ($p<0.001$). Vaccinated groups showed significantly lower extent of lung involvement (severity scores in CT cohort and x-ray cohort both $p\leq0.020$; ARDS 42% in unvaccinated CT cohort *vs*. 8% in vaccinated CT cohort). Furthermore, vaccinated patients in the CT cohort had significantly less need for intensive care treatment ($p=0.040$).

Conclusion:

Our data suggest that vaccination, in the case of breakthrough infection, favours a milder course of illness concerning lung parenchymal involvement and the need for intensive care, despite negative predictors, such as immunosuppression or other pre-existing conditions.

Keywords: ARDS, COVID-19, CT, X-ray, Genome sequencing, Viral infection.

Article History	Received: October 23, 2023	Revised: November 29, 2023	Accepted: December 06, 2023

1. INTRODUCTION

The COVID-19 pandemic has posed a significant global health threat, with over 770 million cases and nearly 7 million deaths reported worldwide as of November 2023 [1].

The clinical spectrum of COVID-19 ranges from asymptomatic or mild disease to severe respiratory illness with acute respiratory distress syndrome (ARDS) and death. The severity of COVID-19 can be judged based on the hospitalization rate, the need for additional oxygen supply, or the occurrence and severity of disease-related lung changes. Involvement of lung parenchyma is a common imaging feature of COVID-19, which is typically assessed using chest computed tomography (CT) or x-rays [2 - 7]. The severity of lung involvement is associated with the severity of the disease and the risk of mortality [8, 9]. Furthermore, there are various comorbidities considered as negative predictors for the course of COVID-19, like cardiovascular, haemato-oncological diseases, immunosuppression or obesity [10].

To control the spread of the virus and mitigate its impact on public health, vaccination has emerged as a critical tool in the fight against COVID-19. According to the WHO, about 13.5 billion doses of vaccines have been administered worldwide by November 2023 [1]. Vaccines have been identified as an effective strategy to control the spread of the virus and reduce the burden of COVID-19. The effectiveness of COVID-19 vaccination has been demonstrated in several studies, which have shown that vaccination reduces the risk of infection, hospitalization, and death [11, 12]. For what period of time and to what extent a vaccination offers protection depends on the vaccine and the body's immune system [13].

Several large-scale clinical trials have demonstrated the efficacy of COVID-19 vaccines in preventing symptomatic infections and severe illness. For example, a phase 3 trial of the Pfizer-BioNTech mRNA vaccine found that it was 95% effective in preventing symptomatic COVID-19 infections [14]. Similarly, a phase 3 trial of the Moderna mRNA vaccine reported an efficacy of 94.1% in preventing symptomatic infections [15]. In addition, a phase 3 trial of the AstraZeneca-Oxford adenovirus vector vaccine found that it was 70.4% effective in preventing symptomatic infections [16]. The efficacy of COVID-19 vaccines in preventing severe disease, hospitalization and deaths has also been demonstrated in real-world settings [15, 17, 18]. A study of healthcare workers in Israel found that the Pfizer-BioNTech vaccine was effective in preventing symptomatic COVID-19 infections, in preventing hospitalization, and in preventing severe illness [18].

It is being discussed whether breakthrough infections correlate with antibody titres. As with other vaccinations, antibody titres decline over time [19]. This is the reason why a booster vaccination for SARS-CoV-2 has been recommended in vaccinated patients at an average time of about three months following full vaccination. Again, booster vaccinations are common in most vaccinations, such as hepatitis B, tetanus, pertussis, and diphtheria vaccinations [20 - 22]. Either a fixed vaccination period or a specific antibody titre is set for indication of the booster vaccination in those cases [22]. In addition to a decrease in titres over time, there are several parameters that influence vaccine efficacy, *e.g.*, age, obesity, behavioural factors, underlying diseases, or immunomodulating therapy [23, 24]. Studies indicate that the efficacy of COVID-19 vaccines may be reduced in this population, who may be at increased risk of severe disease and poor clinical outcomes [23].

Some of these patients require several booster vaccinations to achieve an adequate antibody titre [23, 25]. This is true for patients with medication-associated immunosuppression, for example, in the context of organ transplantation, and for patients with underlying diseases, such as congenital immune deficiencies or acquired immunosuppressive diseases, such as HIV [25].

New virus variants pose another challenge to the effectiveness of vaccines developed so far [26 - 28]. The mutations in the spike protein may affect the efficacy of the vaccines developed so far, as they include the spike protein as a key component [29]. The Delta variant and Omicron variant are two of the more concerning variants of the SARS-CoV-2 virus that cause COVID-19. Studies have shown that the Omicron variant has more mutations in the spike protein compared to other variants, a significantly increased rate of transmission compared to previous variants and is associated with a higher risk of breakthrough infections [4, 27, 30 - 33]. Although vaccination does not completely prevent a breakthrough infection with the coronavirus, immunization reduces the risk of contagion and the severity of coronavirus disease [4, 34, 35]. When a point has been reached where vaccinations ensure a mild course of the disease, even in pre-diseased patients, and infection transmissions are also reduced, then one can speak of a success that helps in managing pandemics.

The purpose of this study was to determine whether there is a radiological difference in lung parenchymal involvement between SARS-CoV-2-infected vaccinated and unvaccinated patients. Additionally, we aimed to investigate whether vaccination has an impact on the course of illness and the need for intensive care treatment. This information will be crucial for public health policymakers in making evidence-based decisions on a) COVID-19 vaccination strategies, b) the need for booster vaccination, especially in pre-diseased patients, and c) future management of pandemics.

2. MATERIALS AND METHODS

2.1. Sample and Data

Adult patients with confirmed SARS-CoV-2 infection who presented to University Hospital Düsseldorf, Germany, between September and November 2021 were included in this study if lung imaging (CT or x-ray) had been performed in the local radiology department. Patients were either admitted to the hospital *via* the local emergency department or transferred from another hospital. All SARS-CoV-2 infections were regularly monitored by quantitative polymerase chain reaction

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(qPCR) during their hospital stay, along with the screening test in the emergency room and a follow-up for viral load determination and disease status in the inpatient setting. All patients with confirmed SARS-CoV-2 infection, imaging (CT and/or chest x-ray) and with or without COVID-19 vaccination were included. Patients with unknown vaccination status were excluded.

2.2. Measures of Variables

All clinical and epidemiologic data were taken from the local hospital information system (Medico, CGM, Koblenz, Germany). The vaccination status, the vaccination manufacturer, the number of vaccinations and the last vaccination date were documented for all patients. Complete vaccination protection (based on the declarations of the health authorities) was defined as double vaccination (except for Janssen, Johnson & Johnson) and a passed time period of at least 14 days after the second vaccination. In patients vaccinated with the Johnson & Johnson product and in those with previous SARS-CoV-2 infection, 14 days after one vaccination were considered fully vaccinated. Pre-existing conditions of the cardiovascular system, diabetes mellitus, obesity, haemato-oncological diseases, or existing potential immunosuppression were evaluated for all patients. The subjective onset of symptoms, the symptoms, and the date of the respective radiological examination were considered. The inpatient course of the patients' illness (normal ward or intensive care unit (ICU)), the date of death in the event of a death, and the presence of an ARDS were recorded.

CT and x-ray examinations covering the lung were assessed. The time interval between imaging and subjective symptom-onset was documented if symptom onset could be defined. CT contrast agents containing iodine were only given if indicated, *e.g*., in case of a suspected pulmonary artery embolism or abscess formation. All images were taken from the local image archive (PACS, Sectra, Linköping, Sweden) and were pseudonymized. CT images were performed on one of three CT scanners (Somatom Definition Flash, Somatom Definition Edge, Somatom Definition AS, all Siemens Healthineers, Forchheim, Germany). In case of more than one CT per individual patient, the first CT was evaluated to have a better comparability between the groups. Usually, findings on the initial CT are not as biased as findings on follow-up CTs are (by either an initialized treatment or a worsening of symptoms in case of a complex case). All x-ray images were performed on mobile x-ray units Mobilett Elara Max, Mobilett Mira Max, and Mobilett Mira (all Siemens Healthineers, Forchheim, Germany) or FDR Go Plus (FujiFilm, Tokyo, Japan). In case a patient received several x-ray examinations during the COVID-19 treatment, the first one was evaluated. The radiation exposure of all CT- and x-ray examinations was obtained from the institutional dose management system (DoseTrack, Sectra, Linköping, Sweden). For CT, the volumetric CT dose index ($CTDI_{vol}$, in mGy) and the dose length product (DLP, in mGycm) were documented; for x-ray imaging, the dose area product (DAP, in $cGycm^2$) was noted.

Isolation of viral RNA from respiratory samples and quantification of SARS-CoV-2 by the cobas® SARS-CoV-2 test on the cobas®6800 system (Roche) or by the SARS-CoV-2 test on the NeuMoDx™ platform (Qiagen) with a plasmid-standard for quantification was performed as previously described [36]. SARS-CoV-2 whole genome sequencing was performed by Nanopore sequencing based on the Artic protocol as described previously [37].

2.3. Data Analysis Procedure

The image data sets were evaluated in consensus by two medical examiners (B.V., assistant physician (radiology), 4 years of professional experience; A.L., board certified radiologist, 7 years of professional experience). Each imaging modality was evaluated independently. The CT examinations were analyzed according to a modified assessment of lung parenchymal involvement in CT images was performed based on Ooi *et al*. [38], in which an involvement score was assigned for each of the five lung lobes (score 0 for 0% involvement, 1 for <25%, 2 for 25% to <50%, 3 for 50% to <75% and 4 ≥ 75% involvement). The individual CT examinations were classified using an internal score (Table **S1**). This resulted in an image morphological assessment of the disease at the time of examination of mild at 1-2 points, moderate at 3-4 points, and severe at ≥5 points. A classification based on CO-RADS was not performed since all included patients had a confirmed infection and thus would have been classified as CO-RADS 6 [6]. The x-ray examinations were analyzed according to a standardized protocol (Table **S2**). A modified assessment of lung parenchymal involvement was performed, based on Ooi *et al*. [38], according to 6 regions (upper field bi-pulmonary, middle field bi-pulmonary- and lower field bi-pulmonary) and with a score of 1 (up to 25% involvement), 2 (26%-50% involvement), and 3 (> 50% involvement). The presence of shadowing and pleural effusions was documented. In addition, the radiographic density of shadowing was differentiated into the following three categories: 1 mild, 2 moderate, and 3 severe. Lung involvement scores were averaged across the six regions and summed with radiographic density scores. Thus, a scoring scheme was assigned for the severity of the disease based on the radiograph: 0-2: mild, 3-4: moderate, ≥5: severe. Furthermore, x-ray images were evaluated using the previously published CARE score and BRIXIA score [39 - 42].

Statistics were conducted utilizing SPSS Statistics version 29 (IBM, Chicago, IL, USA) and Microsoft Excel 2016 (Redmond, WA, USA). Discrepancies were critically assessed in relation to vaccination status, pre-existing medical conditions, hospitalization status (including outpatient, inpatient, and intensive care unit classifications), manifestation of ARDS, and evaluations based on CT and x-ray imaging, as well as survival outcomes. For nominal scale variables, such as pre-existing medical conditions and ARDS, Pearson's Chi-Square test was employed for comparison. Conversely, ordinal scale and metric variables, exemplified by age and various scores, were scrutinized using the Wilcoxon rank-sum test. A predetermined significance threshold of 0.05 was consistently applied across all tests. For metric variables, both median values and total ranges are provided.

3. RESULTS

3.1. Patient Population, Pre-diseases and SARS-CoV-2 Variants

This study included 39 patients who received a chest CT

scan and 179 who received one or more chest x-ray examinations (Fig. **1**). One patient in the CT cohort and eleven patients in the x-ray cohort were excluded due to a lack of information on the vaccination status. Hence, 38 patients in the CT cohort and 168 patients in the x-ray cohort were enrolled. Of the 38 patients included in the CT cohort, 33 patients were also part of the x-ray cohort (overlapping populations). The median age of the CT population was 59 years (total range 23-94), and of the x-ray population, it was 57 years (total range 18-94), Table **1**.

In the CT collective, 12/38 (32%) patients and 76/168 (45%) patients in the x-ray collective were fully vaccinated (Table **1**). For both collectives, the time interval between immunization and the first symptom onset of infection was 5 months (median).

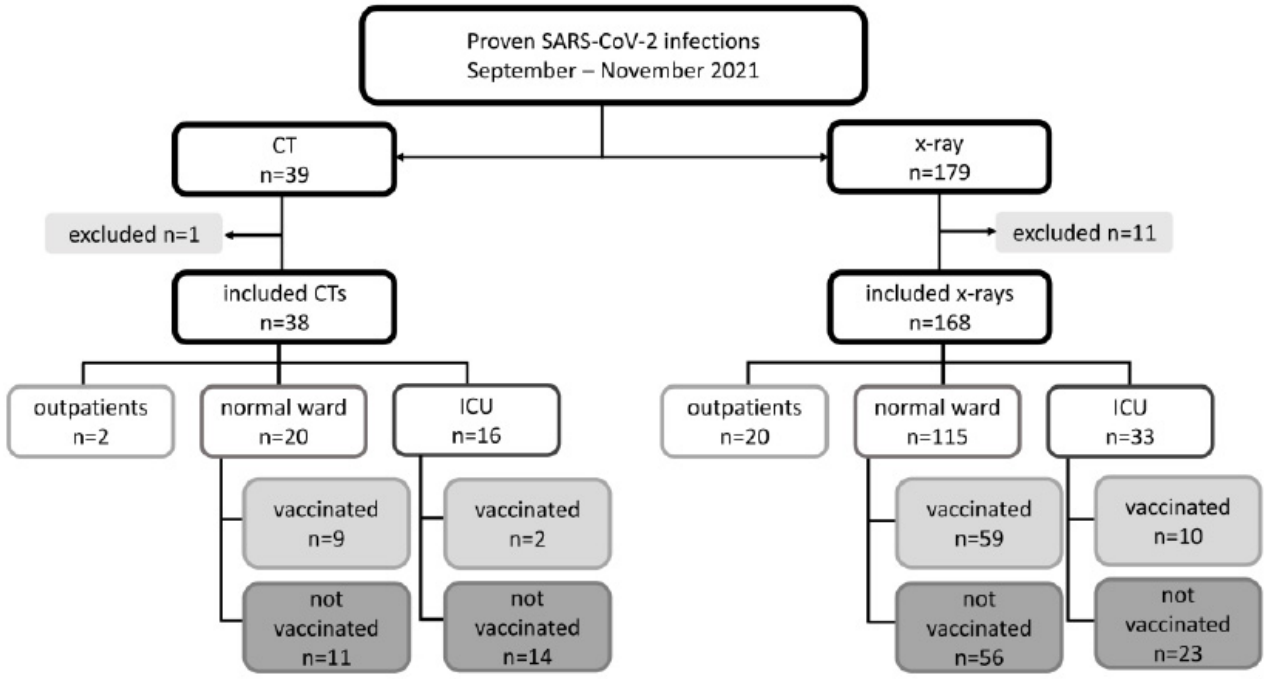

Fig. (1). Flow chart of the included study patients. Shown is the group of patients with CT and x-ray examinations. These are subdivided into outpatient, normal ward and ICU according to vaccination status. Abbreviations: CT = computed tomography, ICU = intensive care unit

Table 1. Patient characteristics and clinical findings in the computed tomography (CT) and x-ray cohort. Data were retrieved between September and November 2021 from a university hospital in Germany.

Parameter	CT Cohort n=38		X-ray Cohort n=168	
	n	%	n	%
Male	26	68	109	65
Female	12	32	59	35
Vaccinated	12	32	76	45
Pre-existing medical conditions	22	58	96	57
Immunosuppressed	3	8	21	13
Haemato-oncological	2	5	16	10
Diabetes mellitus	8	21	24	14
Cardiovascular	17	45	77	46
Overweight	12	32	57	34
Obese	13	34	42	25
Inpatient	36	95	148	88
ICU	16	42	33	20
ARDS	12	32	-	-
Deceased	12	32	19	11

Abbreviations/declarations: ARDS = acute respiratory distress syndrome, ICU = intensive care unit, obese = body mass index ≥30 kg/m2; overweight = body mass index ≥ 25 kg/m2 and <30 kg/m2.

In the CT cohort, vaccinations included Comirnaty (BioNTech, Pfizer) in 8/12 (67%), Janssen (Johnson & Johnson) in 2/12 patients (17%), Spikevax (Moderna) in one patient (8%), and one patient without information on the vaccination product. Four patients in the x-ray population had incomplete vaccination protection at the time of admission. For the x-ray cohort, the vaccines were as follows: 52/80 (65%) Comirnaty (BioNTech, Pfizer), 7/80 (8%) Janssen (Johnson & Johnson), 1/80 (1%) Vaxzevria (AstraZeneca), 2/80 (3%) Vaxzevria & Comirnaty (AstraZeneca & BioNTech, Pfizer), 1/80 (1%) Spikevax (Moderna), 17/80 (21%) unknown vaccination products.

In 20 cases of the CT cohort (51%) and in 114 cases of the x-ray cohort (68%), SARS-CoV-2 sequencing was successful. All sequenced virus strains resulted in B.1.617.2 and further Delta-variants (AY.4, AY.7.1, AY.9, AY.12, AY.33, AY.34, AY.43, AY.122, AY.122.1).

Patient characteristics and clinical findings of the CT and x-ray cohort are presented in Table **1**. In the CT cohort, there was no significant difference in patient age between vaccinated (median: 62 years) and unvaccinated (median: 57 years) patients. Vaccinated patients in CT were significantly less in need of ICU treatment (p=0.040) (see Table **2**). No significant difference was observed in terms of previous illnesses like cardiovascular diseases, haemato-oncological diseases or immunosuppression.

In the x-ray cohort, there was a significant difference in patient age between vaccinated (median: 62 years) and unvaccinated (median: 54 years) patients (p<0.001). Significantly more patients in the unvaccinated cohort suffered from immunosuppression (p=0.004), haemato-oncological (p=0.016), and cardiovascular (p=0.002) disease, Table **3**.

3.2. Imaging

Time of imaging was comparable between the groups of vaccinated and unvaccinated patients. Patients in the vaccinated group received a CT 9 (1-35) days and an x-ray 3 (0-18) days after symptom onset. Patients in the unvaccinated group received a CT 9 (0-43) days and an x-ray 5 (0-27) days after symptom onset.

Table 2. Patient characteristics and radiological findings in the computed tomography (CT) cohort. Data were retrieved between September and November 2021 from a university hospital in Germany. Comparison of vaccinated and unvaccinated patient groups, by means of the Wilcoxon rank-sum test (superscript a) and Pearson-Chi-Squared test (superscript b).

-	Vaccinated (n=12)		Unvaccinated (n=26)		p-value
	n	%	n	%	
Patient Characteristics					
Cardiovascular	8	67	9	35	n.s. [b]
Diabetes	3	25	5	19	n.s. [b]
Immunosuppression	1	8	2	8	n.s. [b]
Haemato-oncological	1	8	1	4	n.s. [b]
ARDS	1	8	11	42	n.s. [b]
Normal ward	9	75	11	42	n.s. [b]
ICU	2	17	14	54	0.040 [b]
Deceased	4	33	8	31	n.s. [b]
Radiological Findings					
Ground-glass opacities	11	92	25	96	n.s. [b]
Consolidation	7	58	23	88	n.s. [b]
Crazy paving pattern	9	75	8	31	0.016 [b]
Bilateral infestation	11	92	25	96	n.s. [b]
Consolidation > 50% of a lobe	2	17	13	50	n.s. [b]
-	**Median**	**Range**	**Median**	**Range**	-
Involvement upper lobe left (score)	3	0-4	4	0-4	n.s.[a]
Involvement lower lobe left (score)	3	0-4	4	0-4	n.s.[a]
Involvement upper lobe right (score)	2	0-4	4	0-4	0.026 [a]
Involvement middle lobe right (score)	2	0-4	4	0-4	0.005 [a]
involvement lower lobe right (score)	3	0-4	4	0-4	0.041 [a]
CT severity score	13	0-20	19	0-20	0.020 [a]
Time of imaging after symptom onset in days	9	1-35	9	0-43	n.s. [a]

Abbreviations: ARDS = acute respiratory distress syndrome; ICU = intensive care unit, median score = CT info score assessment (Table **S1**), n.s. = not significant.

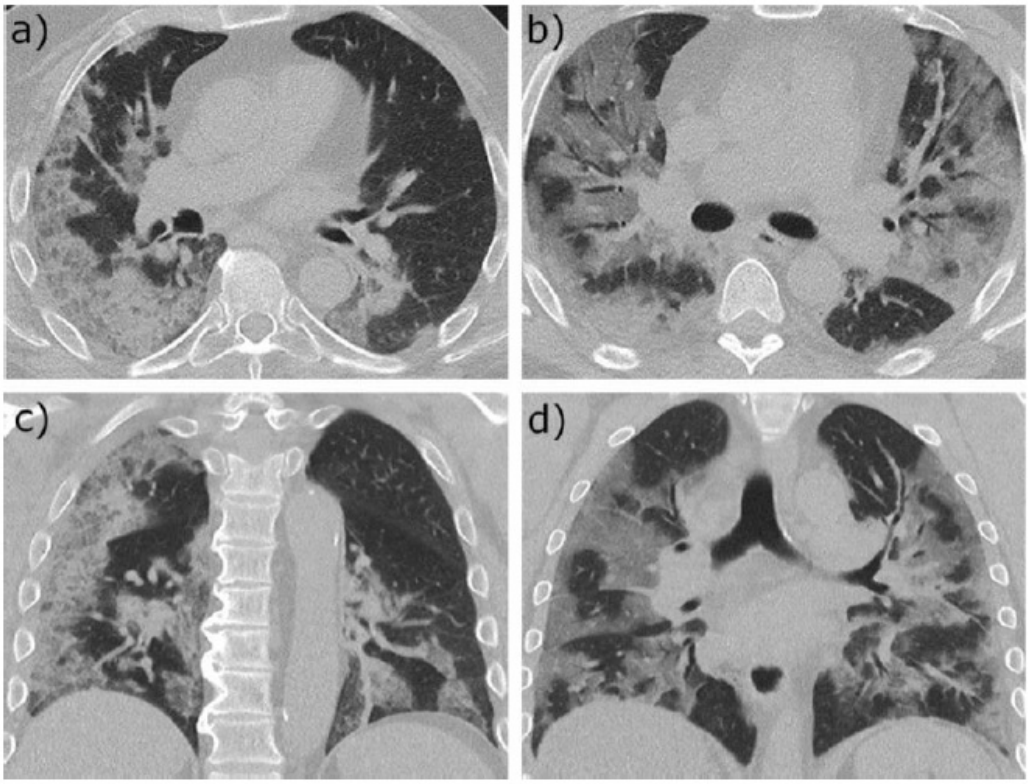

Fig. (2). Representative axial (**a**-**b**) and coronal (**c**-**d**) slices of chest computed tomography (CT) images of unvaccinated patients are shown. Patients 1 (**a** & **c**) and 2 (**b** & **d**) show air bronchogram, crazy-paving pattern, ground-glass opacities, and high expansion of pulmonary patterns. Patient 1 was 64 years old and achieved a CT severity score of 5. Patient 2 was 48 years old and achieved a CT severity score of 9.

Table 3. Patient characteristics and radiological findings in the x-ray cohort. Data were retrieved between September and November 2021 from a university hospital in Germany. Comparison of vaccinated and unvaccinated patient groups, by means of the Wilcoxon rank-sum test (superscript a) and Pearson-Chi-Squared test (superscript b).

-	Vaccinated (n=76)		Unvaccinated (n=92)		p-value
Patient characteristics	**n**	**%**	**n**	**%**	
Cardiovascular	45	59	32	35	0.002 [b]
Diabetes	12	16	12	13	n.s. [b]
Immunosuppression	16	21	5	5	0.004 [b]
Haemato-oncological	12	16	4	4	0.016 [b]
Normal ward	59	78	56	61	0.030 [b]
ICU	10	13	23	25	n.s. [b]
Deceased	7	9	12	13	n.s. [b]
Radiological Findings	**Median**	**Range**	**Median**	**Range**	**p-value**
Involvement upper field left (score)	0	0-3	0	0-3	0.001 [a]
Involvement middle field left (score)	0	0-3	1	0-3	0.021 [a]
Involvement lower field left (score)	1	0-3	2	0-3	0.029 [a]
Involvement upper field right (score)	0	0-3	0	0-3	0.042 [a]
Involvement middle field right (score)	0	0-3	1	0-3	0.012 [a]
Involvement lower field right (score)	1	0-3	2	0-3	0.009 [a]
Density (score)	1	0-3	1	0-3	0.016 [a]
X-ray severity score	2	0-7	3	0-7	0.010 [a]
Time of imaging after symptom onset in days	3	0-18	5	0-27	0.007 [a]

Abbreviations: ICU = intensive care unit, median score = x-ray info score assessment (Table **S2**), n.s. not significant.

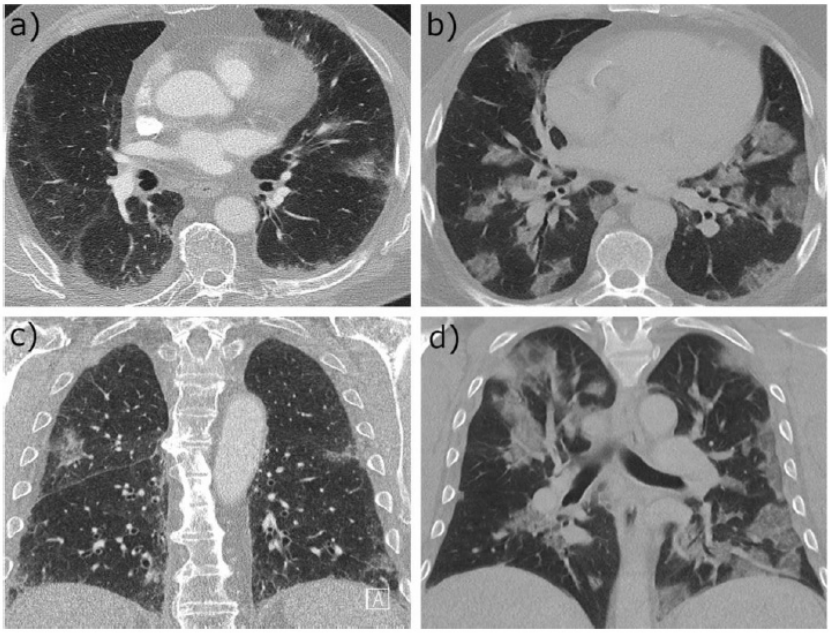

Fig. (3). Representative axial (**a**-**b**) and coronal (**c**-**d**) slices of chest computed tomography (CT) images of vaccinated patients are shown (**a** & **c** : patient 3; **b** & **d** : patient 4). SARS-CoV-2-typical patchy appearance of ground-glass opacities is visible in patient 4. Both patients showed less expansion of pulmonary patterns compared to patients 1 and 2 in Fig. **2**. Patient 3 was 73 years old and achieved a CT severity score of 2. Patient 4 was 54 years old and achieved a CT severity score of 4.

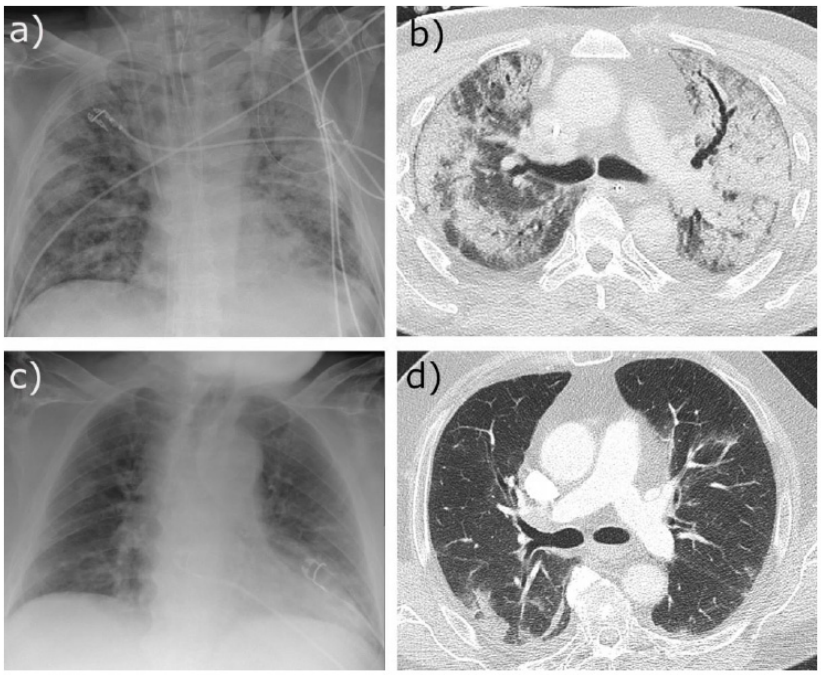

Fig. (4). The figure presents x-ray images (**a** & **c**) and representative layers of a computed tomography (CT) examination (b&d) of an unvaccinated (top) and a vaccinated (bottom) patient. The unvaccinated, 64-year-old patient received the x-ray examination (**a**) and a chest CT (**b**) on the same day. This patient achieved an x-ray score of 5, a CARE score of 35, a BRIXIA score of 16 and a CT score of 10. The vaccinated, 74-year-old patient achieved a score of 4 on x-ray, a CARE score of 24, a BRIXIA score of 13 (**c**) and later that day, a score of 2 on CT (**d**).

All patients undergoing CT imaging showed parenchymal patterns typical of SARS-CoV-2 infection, such as ground-glass opacities with bi-pulmonary involvement. Vaccinated patients showed a significantly lower extent of lung involvement and significantly lower CT severity scores. See Fig. (**2**) for an example of unvaccinated patients, Fig. (**3**) for

vaccinated patients and Table **2** for the statistical comparison.

In the x-ray cohort, vaccinated patients showed significantly less lung parenchyma involvement and significantly lower x-ray severity score, BRIXIA and CARE score (Fig. **4**, Table **3** and Tables **S3**-**S4**). Vaccinated patients in this group had significantly more cardiovascular diseases, haemato-oncological diseases, and were significantly more often immunosuppressed. Outpatients were significantly younger, had less cardiovascular disease, lung parenchyma involvement and significantly lower x-ray severity scores.

Median $CTDI_{vol}$ and DLP were 5.0 mGy (range 2.3-21.9 mGy) and 153.0 mGycm (range 77.7-2073.8 mGycm, respectively. All scans covered the lung, though 11/38 (29%) examinations additionally covered the abdomen. For the x-ray examinations, the median DAP amounted to 6.8 $cGycm^2$ (range 2.6-14.8 $cGycm^2$).

4. DISCUSSION

We were able to demonstrate that vaccinated patients exhibited a significantly milder lung involvement, less severe course of illness, less need for hospitalization and especially less need for ICU treatment, despite the presence of negative predictors such as some pre-existing conditions. Though there was no significant difference in mortality outcome, this study suggests that vaccination is effective in reducing the incidence of severe respiratory complications in COVID-19 patients.

COVID-19 vaccines were initially developed based on the genetic sequence of the original SARS-CoV-2 virus, which was first identified in Wuhan, China, in December 2019. Our cohort includes solely the Delta type and several Delta variants. Nevertheless, despite the differences between the original viral strain and the Delta variant, we were able to show a significant effect of vaccination on disease severity in our cohort. To obtain better protection against new variants and breakthrough infections, booster vaccinations are recommended after basic immunization [43]. Uzun *et al*. studied the effect of vaccinations in Turkey, including patients without vaccinations, with two vaccinations and with an additional booster [44]. They noticed differences in vaccination efficiency between vaccines from different vendors and between the numbers of vaccinations. A booster vaccination from a different vendor can increase the immune reaction even if the primary response is low [44]. Another study by Ferri *et al*. was able to demonstrate the effectiveness of a booster in immunocompromised patients whose immune response was not adequate after the primary vaccination [24]. Because booster vaccination was administered first to healthcare workers in our region at the time of the study, only seven patients received a booster by the time of study evaluation. Therefore, the comparison between fully vaccinated patients and boostered patients was not expressive and hence, not part of this analysis. Our results suggest that better immunization leads to a reduction in hospitalization rates and disease severity. Especially in the context of immunocompromised patients, a booster vaccination and regular refresher vaccinations are needed, as the immune response to vaccination can be significantly reduced due to the use of medications, such as Rituximab [24]. Several studies involving immunosuppressed patients emphasize the importance of effective immunization due to the increased mortality associated with existing immunosuppression and the different virulences of SARS-CoV-2 strains [23, 45].

We were able to demonstrate that the vaccinated x-ray cohort was significantly older compared to the unvaccinated group. This observation may be explained by several factors, including vaccine prioritization for older adults and the increased vulnerability of older adults to severe disease outcomes. In our country, COVID-19 vaccine allocation was prioritized for those at the highest risk of severe illness and death, including older adults, healthcare workers, and individuals with underlying health conditions [46]. As a result, older adults were among the first groups to be vaccinated, which may have contributed to the observed age differences between vaccinated and unvaccinated individuals who contract the disease. For example, data from the CDC showed that as of August 2021, nearly 80% of adults aged 65 and older had received at least one dose of the COVID-19 vaccine, compared to only 60% of adults aged 18-49 [47]. This higher uptake of the vaccine in older adults may also contribute to the age differences observed between vaccinated and unvaccinated patients with COVID-19. As a result, the observed difference in vaccination status between the older and younger age groups may reflect a higher vaccine coverage in the older population rather than a causal relationship between age and vaccination status. Finally, older adults are more likely to experience severe illness and hospitalization if they contract COVID-19 [48 - 49].

Typical image findings in our cohort were ground-glass-opacities, consolidation, crazy-paving pattern, and bilateral lung involvement, such as was seen in the patient cohorts of Htay *et al*. and Doncheva-Dilova *et al*. [45, 50]. In our study, disease severity was significantly lower in the unvaccinated cohort compared to the vaccinated cohort. This was reflected in significantly less pulmonary involvement, crazy paving pattern, and lower CARE and BRIXIA scores in the vaccinated cohort. In the case of inflammation, the pathophysiology of lung consolidations involves the accumulation of fluid and inflammatory cells in the alveoli. A significantly higher appearance of consolidation suggests a more severe illness [8]. These findings suggest that vaccinated patients have fewer and less severe pulmonary involvement compared to unvaccinated patients. Previous studies have also demonstrated the effectiveness of vaccination against COVID-19 in reducing disease severity. A study conducted in Israel found that vaccinated individuals were less likely to develop severe disease, require hospitalization, or die from COVID-19 [18]. Furthermore, the study showed that vaccinated patients had significantly less lung involvement on chest CT scans compared to unvaccinated patients [18]. The vaccinated patients had fewer ground-glass opacities and consolidations, which are the most common radiological findings in COVID-19 patients. Consistent with our data and Griffin *et al*., Lee *et al*. state that vaccinated patients showed less to no pulmonary involvement on CT [34, 51]. Another study conducted in Scotland showed that vaccinated individuals had a lower risk of developing severe disease compared to unvaccinated individuals [52]. Furthermore, a recently

published comment in The Lancet confirms these results and summarizes the findings of a total of 68 studies, indicating that vaccination contributes to protection against infection, hospitalization, and improvement of mortality [35]. These studies, together with the present study, highlight the importance of vaccination in reducing the severity of COVID-19.

In a large cohort of over 7300 patients, Myers *et al*. were able to show that vaccinated patients with SARS-CoV-2 infection are less likely to die compared to unvaccinated patients [53]. Our results showed no significant difference between vaccinated and unvaccinated patients and mortality, so did Mirouse *et al*. in patients treated in ICU [54]. The different results compared to Myres *et al*. could be caused by the fact that we had a considerably smaller patient cohort, a fairly low incidence compared to other regions and countries and a dedicated COVID-19 intensive care unit in our hospital, established in 2020. However, this does not imply that vaccination has no effect. As our data show, lung involvement in the unvaccinated group was significantly higher, as was the need for intensive medical care. Additionally, vaccinated patients more frequently required care in the general ward compared to unvaccinated patients, proportionally speaking. Therefore, based on our data, we assume an effect of vaccination on pulmonary involvement and disease course, even though no statistical impact on mortality was observed in our cohort.

We were able to demonstrate that the unvaccinated patients had a significantly higher need for intensive care in the CT cohort. Griffin *et al*. showed a significantly higher hospitalization rate and disease incidence in unvaccinated patients compared to vaccinated patients [34]. By the time of the study, the majority of inhabitants were fully vaccinated (67% of all adults and children) in our country [55]. Hence, there is a higher percentage of unvaccinated patients in our study compared to the population. They further describe that vaccinated patients were less likely to be admitted to ICU, to require mechanical ventilation or to die from a SARS-CoV-2 infection [34]. Our results are in accordance with the hospitalization rate and need for ICU treatment.

Lee *et al*. state that vaccinated patients had a lower likelihood of ICU treatment as well as need of oxygen supply [51]. Furthermore, Ravindra Naik *et al*. report that vaccinated healthcare workers had milder disease compared to unvaccinated workers [56]. This is in line with our results. Lung parenchymal involvement was significantly severe in the unvaccinated patients, both in the x-ray as well as the CT cohort. Both results are in line with Juthani *et al*., who were able to show that the presence of severe disease is reduced with complete vaccination [57]. Nevertheless, some vaccinated patients also showed a severe course of disease. Juthani *et al*. argued with a physiologically reduced vaccination effectiveness, for example, due to high age and presence of comorbidities, and with reduced vaccination effectiveness through *e.g*., immunosuppressants [57]. Age and comorbidities are known risk factors for severe COVID-19 disease, hospitalization, and death [54]. The older population is more likely to have comorbidities, such as diabetes, obesity, and cardiovascular disease, which can increase the risk of severe COVID-19 disease [9, 58 - 60]. Our x-ray cohort results confirm a significantly higher number of comorbidities in the older, vaccinated group. Nevertheless, we demonstrated that despite the higher risk for severe disease and death of older adults with comorbidities, these vaccinated patients had a significantly milder disease course with significantly less lung parenchymal involvement.

Sun *et al*. described that the probability of a breakthrough infection increases with the presence of immune dysfunction [61]. Schmidt *et al*. were able to show that haemato-oncological patients also have a higher tendency to develop breakthrough infections [62]. Suleyman *et al*. reported an increased hospitalization rate in vaccinated patients with older age, cardiovascular comorbidities and immune dysfunction, which is in line with our x-ray cohort results [63]. In the x-ray cohort, we observe a tendency towards older age and the occurrence of comorbidities associated with breakthrough infections.

As summarized by Coccia, the development and implementation of vaccinations against pandemic pathogens are essential but only promising in conjunction with other strategies [64]. Within the framework of pandemic preparedness, it is imperative that information and knowledge are exchanged worldwide quickly and efficiently to contain future pandemics more rapidly and effectively and to support the development of therapeutic concepts globally through collaboration. Considering globalization, rapid global mobility, and the associated swift spread of pathogens, close collaboration worldwide is necessary. In Germany, the RACOON network was initiated through national funding to address this need. Here, nationwide university radiology departments have joined forces to create a platform for evaluating image-morphological features and the possibility of rapid information exchange in the event of a new epidemic or pandemic. Furthermore, it is crucial to establish faster and more efficient crisis management not only in terms of mortality but also the global economic impact of a pandemic. As COVID-19 can affect various organs and lead to chronic conditions such as long Covid or, for example, vasculitides or multisystemic inflammatory syndrome, it becomes even more important to be prepared for future pandemics [50, 65]. This preparedness is essential to minimize global health and economic burdens.

This study has some limitations. This is a single-center study. Comirnaty (BioNtech, Pfizer) was administered proportionally more frequently than any other SARS-CoV-2 vaccine in our country [66]. Therefore, reliable conclusions regarding the differences in pulmonary affection when comparing breakthrough infections after vaccination with different vaccines cannot be drawn. Furthermore, the exact date of the vaccinations was not always provided by the patients.

The study refers to the Delta variant since only Delta variants could be virologically detected. We could not perform an evaluation between vaccination and different virus variants because all sequenced virus strains resulted in B.1.617.2 and further delta variants. The later developing Omicron variant showed a milder course than the Delta variant [67, 68].

Nevertheless, new variants continue to develop, with the possibility of similar vaccination effectiveness, severe course as with the Delta variant, and similar characteristics of the variant so that the results can also be applied to these new variants [29]. Despite the prevalence of the Delta variant with novel mutations in the spike protein at the time of study, we observed vaccine protection in patients.

x-ray imaging is inferior to CT imaging with regard to the spatial differentiation of lung parenchymal involvement. Visible GGO on CT might be invisible on x-ray images due to superimposed structures in planar imaging. Therefore, a direct comparison of x-ray imaging and CT imaging was not performed. Furthermore, the number of patients in the CT cohort is considerably smaller than the number of patients in the x-ray cohort. The indication for a CT acquisition was strict, and CT was not employed as a screening tool for diagnosis of COVID-19.

Nevertheless, the present study adds to the growing body of evidence that vaccination against COVID-19 is effective in reducing disease severity and should be encouraged.

CONCLUSION

In conclusion, the present study demonstrates that vaccination against COVID-19 can significantly reduce the severity of the disease in case of breakthrough infections, as evidenced by the significant reduction in lung parenchymal involvement and the need for ICU treatment observed in vaccinated patients. Furthermore, the study indicates that vaccination has a positive impact on the course of the disease despite the presence of negative predictors. The findings highlight the importance of vaccination in reducing the burden on the healthcare system and preventing severe respiratory complications in COVID-19 patients.

Nevertheless, the development of vaccines and the implementation of vaccinations are not the sole solution for combating a pandemic. This pandemic has highlighted the importance and need for rapid and efficient collaboration among governments, health-organizations, and researchers to contain a pandemic [64]. Therefore, it is crucial to establish functional networks and alliances for rapid data and information exchange and to achieve pandemic preparedness, such as the RACOON network founded in Germany. We are convinced that only a combination of primary protective measures, alliances, quick and efficient information exchange, and the development and application of vaccines can adequately contain future virus variants and new pandemics as well as their health consequences.

LIST OF ABBREVIATIONS

CT	=	Computed Tomography
qPCR	=	quantitative polymerase chain reaction

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The research ethics committee at the medical faculty of the Heinrich-Heine-University of Düsseldorf approved the study.

HUMAN AND ANIMAL RIGHTS

No animal were used that are the basis of this study. This study was performed in line with the principles of the Declaration of Helsinki.

CONSENT FOR PUBLICATION

The local ethics committee waived the need for informed consent due to the retrospective nature of the study. All examinations were carried out as part of the clinical diagnostics. No examination was ordered separately for the study.

No personal individual data are published in this manuscript.

STANDARDS OF REPORTING

STROBE guidelines were followed.

AVAILABILITY OF DATA AND MATERIALS

The underlying data cannot be made publicly available upon publication because they contain sensitive personal information. The data that support the findings of this study are available upon reasonable request from the authors.

FUNDING

Open access publication was partially funded by the Open-Access-grand of the Heinrich-Heine-University Düsseldorf Funded by "NUM 2.0" (FKZ:01KX2121).

CONFLICT OF INTEREST

The authors declare no conflict of interest financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

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