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Omicron Infections in Otolaryngology Practice: A Retrospective Observational Study on Testing, Symptoms and Vaccination Status

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Abstract

Background: With the appearance of the SARS-CoV-2 Omicron variant the high rate of vaccination breakthroughs showed that current vaccines against COVID-19 can no longer provide adequate protection against infection. However, it is still assumed that vaccination might have a positive effect on the course of the disease. In Germany, general practitioners and specialists are usually the first treatment providers for acute illnesses. In addition, patients with infections of the upper respiratory tract often primarily consult an ear, nose and throat specialist. Most of the Omicron-infected people have a mild course of the disease and, if necessary, receive medical care on an outpatient basis. Little is known about the effectiveness of corona vaccinations on Omicron infections in relation to the clinical symptoms. In our outpatient office, we recorded a sharp increase of corona positive Omicron-infections in the beginning of 2022, despite of vaccinations against COVID-19. In a retrospective analysis, we evaluated the data of our SARS-CoV-2 tested patients with regard to clinical symptoms reported and vaccination status. The focus was particularly on the question to what extent the vaccination status in the case of Omicron infections influences the symptoms of the disease. **Methods:** We retrospectively evaluated the data of all patients in the first quarter of 2022 who were suspected for COVID-19. At that time, the Omicron variant was dominant in Germany. Clinical symptoms, cycle threshold (Ct) values, and the vaccination status were recorded. Symptomatic patients who tested negative for SARS-CoV-2 served as a control group. **Results:** Of the total cohort (n = 353), 241 (68%) patients were tested SARS-CoV-2 positive. The symptoms of the corona-positive patients were essentially similar to those of a mild to moderate cold, but compared to SARS-CoV-2-negative patients (n = 69) with a clear shift in favor of fever (35% versus 16%), cough (76% versus 52%)

and increased feeling of illness (59% versus 43%), respectively. Ct values revealed no difference between unvaccinated (mean 19.15; SD 3.52) and vaccinated cases (mean 18.15; SD 3.87; p = 0.272). There was no significant correlation between the vaccination status and clinical symptom score in different age groups (age 12 to 17, r (28) = 0.26, p = 0.26; age > 18 to 60, r (191) = 0.06, p = 0.378). **Conclusions:** According to our results with infections with the Omicron variant, there were no differences between unvaccinated and vaccinated patients concerning clinical symptoms or potential infectivity, especially in children and adolescents. This might have impact on further vaccination programs.

Keywords

COVID-19, Omicron Variant, Vaccination Effect, Ct Value, Clinical ENT Symptoms

1. Introduction

Since the first appearance of the SARS-CoV-2 pandemic, different SARS-CoV-2 variants have repeatedly occurred worldwide, the last variant of concern (VOC) being the Omicron variant [1] [2] [3].

In Germany, due to a broad vaccination campaign at least 75% of the population had had complete primary immunization against SARS-CoV-2, and over 60% had already received a third vaccination at the beginning of 2022 [2] [4].

Already with the advent of the Delta variant so-called vaccination breakthroughs occurred [5] [6]. The high rate of infections among vaccinated people with the appearance of the Omicron variants BA.1 and BA.2 showed that the vaccinations were no longer able to provide adequate protection against infection. However, it is assumed that vaccination also has a positive effect on the course of the disease in the Omicron variant, especially with regard to hospitalization and patient mortality [7] [8].

In Germany most patients receive first medical care on an outpatient basis.

In our ear, nose and throat medical office, we recorded a sharp increase of corona positive Omicron-infections in the beginning of 2022. In the following retrospective analysis, we evaluated the data of our SARS-CoV-2 tested patients with regard to the clinical symptoms reported and the vaccination status. The focus was particularly on the question to what extent the vaccination status in the case of Omicron infections influences the symptoms of the disease.

2. Material and Methods

In a retrospective and monocentric study, the data of all consecutive patients tested for SARS-CoV-2 in our practice in the 1st quarter of 2022 (01/01/2022-03/31/2022) were evaluated. Only patients who underwent PCR testing for SARS-CoV-2 for the first time in the quarter were included in the study. Control smears were excluded, so that each patient was included in the dataset only once. SARS-CoV-2-positive patients with a cycle threshold (Ct) value > 29 were also excluded.

The swabs were indicated according to the currently valid guidelines of the Federal Ministry of Health (BMG) [9] [10], *i.e.* positive rapid test with or without clinical symptoms and/or specifications from the employer.

2.1. The Smear Technique

The swab for SARS CoV-2 was taken from the nasopharynx in accordance with the recommendations of the WHO and the Robert Koch Institute [11].

2.2. PCR Testing and Sequencing

After collecting the sample, the swab tubes were sent to the laboratory on the same day. The result of the PCR test was usually available 24 - 48 hours upon arrival at the laboratory.

The PCR testing was carried out using a dual-target strategy. At least two independent gene regions of the SARS-CoV-2 virus were detected simultaneously in one examination: E gene, N gene, ORF1a/b gene, S gene. This increased the sensitivity and specificity of the method [12].

During the study period, two different PCR test systems were used to detect the RNA of the SARS-CoV-2 virus:

Method 1: After washing out the swab and extracting the RNA using the Magna Pure 96 device (Roche, Mannheim, Germany), the PCR was detected using a PCR kit from Altona-Diagnostics (Hamburg, Germany) in a Rotorgene thermocycler (Qiagen, Hilden, Germany). This PCR detects gene segments of the E and S genes of SARS-CoV-2 [13].

Method 2: After washing out the swabs, the RNA extraction and amplification took place fully automatically in the Cobas 8800 (Roche, Mannheim, Germany). This PCR system detects fragments of the viral E and ORF gene [14].

The sensitivity of the PCR tests and the resulting cycle threshold (Ct) values depend strongly on the time of sampling during the course of the disease. According to the manufacturer, the detection limit is 100% for method 1 for 0.014 PFU/ml (S gene) and 100% for method 2 for 0.009 TCID50/ml (ORF1ab-gene). The specificity is between 96% - 100%. The Ct value was given for each positive smear.

Ct values below 30 were considered suspicious for the infectiousness of the patients [15].

As part of the legally required random sample survey, full genome sequencing was carried out on 17 of the 241 positive SARS-CoV-2 samples. The Omicron variant BA.1 was detected in 11 cases and BA.2 in 6 cases.

2.3. Data Collection

Each patient tested was included only once.

The following parameters were included in the retrospective analysis:

Gender, age, vaccination status, date of last vaccination, previous COVID-19 disease, test result and Ct value.

The anamnesis recorded the following clinical symptoms in particular:

Runny nose, sore throat, cough, headache, fever, feeling sick and tired, olfactory disorders, breathing difficulties and dyspnea, duration of the symptoms until the smear.

All patients with symptoms had been examined by an ENT doctor, patients with olfactory disorders had an orienting olfactory test with 4 olfactory stimuli, and patients with breathing difficulties had a short pulse oximetry using a pulse oximeter (Medisana, Neuss, Germany).

2.4. Creating a Symptom Score

To quantify the individual clinical symptoms of the patients, we developed a simple symptom score. One point was assigned to each symptom (runny nose, sore throat, cough, headache, fever, feeling sick and tired, olfactory disorders, breathing difficulties). Hence, a maximum of 8 points could be achieved in this way.

The mean symptom score in a specific cohort was calculated by dividing the sum of the symptom score by the number of patients in the particular study group.

2.5. Classification of Patients According to Vaccination Status

A total of four different vaccines (first generation) were used in our patient population: the m-RNA vaccines Comirnaty (Biontech) and Spikevax (Moderna), the vector-based vaccines Vaxzevria (Astra Zeneca) and Janssen (Johnson & Johnson).

The patients' vaccination status was classified based on the EMA (European Medicines Agency) [16].

Unfortunately, the retrospective analysis revealed that not all parameters had been consistently documented in everyday practice. This primarily concerned the date of the last vaccination.

2.6. Statistics

The digital creation of the data set and the graphic representations were carried out using Microsoft Excel 2017 (Microsoft Corporation, USA). In addition to Microsoft Excel, the software from Datatab and Abacus 2.0 (Labanalytics, 2021, Jena, Germany) were used for the statistical evaluation [17] [18]. Spearman correlation and the Kruskal-Wallis test was used to compare the rates of SARS-CoV-2 positive patients in different vaccination groups. One-factorial ANOVA with Bonferroni post-hoc test served for the analysis of Ct values of different vaccination groups. Fisher's exact test was used to compare vaccination status and single symptoms.

2.7. Privacy

The study was conducted according to the guidelines of the Declaration of Helsinki. Since this was a retrospective study, an ethics vote from the North Rhine Medical Association was not necessary. A comprehensive written data protection declaration, which includes data evaluation for medical and scientific purposes, was always routinely obtained from all patients. All data included in this study were recorded completely anonymously. Identification of the patients is not possible using the data used in this analysis.

3. Results

3.1. The Tested Patients

A total of 353 swabs were taken in our practice and tested for infection with SARS-CoV-2 in the laboratory using PCR tests. Of those tested, 194 were female (55%) and 159 male patients. 241 (68%) of these swabs were SARS-CoV-2 positive, of which 127 were female (53%) and 114 males.

Seven patients (2%) had recovered from corona disease by November 2021, of which 6 patients were again positive in our study.

Most PCR swabs were taken because of either cold symptoms and/or a positive rapid test. In 56 patients, the test was not carried out because of clinical symptoms. A PCR smear was required here due to a positive rapid test or a request from the employer or public institution.

Of the symptom-free patients, 13 patients (23%) had a positive test result.

3.2. The Age Structure of the Tested Patients

The proportion of children and young people up to the age of 17 was 25%, 62% were between 19 and 60 years old and 13% were older than 60 years. Compared to the average age of our entire practice clientele, those tested for SARS-CoV-2 were much younger. The proportion of children and young people of all our patients in the first quarter of 2022 was 13%, and 43% were older than 60 years.

3.3. Clinical Symptoms of Tested Individuals

297 tested (84%) showed clinical symptoms. Of these, 228 patients (77%) were corona positive. Of the total of 241 corona-positive cases, 13 patients (5%) showed no symptoms. Out of the 112 corona-negative patients, 44 (39%) were symptom-free.

In most patients with clinical symptoms, no abnormalities were found in the ENT examination. They showed mild to moderate symptoms of a "common cold".

The mean duration of symptoms for all patients until swabbing was 2.6 days (range 1 to 10 days). In the corona-negative patients with cold symptoms of the upper respiratory tract, the average duration of illness until the smear was 2.7 days (range 1 to 10) days. In the SARS-CoV-2 positive patients with symptoms, the mean duration of illness until the smear was 2.4 days (range 1 to 7 days), with no difference between unvaccinated and vaccinated patients.

The most common symptoms reported were a sore throat, runny nose, cough, feeling sick and fever greater 38 degrees Celsius for 1 - 3 days.

15 patients (5%) reported breathing difficulties. Here, the O_2 saturation was determined using a finger sensor, with the lowest measured value being 95%. All patients who reported breathing difficulties also suffered from COPD and/or heavy nicotine abuse. None of our patients had to be admitted to hospital.

Slight differences were found in the symptoms of the disease between corona-positive and corona-negative patients. These mainly concerned the symptoms of initial fever, general malaise and cough. Olfactory disturbances and breathing difficulties were reported only rarely, and an olfactory loss could only be verified in 6 patients.

With the formation of a symptom score, *i.e.* the number of symptoms/patient group, the severity of the disease was recorded further. At 3.2 (range 1 to 7), there was an average slightly higher symptom score in all patients with evidence of SARS-CoV-2 compared to patients without coronavirus evidence (mean symptom scores 2.8 (range 1 to 6). One unvaccinated and one vaccinated SARS-CoV-2-positive adult had the highest symptom score of 7. No hospitalization was necessary even in the patients with a high symptom score.

3.4. Vaccination Status of the Tested Patients

In the study cohort, 264 (75%) patients were considered to be fully immunized, of which 88 (33%) patients were vaccinated twice and 177 (67%) patients three times. The most frequent vaccinations had been carried out with the m-RNA vaccine Comirnaty (148, 56%). Only 5 (2%) patients had been immunized once with the Janssen vaccine. However, there were also numerous mixed vaccinations with the two m-RNA vaccines and the vector vaccines.

25% of our patients (n = 88) were not or only incompletely (n = 4) vaccinated, but most of them were children under the age of 12 (n = 47).

We therefore took a closer look at the age structure of the unvaccinated patients: 47 (75%) were children and young people under the age of 17 and 21(22%) of the unvaccinated fell in the 18 - 59 age group. The unvaccinated over 60 years, who represent the main risk group, were with 3 patients (3%) very marginally represented in our patient population.

3.5. Vaccination Status and Positive PCR for SARS-CoV-2

In our patient population there was a slight difference in the positive rate of unvaccinated compared to those who had been vaccinated twice or three times (58%, 76%, and 69%, respectively) (**Table 1**). The positive rate of the unvaccinated patients was somewhat lower. A statistical analysis (Kruskal-Wallis test) showed no significant difference in the positive rate of unvaccinated subjects and those who had been vaccinated twice or three times (p = 0.264).

Table 1. Vaccination status and the number of positive test results (n = 353).

	Number of patients	SARS-CoV-2 positive (%)
All	353	241 (68)
Unvaccinated	88	51 (58)
2x Vaccinated	88	67 (76)
3x Vaccinated	177	123 (69)

The date of the last vaccination was available in 83% of the vaccinated positive patients. The mean interval from the last vaccination was 15 weeks (range 1 - 36 weeks) in the twice-vaccinated positive patients (n = 49) and 9 weeks (range 1 - 20 weeks) in the triple-vaccinated positive patients (n = 108).

3.6. Vaccination Status and Ct Value

The Ct value was determined for all positive test persons (**Figure 1**). The average Ct value of all positive patients was 18.5 (SD 3.78). The average Ct values of the 2- and 3-fold vaccinated persons were 18.15 (SD 3.87) and slightly lower than those of the unvaccinated positive test persons with an average CT value of 19.15 (SD 3.52). Statistically, one-factorial ANOVA and the Bonferroni post-hoc test did not reveal any significant differences in the distribution of Ct values in unvaccinated, twice-vaccinated, and triple-vaccinated individuals.

3.7. Vaccination Status and Clinical Symptoms

To determine the disease value of unvaccinated and vaccinated corona patients, we used a symptom score as described above.

Overall, the average symptom score in the corona-positive patients was 2.78 to 3.46, with a median of 3 (Quartile range 2 - 4) or 4 (Quartile range 3 - 5), depending on the vaccination status. Most of the unvaccinated infected people only had up to 3 symptoms, the number of symptoms was slightly higher in the vaccinated, especially in the boosted patients. However, this did not reach statistical significance ($P = 0.53$). Also, the median symptom score in respiratory infections unrelated to SARS-CoV-2 (RIU) was comparable and not significantly different to patients with COVID-19 (**Table 2**).

Since most of the unvaccinated patients in this study were children and adolescents, the symptom score in the unvaccinated SARS-CoV-2-positive patients was analyzed according to different age groups (**Table 3**).

We also evaluated the frequency of symptoms according to the age of the patients. Since only four patients had been triple vaccinated in the age group of children and adolescents, those who had been vaccinated twice and three times were combined in this age group (**Table 4**). The analysis of the symptom scores in the age group ≥ 18 years is shown in **Table 5**.

The result of Spearman's rank correlation showed that there was no significant correlation between the number of vaccinations and symptom score in both age groups (Age 12 - 17, $r(28) = 0.26$, $p = 0.26$; Age > 18, $r(191) = 0.06$, $p = 0.378$).

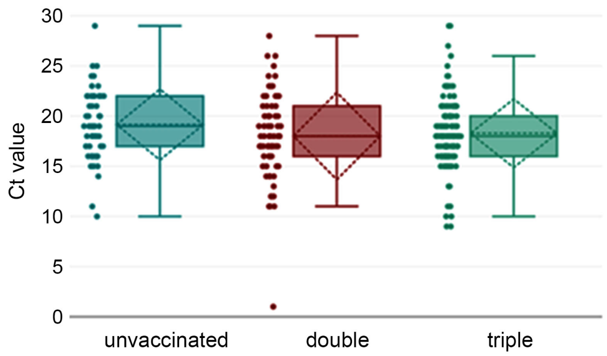

Figure 1. Box plot evaluation of Ct values according to vaccination status.

Table 2. Mean and median symptom score according to vaccination status (n = 310). RIU: respiratory infection unrelated to SARS-CoV-2.

Number of symptoms	Unvaccinated (%)	2x Vaccinated (%)	3x Vaccinated (%)	RIU (%)
0	4 (7.8)	6 (8.9)	4 (3.3)	0 (0)
1	5 (9.8)	5 (7.5)	6 (4.9)	5 (7.2)
2	15 (29.4)	11 (16.4)	22 (17.9)	23 (33.3)
3	11 (21.6)	20 (29.9)	24 (19.5)	26 (37.7)
4	8 (15.7)	12 (17.9)	32 (26)	12 (17.4)
5	5 (9.8)	9 (13.4)	26 (21.1)	2 (3)
6	2 (3.9)	3 (4.5)	9 (7.3)	1 (1.4)
7	1 (2.0)	1(1.5)	0 (0)	0 (0)
8	0 (0)	0 (0)	0 (0)	0(0)
All patients	51 (100)	67 (100)	123 (100)	69 (100)
Symptom score:				
Mean	2.8	3.1	3.5	2.8
Median [$Q_{0.25}$ - $Q_{0.75}$]	3 [2 - 4]	3 [2 - 4]	4 [3 - 5]	3 [2 - 3]

Table 3. Symptom score and age of unvaccinated patients positive for SARS-CoV-2.

Age (years)	0 - 6	7 - 11	12 - 17	>18	Of which >50
Number of patients	9	10	12	20	7
Symptom score:					
Mean	1.2	2.8	2.5	3.6	3.1
Median	2	3	2	3	3

Table 4. Symptom score and vaccination status by patient age 12 - 17 years (n = 30).

	Unvaccinated	Vaccinated
Patients	12	18
Total score points	30	53
Symptom score:		
Mean	2.5	2.9
Median	2	3

Table 5. Symptom score and vaccination status of patients aged 18 and older (n = 191).

	Unvaccinated	2x Vaccinated	3x Vaccinated
Patients	20	52	119
Total score points	72	164	419
Symptom score:			
Mean	3.6	3.2	3.5
Median [$Q_{0.25}$ - $Q_{0.75}$]	3[3 - 4]	3[2 - 4]	3[2 - 4]

When determining the symptom score, no weighting was carried out with regard to the individual symptoms. For illustration purposes, the individual symptoms and their frequency in unvaccinated, double-vaccinated and triple-vaccinated Omicron-positive patients are shown in **Figure 2** in comparison to patients with symptoms but negative PCR results for SARS-CoV-2, representing RIU.

Slight differences were found in the symptoms of the disease between SARS-CoV-2-positive, vaccinated, unvaccinated and SARS-CoV-2-negative patients.

Most patients had the same symptoms as in a common cold, but with a symptom score average of 2,8 SARS-CoV-2-negative patients showed slightly milder symptomatic. Only under clinical aspects without the knowledge of a positive PCR-test Omicron disease appeared as a common cold and could not have been diagnosed.

Of all patients, 90 suffered from fever, with an equal share of 39% in the unvaccinated and 2-fold-vaccinated Omicron patient group.

Compared to the patients with corona negative cold symptoms, fever was more than twice as common in corona positive patients (39% compared to 16%). The symptoms feeling sick and cough showed to be more prominent in Omicron patients as well. Of all symptoms, there was a significant difference between Omicron infected patients and patients with RIU for fever and cough (fever $p = 0.0066$; cough $p = 0.0036$; Fisher exact test). There was a trend for a higher prevalence of the symptom "fever" in unvaccinated (39%) versus triple-vaccinated Omicron patients (27%), but this did not reach statistical significance ($p = 0.1471$; Fisher exact test).

4. Discussion

Early descriptions of omicron cases from South Africa and Korea indicated that this new corona variant was highly infectious, but seemed to be significantly less dangerous [19] [20] [21]. There are now numerous studies on the reduced severity of the Omicron variant compared to the Alpha and Delta VOCs [22]. They demonstrate that although the current variants with the subtypes BA.1-BA.5 are highly contagious, infection rarely requires hospitalization or intensive care [4] [23].

Despite a high vaccination rate, the Omicron variant spread rapidly in the population worldwide. Also, in our outpatients we observed a sharp increase in the number of people infected with SARS-CoV-2 during the first quarter of 2022

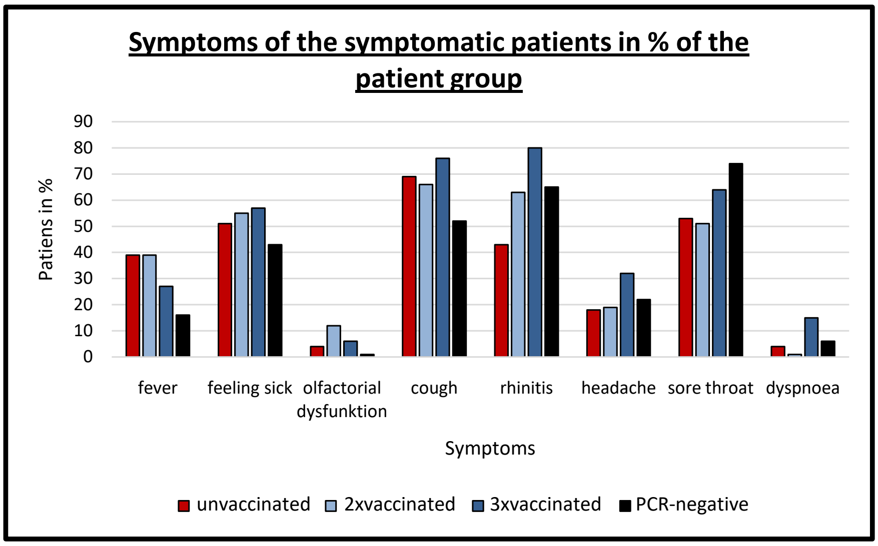

Figure 2. Relative symptom frequency of the tested patients (n = 353).

compared to the previous year. As shown above, based on the epidemiological situation in our Corona-positive patients in Germany, we assumed an infection with the Omicron variants BA.1 and BA.2 in our patients [4]. This could be confirmed by random samples in our study. Meanwhile, vaccine manufacturers have confirmed that a double or triple vaccination against the spike protein of the wild type of the SARS-CoV-2 virus no longer protects against infection, especially with the Omicron variant. Therefore, new vaccines adapted to variants have already been developed [24] [25] [26].

In some studies, the harmless course of the Omicron variant is attributed to the high level of immune protection of the population, mainly due to the corona vaccinations [14] [15] [27]. However, because of the high vaccination rate now, especially in Europe, the effect of vaccination on the course of the disease induced by the Omicron variant is difficult to determine, since there is hardly any unvaccinated comparison group [22].

In our study, the group of unvaccinated patients, at around 25%, was significantly smaller than that of the 2- and 3-fold vaccinated patients. In addition, when comparing unvaccinated and vaccinated Omicron patients, there was a selection bias with regard to the age structure of the patients. Particularly children and young people were not vaccinated in our study cohort, which was also due to the relatively late vaccination recommendation for 12 to 17-year-old adolescents in Germany at that time [28]. As early as 2021, a large-scale German study described the mild course of COVID-19 infections in children [29]. Compared to other publications, regardless of vaccination status, the clinical symptoms in children and adolescents in our patient population were milder than in adults, too.

Our analysis showed a median symptom score of 2 in unvaccinated SARS-CoV-2 positive children, which was comparable to all double or triple vaccinated patients. This was particularly noticeable in the group of elder children and adolescents, where vaccination even seemed to have no benefit. However, this observation needs to be confirmed in larger cohorts with higher case numbers.

PCR detection was carried out in all SARS-CoV-2 positive patients. The Ct value indicates the number of measurement cycles above which a fluorescence signal is detectable. The fewer cycles are necessary for a measurable signal, the higher the RNA concentration in the patient's sample [15]. According to a study by Singanayagam *et al.* [30] the Ct value correlates with the viral load detected in virus cultures. Therefore, in dealing with the pandemic, the Ct value is regarded as an indicator of the viral load in patients who have been tested positive and allows an estimation of their possible infectiousness. In Germany, a patient with a Ct value of >30 is no longer considered to be infectious, although individual and preanalytical factors must be considered [31]. In recent studies, the validity of the Ct value with regard to the infectivity of a patient as the sole parameter is now being questioned [32] [33]. In our study, no difference was found between vaccinated and unvaccinated SARS-CoV-2 patients concerning Ct values, with the time from onset of disease to sample collection being comparable for all patients. This is in line with a published study from Fall *et al.* [34].

Also, the vaccination status did not have an effect on the clinical symptoms in our Omicron cases. The assumption that omicron infection is less severe in vaccinated than in unvaccinated patients could not be confirmed in our outpatients. In our Omicron infected patients, the symptom scores were comparable between non-vaccinated and vaccinated persons, regardless of the number of vaccinations. Remarkably, respiratory infections unrelated to SARS-CoV-2 presented with symptoms comparable to infections by the Omicron variant. Only the symptom fever, which occurred in 37% of the Omicron cases, was reported half as often in those who had been triple vaccinated as in those who had not been vaccinated.

Meanwhile the effect of vaccination in Omicron infection is discussed controversially. Hospitalization and morbidity are still the main criteria for a positive vaccination effect [8] [24] [26] [27] [35]. This is certainly still true for elderly and multimorbid patients, who were hardly represented in our particular setting. Therefore, our results have to be interpreted with caution. However, the study allows conclusions to be drawn about the effectiveness of the vaccination in relation to the clinical symptoms of an infection with the Omicron VOC.

Compared to the most recent studies on Omicron our study represents only one component of Omicron research.

However, unlike the most other publications, in our clinical observational study vaccination status and disease symptoms can be attributed to each case individually.

Further investigations like this data collection approach might be useful for the assessment of future vaccination programs.

5. Limitation

Limitations of this study are that there was no data available on the duration of the disease and possible late effects such as multisystem inflammatory syndrome in children (MIS-C), Post COVID Syndrome or Long COVID Syndrome [36] [37]. Also, elderly and especially high-risk patients were hardly represented in our patient population, so that no statement can be made about the effect of the vaccinations in case of an Omicron infection in older and, above all, multimorbid patients.

6. Conclusion

According to our observational study, neither double nor triple vaccination against SARS-CoV-2 had a significant impact on the percentage distribution of infections with that virus, viral load or disease symptomatology in Omicron infections in outpatients. This seemed to be particularly true for children and adolescents without previous diseases and might have impact on further vaccination programs.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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