



CLINICAL CHARACTERISTICS AND OTORHINOLARYNGEAL MANIFESTATION OF COVID 19 AND THEIR ASSOCIATION WITH DISEASE SEVERITY

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Abstract

COVID-19 presents with diverse systemic, respiratory, and otorhinolaryngeal manifestations that may vary according to disease severity. This study evaluated the clinical and ENT characteristics of COVID-19 patients and their correlation with serious illness. A secondary observational analytical study was conducted using previously collected information from 223 patients with laboratory-confirmed COVID-19. Demographic characteristics, comorbidities, hospitalization status, CT findings, general symptoms, otorhinolaryngeal manifestations, symptom severity, and duration were analyzed. There were four categories for disease severity: mild, moderate, severe, and critical. Kruskal–Wallis H, Fisher's exact, and chi-square, regression, and regression analyses were performed. The mean age was 50.09 ± 16.46 years. Fatigue was the most common general symptom, while taste loss and smell loss were the predominant ENT manifestations. Fever, cough, fatigue, and dyspnea differed significantly across severity groups. Smell loss was more frequent in milder disease and was associated with lower odds of severe/critical COVID-19. Increasing age, comorbidity, CT evidence of viral pneumonia, fever, fatigue, and dyspnea were associated with greater severity. Age remained the only significant independent predictor after adjustment. Clinical and otorhinolaryngeal manifestations varied according to COVID-19 severity. Age and respiratory involvement were important severity indicators, while smell loss was more characteristic of less severe disease.

Keywords: COVID-19; disease severity; otorhinolaryngeal manifestations; smell loss; clinical characteristics

Introduction

Coronavirus disease 2019 (COVID-19) is a significant health issue on a global level due to its spread and wide range of symptoms brought on by the coronavirus that causes severe acute respiratory syndrome (SARS-CoV-2). The manifestations have manifested as mild cases of symptoms of respiratory failure, severe pneumonia, upper respiratory tract, and critical illness in patients. Preliminary clinical descriptions revealed fever, cough, fatigue, dyspnea, and myalgia as the main symptoms, and the level of the disease differed significantly among people and depended on age, underlying diseases, and pulmonary involvement (Huang et al., 2020). The same trends were noted in hospitalized cohorts, where comorbidities and a more comprehensive clinical involvement were linked to worse outcomes (Richardson et al., 2020). COVID-19 has a broader clinical manifestation, with both respiratory and systemic and neurological symptoms. Among affected patients, fever, cough, fatigue, dyspnea, myalgia and headache have been reported repeatedly, but with varying frequency depending on clinical setting and severity. The heterogeneity in the presentation of the disease and symptomatology was described in a descriptive study of patients in Wuhan (Chen et al., 2020), whereas another clinical series of Zhejiang highlighted variability in presenting a confirmed case (Chen et al., 2020). Further systematic review and meta-analysis revealed that respiratory and constitutional symptoms were the most prevalent symptoms of COVID-19 in numerous studies, which supports the significance of thorough clinical examination (Fu et al., 2020).

Otorhinolaryngeal manifestation came to be valued as a significant aspect of COVID-19. ENT symptoms have comprised nasal congestion, rhinorrhea, sore throat, dry throat, olfactory impairment, gustatory impairment, earache, dizziness, and hearing disturbances (El-Anwar et al., 2020). Particular attention was paid to smell and taste disturbances since they were frequent and early onset and observed in otherwise mildly diseased patients. A multicenter European study found olfactory and gustatory dysfunction to be frequent manifestations of mild-to-moderate COVID-19 (Lechien et al., 2020), and outpatient studies also reported changes in smell or taste in mildly symptomatic patients (Spinato et al., 2020). Systematic reviews have provided evidence that the chemosensory dysfunction is a mutual result of SARS-CoV-2 infection. The abnormalities of smell and taste were reported in a consistent manner among various groups of people, but their prevalence rates differed depending on the methods used to assess it and the level of clinical severity (Agyeman et al., 2020). Specialized reviews on olfactory and gustatory disorders also confirmed their diagnostic value and revealed the differences in the onset, duration, and recovery (Costa et al., 2020; Boscutti et al., 2021). In other cases, anosmia has been reported as an initial or isolated symptom, which adds more clinical utility to the symptom in the identification of otherwise less evident infections (Hopkins et al., 2020; Klopfenstein et al., 2020).

There is still clinical interest in the relationship between ENT manifestations and the sternness of the disease. Multiple reports have proposed that smell and taste impairments might become more prevalent in mild or moderate disease, with severe respiratory involvement potentially being predominant in advanced disease (Boscolo-Rizzo et al., 2020). There have also been differences in the timing and intensity of sinonasal symptoms among patients (Speth et al., 2020). In addition to the olfactory and gustatory dysfunction, it has been revealed that hospitalized patients have other otolaryngological complaints, indicating that the addition of chemosensory disturbance is not the only ENT activity

(Özcelik Korkmaz et al., 2021). Audiovestibular symptoms, such as dizziness and hearing-related issues have also been reported, but seem to be less prevalent (Gallus et al., 2021). The knowledge of these patterns can enhance clinical characterization and aid differentiation of symptom patterns with various disease severity levels. Previous recovery investigations have demonstrated that certain olfactory impairments are resolved quickly, and others might not be resolved even after the acute period (Hopkins et al., 2020). Although there has been an increase in literature, few studies have specifically looked at general clinical features and a wide spectrum of ENT manifestations in the same group of patients and directly linked them to disease severity. Consequently, the following study has attempted to characterize clinical and otorhinolaryngeal features of COVID-19 and correlate them with the sternness of the disease.

Objectives of the study

1. To describe the clinical and otorhinolaryngeal characteristics of COVID-19 patients.
2. To assess their association with disease severity and identify predictors of severe/critical COVID-19.

2. Methodology

2.1 Study Design

The study was a secondary observational analytical study based on patient-level data collected previously on individuals with COVID-19 confirmed by laboratory testing. The analysis was aimed to describe demographic and clinical features, general and otorhinolaryngeal manifestations, and determine their relationship with the severity of the disease. The recruitment of no new participants, clinical assessment, or prospective follow-up was not performed. The final analysis involved inclusion of only the variables that were important to the aims of the current research.

2.2 Data Source

The data were obtained from the publicly available Mendeley Data repository (Salepci et al., 2020). The source included 223 patients with laboratory-confirmed COVID-19, their demographic features, comorbidity status, hospitalization, PCR, CT, severity of the disease, the information about the treatments, general clinical manifestations, and otorhinolaryngeal manifestations. The reviewing of the records was followed by an analysis, and only the variables that are directly related to the aims of the current study were kept.

2.3 Study Population and Variables

The sample size was 223 patients with proven SARS-CoV-2 infection, both hospitalized and outpatient. The variables chosen were age, sex, comorbidity status, hospitalization status, CT findings that were suggestive of viral pneumonia, and the severity of the clinical disease. The general manifestations were headache, myalgia/arthralgia, fever, cough, exhaustion, and dyspnea. Otorhinolaryngeal manifestations were frontal headache, nasal congestion, rhinorrhea, sore throat, dry throat, facial paralysis, hearing loss, dizziness, earache, loss of taste, and loss of smell.

2.4 Assessment of Clinical and Otorhinolaryngeal Manifestations

General and otorhinolaryngeal manifestations were rated based on their presence or absence recorded previously. Symptom severity scores and symptom duration scores were also available and evaluated on affected patients. General manifestations were systemic and respiratory manifestations, and otorhinolaryngeal manifestations were nasal, pharyngeal, olfactory, gustatory, otologic, and vestibular.

Smell and taste disturbances were considered independently due to their clinical implications of COVID-19. The severity and duration of the symptoms were also compared in disease-severity categories in which there were sufficient observations.

2.5 Classification of Disease Severity

Four categories of COVID-19 clinical severity were identified: mild, moderate, severe, and critical disease. These classifications were kept to make descriptive comparisons and assess the variations in clinical and otorhinolaryngeal manifestations. To do a regression analysis, disease severity was further classified into mild/moderate and severe/critical. Severe/critical disease was the outcome of interest that would be used to establish factors linked with an increased clinical severity and to classify likely independent demographic, clinical, radiological, and symptom-related predictors.

2.6 Data Preparation

Complete review, duplicate entries, inconsistent coding, and missing information were reviewed to ensure completeness of the records and statistical analysis was performed. Continuous variables were transformed into proper numerical forms and the responses that are categorical were transformed into uniform categories. The dates were recorded when the information on the available symptom duration and time was needed. Variables that did not vary were not subjected to inferential testing and those that had very low frequencies were subjected to descriptive reporting but were used with caution when performing association and regression analyses.

2.7 Statistical Analysis

Descriptive and inferential statistics were used to examine the information. Continuous variables were summarized using the mean, SD, or median, whereas categorical variables were summarized using frequencies and percentages. The chi-square test was used to determine associations among categorical variables and the severity of the disease with the Fisher exact test when cell frequencies were expected to be small. The Kruskal–Wallis H test was used in comparison of continuous variables across disease-severity groups. The regression was conducted to regulate factors related to severe/critical COVID-19, and multivariate logistic regression was conducted, to establish independent predictors. The results were presented in the form of odds ratios, adjusted odds ratios, 95% confidence intervals, and p-values, where $p < 0.05$ was regarded as statistically substantial.

3. Results

3.1 Demographic and Clinical Profile

The analysis included 223 patients and the age data and no duplicates of the same patient were found. The mean age was 50.09 ± 16.46 years. The proportion of males in the study population was 50.7 and females were 49.3. It had comorbidities in 52.5% of the patients and 72.6% of patients were hospitalized. The most common clinical category was moderate disease, and the initial CT finding was suggestive of a viral pneumonia in 81.6% of patients (Table 1).

Table 1. Demographic and clinical features of the study population

Characteristic	Category	n (%) / Mean $\pm$ SD
Age, years	Mean $\pm$ SD	50.09 $\pm$ 16.46
Sex	Male	113 (50.7%)

	Female	110 (49.3%)
Comorbidity	Present	117 (52.5%)
	Absent	106 (47.5%)
Hospitalization	Hospitalized	162 (72.6%)
	Outpatient	61 (27.4%)

Figure 1 shows the distribution of the severity of the illness and the patients' initial CT results with COVID-19.

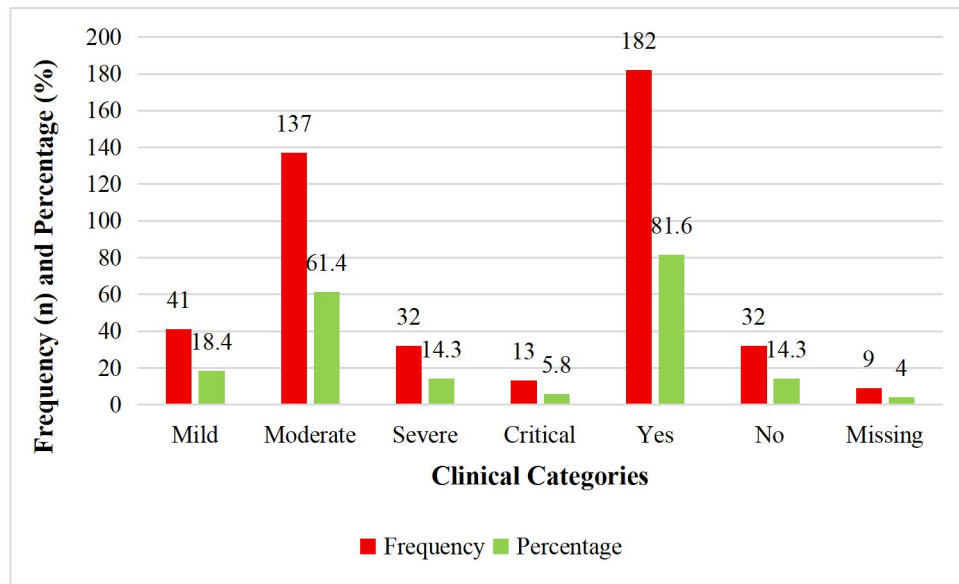


Figure 1. COVID-19 Severity and CT Findings

Figure 1 illustrates the general distribution of the study population in relation to severity of COVID-19 and the initial CT results. The clinical category of moderate disease was the most common, and CT findings that were suggestive of viral pneumonia were frequently seen. The figure gives a brief visual comparison of frequency and percentage of the evaluated clinical categories.

3.2 General Clinical Manifestations

The most mutual general symptom was fatigue, which happened in 71.3% of patients, and cough (54.3). The reported fever and myalgia/arthritis were 50.7 and 50.7, respectively, and dyspnea was 37.7 and headache 26.5. Fever, cough, fatigue and dyspnea showed significant differences among disease-severity groups. The highest increase in severity was observed in dyspnea with the values of 19.5% in mild cases and 100% in critical cases. No significant association with severity was found with myalgia/arthritis and headache (Table 2).

Table 2. General symptoms according to COVID-19 disease severity

Symptom	Overall n (%)	Mild n/N (%)	Moderate n/N (%)	Severe n/N (%)	Critical n/N (%)	p-value
Fever	113 (50.7)	12/41 (29.3)	71/137 (51.8)	22/32 (68.8)	8/13 (61.5)	0.0062

CLINICAL CHARACTERISTICS AND OTORHINOLARYNGEAL MANIFESTATION OF COVID 19 AND THEIR
ASSOCIATION WITH DISEASE SEVERITY

Cough	121 (54.3)	13/41 (31.7)	78/137 (56.9)	18/32 (56.2)	12/13 (92.3)	0.0009
Fatigue	159 (71.3)	22/41 (53.7)	99/137 (72.3)	27/32 (84.4)	11/13 (84.6)	0.0178
Dyspnea	84 (37.7)	8/41 (19.5)	44/137 (32.1)	19/32 (59.4)	13/13 (100.0)	<0.001
Myalgia/arthritis	113 (50.7)	16/41 (39.0)	75/137 (54.7)	17/32 (53.1)	5/13 (38.5)	0.2629
Headache	59 (26.5)	8/41 (19.5)	40/137 (29.2)	11/32 (34.4)	0/13 (0.0)	0.0643

Figure 2 shows the distributions of the major general clinical symptoms by COVID-19 disease-severity groups.

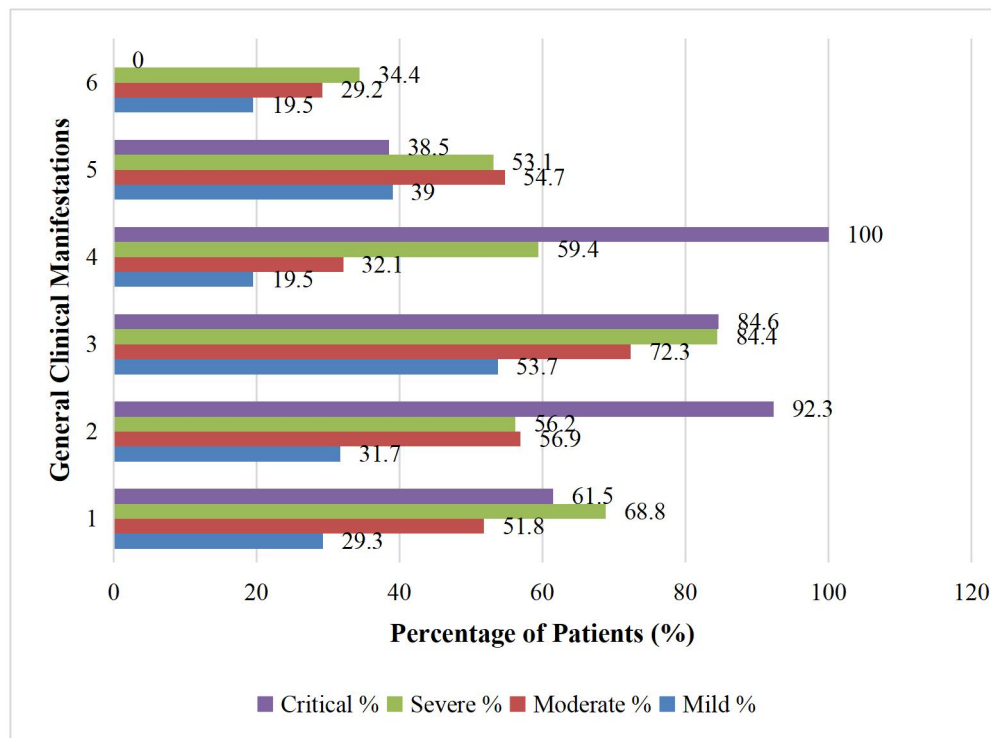


Figure 2. General Symptoms Across COVID-19 Severity Groups

Figure 2 shows that there is evident differences in general clinical manifestations between disease-severity categories. Symptoms (respiratory and systemic) were more likely to become more significant with clinical severity (severe and critical), especially in severe and critical cases. The trend shows the increasing clinical load of COVID-19, as well as variability in symptom presentation among severity groups.

3.3 Otorhinolaryngeal Manifestations

The most common otorhinolaryngeal manifestations were taste loss (34.5% of patients), smell loss (31.8% of patients), and sore throat (26.0% of patients). It was found that nasal congestion and dry

throat were present in 16.6 and 16.1, respectively. Frontal headache and rhinorrhea were found in 11.7 and 10.8. Earache, dizziness and loss of hearing were not common, and facial paralysis was not reported. The mean severity scores of smells and taste were 7.54 and 7.61, respectively, which are relatively high (Table 3).

Table 3. Prevalence and characteristics of otorhinolaryngeal manifestations

ENT manifestation	Present n (%)	Mean severity $\pm$ SD	Median duration, days
Taste loss	77 (34.5)	7.61 $\pm$ 2.40	8.0
Smell loss	71 (31.8)	7.54 $\pm$ 2.63	8.0
Sore throat	58 (26.0)	4.79 $\pm$ 1.67	5.0
Nasal congestion	37 (16.6)	5.59 $\pm$ 2.27	8.0
Dry throat	36 (16.1)	5.58 $\pm$ 2.38	6.0
Rhinorrhea	26 (11.7)	4.50 $\pm$ 1.94	5.0
Frontal headache	24 (10.8)	6.21 $\pm$ 2.23	5.0
Earache	6 (2.7)	4.83 $\pm$ 2.23	7.5
Dizziness	5 (2.2)	5.20 $\pm$ 2.39	7.5
Hearing loss	2 (0.9)	6.50 $\pm$ 2.12	22.5
Facial paralysis	0 (0.0)	-	-

Figure 3 represents the mean severity scores and variability of the individual manifestations of ENT.

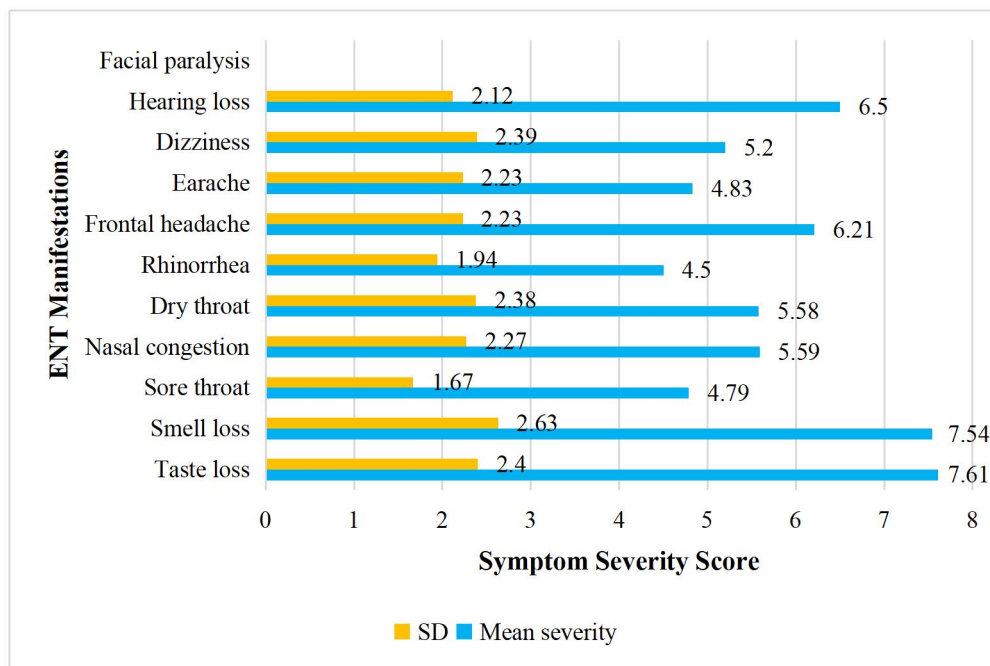


Figure 3. Severity of ENT Manifestations

Figure 3 demonstrates that there are variations in the reported severity of otorhinolaryngeal manifestations in patients with the disease. Smell and taste disturbances showed a relatively higher level of symptom severity, and some nasal, throat, otologic and vestibular manifestations were

moderately severe. The standard deviations show variability of the intensity of symptoms between patients who experience each manifestation.

3.4 Otorhinolaryngeal Manifestations According to Disease Severity

The loss of smell demonstrated substantial correlation with the severity of the disease with the highest percentage of 43.9% in mild cases, 12.5% in severe cases, and 15.4% in critically ill cases. Dizziness and hearing loss were more common in severe cases and were also found to have statistically significant relationships. Conversely, the loss of taste, nasal congestion, rhinorrhea, sore throat, dry throat, frontal headache, and earache did not differ significantly in the severity categories. The outcomes of dizziness and hearing loss are to be considered with caution due to the extremely low frequencies (Table 4).

Table 4. Otorhinolaryngeal manifestations according to COVID-19 disease severity

ENT manifestation	Mild n/N (%)	Moderate n/N (%)	Severe n/N (%)	Critical n/N (%)	p-value
Frontal headache	4/41 (9.8)	14/137 (10.2)	6/32 (18.8)	0/13 (0.0)	0.2863
Nasal congestion	8/41 (19.5)	22/137 (16.1)	4/32 (12.5)	3/13 (23.1)	0.7860
Rhinorrhea	6/41 (14.6)	14/137 (10.2)	4/32 (12.5)	2/13 (15.4)	0.8434
Sore throat	11/41 (26.8)	36/137 (26.3)	7/32 (21.9)	4/13 (30.8)	0.9283
Dry throat	3/41 (7.3)	24/137 (17.5)	5/32 (15.6)	4/13 (30.8)	0.2026
Smell loss	18/41 (43.9)	47/137 (34.3)	4/32 (12.5)	2/13 (15.4)	0.0164
Taste loss	18/41 (43.9)	47/137 (34.3)	9/32 (28.1)	3/13 (23.1)	0.4024
Earache	3/41 (7.3)	1/137 (0.7)	2/32 (6.2)	0/13 (0.0)	0.0637
Dizziness	0/41 (0.0)	1/137 (0.7)	4/32 (12.5)	0/13 (0.0)	0.0004
Hearing loss	0/41 (0.0)	0/137 (0.0)	2/32 (6.2)	0/13 (0.0)	0.0072
Facial paralysis	0/41 (0.0)	0/137 (0.0)	0/32 (0.0)	0/13 (0.0)	-

3.5 Age and Symptom Characteristics Across Severity Groups

Mean age significantly rose with groups of disease-severity, with 36.17 +/-14.28 years in mild cases, 50.28 +/-14.88 years in moderate cases, 62.75 +/-13.63 years in severe cases, and 60.85 +/-11.19 years in critical disease. The alteration was not only substantial ($H = 52.094$, $p < 0.001$) but also statistically significant. The severity and duration of fever, fatigue, duration of dyspnea and duration of myalgia/arthritis were also found to differ significantly, but the severity and duration of smell- and taste-related measures were not statistically significant (Table 5).

Table 5. Comparison of selected continuous variables across COVID-19 disease severity groups

Variable	H statistic	p-value
Age	52.094	<0.001
Fever severity	7.985	0.0463
Fatigue severity	12.232	0.0066
Fatigue duration	17.121	0.0007
Dyspnea duration	16.434	0.0009

Myalgia/arthralgia duration	8.877	0.0310
Smell-loss severity	1.777	0.6199
Smell-loss duration	6.518	0.0890
Taste-loss severity	7.795	0.0505
Taste-loss duration	4.049	0.2562

3.6 Factors Associated with Severe/Critical COVID-19

Univariable logistic regression revealed that growing age, comorbidity, CT manifestations of viral pneumonia, fever, fatigue, dyspnea, loss of smell, and dizziness were significantly correlated with severe/critical COVID-19. The odds were raised by about 6.8 per every extra year of age. Dyspnea was correlated with nearly six-fold increased odds, but loss of smell had significantly decreased odds of severe/critical disease. The odds of dizziness were higher but its confidence interval was broad due to low number of patients reporting this manifestation (Table 6).

Table 6. Univariable predictors of severe/critical COVID-19

Predictor	OR	95% CI	p-value
Age, per year	1.068	1.041–1.095	<0.001
Comorbidity	3.538	1.686–7.422	0.0008
CT suggestive of viral pneumonia	12.754	1.703–95.485	0.0132
Fever	2.289	1.153–4.547	0.0180
Fatigue	2.557	1.076–6.076	0.0335
Dyspnea	5.964	2.900–12.267	<0.001
Smell loss	0.267	0.107–0.666	0.0046
Dizziness	17.268	1.880–158.601	0.0118

3.7 Independent Factors Associated with Severe/Critical Disease

In multivariate logistic regression, age was the sole significant independent variable that was found to be related with severe/critical COVID-19. The adjusted odds of severe/critical disease rose by 5.9% with each extra year of age. After correction, male sex, comorbidity, CT appearances indicative of viral pneumonia and fever were no longer statistically significant. There was an increased adjusted odds ratio in CT evidence of viral pneumonia, with a wide confidence interval and not statistically significant (Table 7).

Table 7. Multivariable logistic regression for severe/critical COVID-19

Predictor	Adjusted OR	95% CI	p-value
Age, per year	1.059	1.027–1.093	0.0003
Male sex	1.426	0.679–2.995	0.3480
Comorbidity	1.362	0.554–3.352	0.5007
CT suggestive of viral pneumonia	5.778	0.715–46.704	0.0999
Fever	1.891	0.885–4.042	0.1001

4. Discussion

The study has revealed that there were apparent disparities in demographic, clinical, and otorhinolaryngeal features with respect to COVID-19 severity. In multivariate analysis, increasing age was significantly correlated with severity of the disease and it was the only independent predictor. Other univariable predictors of severe/critical disease included fever, fatigue, dyspnea, comorbidity, and CT evidence of viral pneumonia. Those results align with previous evidence in hospitals indicating that advanced age and comorbidity, respiratory dysfunction, and pulmonary involvement were the salient characteristics among patients with more severe clinical outcomes (Wang et al., 2020). Likewise, mortality-based studies found age and systemic disease burden to be significant factors leading to poor outcomes in hospitalized COVID-19 groups (Zhou et al., 2020). Fatigue was the most common general manifestation, whereas fever, cough, and dyspnea differed greatly in terms of severity. Dyspnea demonstrated the most apparent increment with disease deterioration and a powerful relationship with severe/critical COVID-19. Such a pattern is clinically plausible as the progressive respiratory involvement indicates progressive pulmonary compromise. The noted correlation between CT findings that are suggestive of viral pneumonia and severity of disease further substantiate involvement of lower respiratory tract in clinical progression. These results suggest that general respiratory symptoms continued to be more informative to determine severe disease than most symptoms of the upper-airway. The manifestation of otorhinolarynx was different. Taste loss and smell loss were the most common ENT symptoms, followed by sore throat, nasal congestion, dry throat, and rhinorrhea. The eminence of chemosensory impairment is consistent with prior systematic data that showed that olfactory and gustatory impairments were common presentations of SARS-CoV-2 infection (Tong et al., 2020). The presence of objective clinical assessment of the significant level of anosmia and ageusia in infected patients has also proven the biological and clinical significance of these symptoms (Vaira et al., 2020). More extensive systematic evidence has also revealed a significant difference in prevalence in relation to population characteristics and assessment methods (Wu et al., 2022). One of the most significant results was that there was an inverse relationship between smell loss and severe/critical disease. In mild and moderate cases, the loss of smell was more common and was linked to the lower odds of severe/critical illness. This trend is in line with the indications that chemosensory dysfunction can be a more typical feature of less severe COVID-19 manifestations (Yan et al., 2020). There was a similar numerical decrease in taste loss between severity categories, but the relationship was not statistically significant. These results could indicate that smell disturbance is more of an indicator of upper-airway or regional sensory impairment than of the progression of systemic disease.

Among severe cases, dizziness and hearing loss were more common, but these results should be viewed with caution as very few patients had these manifestations. Their frequencies were low, resulting in unstable estimates and restricting firm interpretation. Conversely, the dysfunction of smell and taste were prevalent enough to allow more valid comparisons. The clinical importance of the persistence and recovery of these symptoms is also of clinical significance as subsequent meta-analytic results indicated that recovery courses differ and that some patients might have chronic chemosensory impairment (Tan et al., 2022). The results have clinical implications in clinical assessment. General respiratory symptoms, especially dyspnea, could be used to warn of progression of the disease, but the loss of smell could be a more typical feature of mild manifestations. Systemic, respiratory, radiological, and ENT findings can be combined thus enhancing clinical characterization. The study however was limited due

to its secondary observational design, use of information previously recorded, small numbers of rare ENT manifestations and lack of causality. Future research must include larger multicenter cohorts, objective ENT testing, and longitudinal follow-up to elucidate whether certain otorhinolaryngeal symptoms can be reliably used to aid in early severity stratification and prognosis.

5. Conclusion

This study has revealed that COVID-19 manifested a wide range of clinical and otorhinolaryngeal symptoms, with an obvious difference by the severity of the disease. The most typical general symptoms were fever, coughing, and exhaustion, dyspnea, and myalgia/arthritis, whereas the most common of the otorhinolaryngeal manifestations were sore throats, loss of taste, and loss of smell. Older age was closely linked to more severe disease and the only independent predictor of severe/critical COVID-19 in the presence of multivariate factors. Greater severity was also linked to comorbidity, CT evidence of viral pneumonia, fever, fatigue and dyspnea with univariable analysis. Of ENT manifestations, loss of smell was more prevalent in cases of mild to serious illness, and was less likely to represent severe/critical disease, indicating that olfactory dysfunction might be more typical of less severe manifestations. Dizziness and hearing loss were reported in severe cases only, but very rarely, which makes their interpretation difficult. On the whole, the presented results point out that the combination of general clinical manifestations with otorhinolaryngeal manifestations can better represent the presentation and severity of COVID-19. The special focus on age, respiratory symptoms, radiological results, and issues with smell can be used in clinical evaluation. To establish these associations and to understand the prognostic implications, larger prospective multicenter studies that use a standardized ENT evaluation should be conducted.

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