

# Ocular Symptoms in Long COVID: A Cross-Sectional Study

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**Introduction:** This study compared demographics, socioeconomic characteristics, pre-pandemic health conditions, newly diagnosed health conditions, and long COVID symptoms between participants with and without self-reported new-onset ocular symptoms after COVID-19 infection.

**Material and Methods:** We performed a cross-sectional analysis of the Listen to Immune, Symptom, and Treatment Experiences Now (LISTEN) study. Adults who self-reported long COVID, completed surveys between May 2022 and October 2023, and did not report post-vaccination syndrome were included. Ocular symptoms were defined as self-reported new-onset blurring or loss of vision, dry eyes, or floaters/flushes of light attributed to long COVID. Group comparisons used percentages for categorical variables and median and interquartile range (IQR) for continuous variables as well as Bonferroni-adjusted P-values. A gradient-boosted tree model was used to identify symptoms that differentiated groups.

**Results:** Among 595 participants (median age 46 years [IQR 38–56]; 73% female), 341 (57%) reported ocular symptoms. Pre-pandemic comorbidities were similar between groups. Participants with ocular symptoms had lower EuroQoL visual analogue scale health scores (median 40 [IQR 30–59] vs 51 [IQR 39–70],  $P < 0.001$ ), greater financial difficulties (20% vs 8.8%,  $P < 0.001$ ), increased worry about housing stability (16% vs 5.4%,  $P < 0.001$ ), and higher rates of new-onset dysautonomia (38% vs 15%,  $P < 0.001$ ) and myalgic encephalomyelitis/chronic fatigue syndrome (21% vs 9.1%,  $P = 0.005$ ). Key differentiating symptoms included dizziness, cold intolerance, pressure at the base of the head, tinnitus, and tremors.

**Conclusion:** Individuals with long COVID with self-reported new-onset ocular symptoms after infection may represent a more severe phenotype, with poorer health status and greater socioeconomic challenges despite similar pre-pandemic health profiles.

**Keywords:** long COVID, vision, public health, epidemiology

## Introduction

Long COVID, characterized by a constellation of symptoms persisting long after the initial recovery from coronavirus disease 2019 (COVID-19), has emerged as a critical area of concern, encompassing a wide range of symptoms, including abnormalities in sensory function.<sup>1,2</sup> Changes in smell and taste have been commonly described as occurring in the acute phase of infection and then continuing as a post-acute condition. However, long COVID symptoms related to changes in vision have not been recognized to the same extent. Previous literature has highlighted ocular symptoms in long COVID, including reading-related issues and blurry vision, with smaller studies reporting prevalence of the condition ranging between 7% and 38%.<sup>3-5</sup> Ocular manifestations following SARS-CoV-2 infection have been reported across a broad

spectrum, ranging from common, typically self-limited ocular surface symptoms such as conjunctivitis to rarer posterior segment and neuro-ophthalmic events, often occurring in the context of systemic illness severity.<sup>6,7</sup> In contrast, population-based studies have not demonstrated a consistent causal association between COVID-19 vaccination and most ocular adverse events.<sup>6</sup> These reports are heterogeneous, spanning distinct ocular pathways and clinical contexts, underscoring the challenge of inferring specific ophthalmic diagnoses from symptom-based data.<sup>6</sup> Signs of direct viral infection in the eye due to SARS-CoV-2 inducing a hyperinflammatory response in the retina and causing apoptosis in the blood-retinal barrier have been documented as part of its pathogenesis, contributing to ocular symptoms.<sup>5,8</sup> As well, eye examinations of individuals with long COVID using retinal vessel analysis has found persistent endothelial dysfunction to be a hallmark of the condition, which may explain ongoing ocular symptoms.<sup>9</sup> Other types of coronaviruses have not been reported in relation to ocular symptoms, making these reports unexpected and warranting further investigation.<sup>10</sup>

Understanding how long COVID affects vision is imperative, as alterations in vision can significantly impede daily activities, increase psychological stress, and lead to substantial healthcare needs. Although each individual ocular symptom category was reported with sufficient frequency, these symptoms were analyzed as a composite outcome because they were self-reported and may reflect overlapping underlying experiences (for example, dry eye may be perceived and reported as blurred vision), raising the risk of misclassification if analyzed separately. Moreover, it is unclear if post-COVID ophthalmic sequelae indicate a more severe form of long COVID or if socioeconomic factors, comorbidities, symptom patterns, and health status are associated with developing ocular symptoms in long COVID. We hypothesized that ocular symptoms in long COVID patients would be associated with a severe disease phenotype, marked by greater health decline and significant socioeconomic challenges, highlighting the need for personalized, comprehensive care strategies to address their unique needs.

The aim of this study was to compare individuals experiencing long COVID with and without ocular symptoms to determine if these symptoms indicate a more severe long COVID phenotype. Understanding this association is crucial for developing targeted and effective care strategies. To achieve this, we used the Listen to Immune, Symptom, and Treatment Experiences Now (LISTEN) study for its comprehensive data on both health and non-health-related characteristics, enabling a thorough and insightful analysis.

## Materials and Methods

### Study Design

Our analysis used data from participants who self-reported long COVID in the LISTEN study, an online observational study enrolling adults aged 18 years or older through the Hugo Health Kindred platform, an online community. Participants provided electronic informed consent and completed structured surveys capturing demographics, pre-pandemic health conditions, newly diagnosed conditions, and symptoms attributed to long COVID. The present study is a retrospective, descriptive, observational analysis based on these survey data. The design of the LISTEN study, including participant enrollment, survey structure, and prior symptom-based subgroup analyses, has been described in detail in prior LISTEN publications, including Zhou et al<sup>11</sup> In brief, the LISTEN study engaged participants through Hugo Health Kindred (closed as of May 2024), an online community of individuals aged 18 and above, who expressed interest in COVID research. The study aimed to encompass individuals reporting symptoms of long COVID, those experiencing post-vaccination syndrome, and suitable controls; however, this paper specifically examines individuals with long COVID. Recruitment for Hugo Health Kindred occurred primarily through word-of-mouth and social media channels. Participants provided electronic informed consent and completed surveys online using a computer or mobile device. To be eligible for the LISTEN study, participants had to be at least 18 years old and fluent in English. The Kindred platform facilitates information exchange and allows members to share survey responses and health data for research only with their explicit permission. Following consent, LISTEN collects participant-reported surveys and narratives and may also collect participant-generated wearable data and linked medical record information; however, the present analysis used survey responses only. Surveys were developed iteratively with participant feedback to maximize relevance and comprehension. Participants completed enrollment surveys covering demographic, infection, vaccination, clinical, social, and health status information on computers or mobile devices, with reminders to encourage completion. In a subset of participants, deep immune phenotyping was also performed, but these data were not used in the present analysis.

## Study Sample

This study included individuals from the LISTEN study who reported having long COVID at the time of survey, between May 2022 and October 2023. Long COVID was defined in LISTEN as self-reported symptoms persisting at least 4 weeks after SARS-CoV-2 infection. A positive SARS-CoV-2 test was not required because early in the pandemic testing was unavailable and access and uptake varied thereafter. Individuals who were regarded as controls, reported vaccine injury, or reported both vaccine injury and long COVID, were excluded from this analysis. Analyses were restricted to participants who completed both the demographic survey and the conditions and symptoms survey, to ensure a consistent analytic dataset.

## Data Collection

Participants in Hugo Health Kindred had the opportunity to fill out various surveys, which were developed through a collaborative and iterative method incorporating feedback from the participants themselves. The surveys inquired about demographic and socioeconomic details such as age, gender, race and ethnicity, marital status, employment and income status before the pandemic, housing stability, and country of residence. The SARS-CoV-2 index infection timing, defined as the first reported COVID-19 infection for each participant, was also surveyed and categorized into variant periods based on dates of dominant circulating strains. Pre-Delta (before June 26, 2021), Delta (June 26, 2021 to December 24, 2021), and Omicron (December 25, 2021 to June 25, 2022) periods were defined according to prior published work.<sup>12</sup> Infections occurring after June 25, 2022 were categorized as Post-Omicron to capture subsequent Omicron subvariant circulation.

To assess the severity of SARS-CoV-2 infections, participants were asked about any hospitalizations due to COVID-19-related conditions. Participants rated overall health using the EuroQoL visual analogue scale (EQ-VAS), a validated component of the EQ-5D instrument, which was administered as a pre-specified item within the LISTEN survey.<sup>13,14</sup> The instrument measures self-reported health status on a vertical visual analog scale from 0 (“worst health you can imagine”) to 100 (“best health you can imagine”) on that specific day, designed to capture respondents’ self-rated overall health from their own perspective. Severity of the individuals’ long COVID symptoms was gauged by asking participants to rate the severity of their symptoms on their worst days on a scale from 0 (trivial illness) to 100 (unbearable condition).

The survey also collected information on health issues before the pandemic, existing health conditions, and symptoms associated with long COVID. To assess pre-pandemic comorbidities, participants were asked whether a physician had diagnosed them with any of 38 broad condition categories before January 2020, a conservative cutoff chosen to ensure that reported conditions clearly predated SARS-CoV-2 infection. These categories reflect major diagnostic groups rather than individual diseases. Options for “other” and “none of the above” were also included. Current health conditions were determined by asking if a doctor had diagnosed them with any conditions from a slightly different list of 39 diagnostic categories, again with options for “other” and “none of the above.” Conditions reported as current but not as pre-pandemic were classified as newly onset conditions.

For long COVID symptoms, the survey inquired about health issues participants attributed to long COVID, offering a list of 96 specific symptoms alongside “other” and “none of the above” within the question within the question “Please select all following health conditions that you have had as a result of long COVID.” The wording for these symptoms was developed with input from participants, and the symptoms were listed as they were presented in the survey. The “runny nose” and “fatigue” symptoms were dropped as they overlapped with the “post-nasal drip” and “excessive fatigue” symptoms. Symptoms were collected using a check-all-that-apply format within the conditions and symptoms survey. Participants were classified as having ocular symptoms if they reported any of three patient-reported items attributed to long COVID: blurred or loss of vision, dry eyes, or floaters or flashes of light. These items were pre-specified in the original LISTEN survey and approved under the initial Institutional Review Board protocol. Because these symptoms may reflect overlapping experiences and variable labeling in self-reported data, they were analyzed as a composite outcome. Participants were instructed to report symptoms that were new-onset after SARS-CoV-2 infection and attributed to long COVID. Ocular symptoms reported as present before infection were not classified as long COVID-related. This approach aligns with the LISTEN survey framework, which distinguishes pre-pandemic symptoms from

symptoms attributed to long COVID. Since the vision-related symptoms are self-reported and may reflect overlapping underlying causes, such as blurred vision being due to ocular surface disease or vitreoretinal phenomena, each item was captured as a distinct, patient-reported symptom in the LISTEN but was analyzed as part of a composite ocular symptom outcome to minimize misclassification from differential symptom labeling. These items were grouped to reflect the presence of any vision-related complaint rather than to infer a specific ophthalmic diagnosis.

## Statistical Analysis

We characterized the participants by calculating percentages for categorical variables and using the median and interquartile range (IQR) for continuous variables. The analysis included comparing participants with and without ocular symptoms across various demographic, socioeconomic, health conditions, and long COVID symptoms. For categorical variables, chi-squared and Fisher's exact tests were utilized, whereas Wilcoxon rank-sum and Kruskal–Wallis rank-sum tests were applied to continuous variables. In examining differences in pre-pandemic comorbidities, new-onset conditions, and long COVID symptoms, we applied the Bonferroni correction for multiple testing within each category, presenting adjusted P-values. Hospitalization for COVID-19-related conditions was evaluated descriptively as an indicator of acute illness severity and was not included as an adjustment variable.

To assess the representativeness of our cohort, we calculated the age, sex, and race distribution of long COVID individuals in the 2023 National Health Interview Survey (NHIS) as a comparison. We limited the sample to individuals who had either a confirmed positive COVID-19 test or a doctor's diagnosis of COVID-19 and responded "yes" to the question "Did you have any symptoms lasting 3 months or longer that you did not have before having coronavirus or COVID-19?"

We used feature importance in gradient-boosted tree machine learning models to identify the most important symptoms from the entire 91 symptoms collected for differentiating participants experiencing ocular symptoms compared to those not experiencing ocular symptoms.<sup>15,16</sup> For these machine learning analyses, the three ocular symptom variables used to define the outcome and overlapping symptoms ("runny nose" and "fatigue") were excluded, leaving 91 candidate non-ocular symptoms. We trained models using the *gbm* package in R (*gbm* *permute*) to predict whether a participant experienced ocular symptoms or not, using information on the presence or absence of other symptoms for each participant, with 5-fold 5-repeat cross-validation.<sup>17</sup> We selected the hyperparameters with the highest area under the curve (AUC) from the internal cross-validation. Then, we computed the importance of each variable in differentiating participants with and without ocular symptoms using a permutation-based approach. Permutation-based variable importance estimates how much model performance decreases when a symptom's values are randomly shuffled, with larger decreases indicating greater importance for distinguishing groups. Variables were considered more important if perturbing their values resulted in larger reductions in model discrimination, indicating a greater contribution to distinguishing participants with and without ocular symptoms rather than an independent or causal effect. We sorted the variables based on their importance and progressively excluded those with the least importance from the model. We evaluated change in AUC, and when the AUC first decreased by at least 1.5%, we stopped excluding variables and selected that model as the best model. If a drop of this magnitude did not occur, we selected the model with the variables before the largest drop in AUC. The variables in the final selected model were used to identify the symptoms most important in differentiating patients with and without ocular symptoms.

To further evaluate the relative importance of the identified variables, we applied a second variation of the modeling approach - XGBoost - and used gain in accuracy metrics (*xgb* *gain*) and Shapley values (*xgb* *shap*) to assess variable importance.<sup>18,19</sup> We compared each variation of the model - *gbm* *permute*, *xgb* *gain*, and *xgb* *shap* - for variable importance values using Pearson correlation coefficients.

All tests were bidirectional, with a P-value of less than 0.05 deemed significant. The Bonferroni method was employed to maintain the family-wise error rate at 0.05. Statistical analysis was conducted using R software, version 4.3.1 (2023-06-15). The Yale University Institutional Review Board granted approval for the LISTEN study on April 1, 2022 (Protocol Number 2000032207). All survey items, including the vision-related symptom questions analyzed in this study, were pre-specified in the original LISTEN survey and approved under the initial Institutional Review Board protocol. Participants provided informed consent to the study through electronic forms. The data used in this study is not

publicly available due to participant privacy, but is accessible in a deidentified format upon reasonable request from the corresponding author, HMK. The conduct of LISTEN adheres to the principles outlined in the Declaration of Helsinki and follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines for observational studies.

## Results

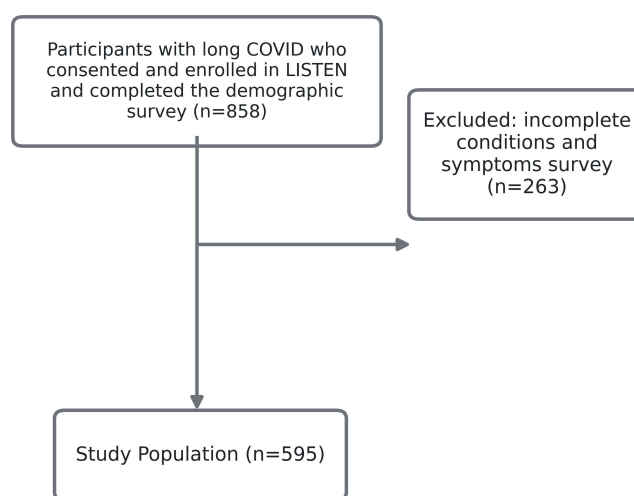
Between May 2022 and October 2023, the LISTEN study had 858 individuals with long COVID that provided consent and completed the initial survey (Figure 1). Of these, 263 (31%) were excluded from the final analysis due to incomplete surveys on demographics, conditions, and symptoms, resulting in a study cohort of 595 (69%) participants (Figure 1). Among the 595 participants, 341 (57%) reported ocular symptoms.

### Demographic and Socioeconomic Characteristics Before the Pandemic

Overall, the participants with long COVID had a median age of 46 years (IQR 38–56), with 73% identifying as female, 86% as Non-Hispanic White, and 93% residing in the United States (Table 1). For context, we compared the demographic composition of the cohort with that of individuals reporting long COVID in the NHIS; this comparison is descriptive and not intended as an inferential benchmark. As shown in Table S1, the NHIS cohort was predominantly female and non-Hispanic White, highlighting limitations for generalizability. Nevertheless, the NHIS analysis was performed to demonstrate that the skew is a national phenomenon. Within our cohort, those with ocular symptoms were more likely to be female (78% vs 68% female,  $P = 0.02$ ), but did not significantly differ by age, race and ethnicity, marital status, pre-pandemic employment status, pre-pandemic household income, and country of residence compared to those without these symptoms. Country-level comparisons were limited by the predominance of U.S.-based participants and should not be interpreted as evidence of no geographic variation.

### Characteristics of SARS-CoV-2 Infection and Post-COVID Socioeconomic Impact

The initial SARS-CoV-2 infection for most participants occurred before the Delta variant wave (41%), with 8.9% requiring hospitalization due to COVID-19 (Table 1). The distribution of index SARS-CoV-2 infection dates across major variant periods is shown in Figure S1. Those with ocular symptoms more frequently reported their initial infection during the pre-Delta period (46% [95% CI, 41–52] vs. 34% [28–41],  $P < 0.001$ ). They also had a significantly greater rate of experiencing hospitalization for COVID-related conditions (6.2% vs. 0.8%,  $P = 0.01$ ). No significant difference in current health insurance status or level of social support was found ( $P > 0.05$ ; Table 1). However, individuals with ocular symptoms reported more current financial hardship (very much financial difficulties, 20% [95% CI, 16–25] vs. 8.8% [5.7–13],  $P < 0.001$ ), housing



**Figure 1** Patient Selection. LISTEN = Listen to Immune, Symptom and Treatment Experiences Now.

**Table 1** Participant Demographics, Socioeconomic Characteristics, and SARS-CoV-2 Infection Characteristics

Characteristic <sup>a</sup>	Overall, N = 595	95% CI <sup>a</sup>	No Ocular Symptoms <sup>b</sup> , N = 254	95% CI <sup>a</sup>	Has Ocular Symptoms <sup>b</sup> , N = 341	95% CI <sup>a</sup>	p-value <sup>c</sup>
Age (years), median (IQR)	46, 38–56		47, 37–58		46, 38–53		0.105
Gender, No. (%)							0.016
Female	437 (73)	70-77	172 (68)	62-73	265 (78)	73-82	
Male	150 (25)	22-29	77 (30)	25-36	73 (21)	17-26	
Non-binary	8 (1.3)	0.63–2.7	5 (2.0)	0.73–4.8	3 (0.9)	0.23–2.8	
Race/Ethnicity, No. (%)							0.969
Asian	17 (2.9)	1.7–4.6	7 (2.8)	1.2–5.8	10 (2.9)	1.5–5.5	
Black	12 (2.0)	1.1–3.6	4 (1.6)	0.51–4.3	8 (2.3)	1.1–4.8	
Latino	13 (2.2)	1.2–3.8	6 (2.4)	0.96–5.3	7 (2.1)	0.90–4.4	
Other	43 (7.2)	5.3–9.7	19 (7.5)	4.7-12	24 (7.0)	4.7-10	
White	510 (86)	83-88	218 (86)	81-90	292 (86)	81-89	
Country of residence, No. (%)							0.772
Canada	18 (3.0)	1.9–4.8	6 (2.4)	0.96–5.3	12 (3.5)	1.9–6.2	
Germany	5 (0.8)	0.31–2.1	1 (0.4)	0.02–2.5	4 (1.2)	0.38–3.2	
United Kingdom	6 (1.0)	0.41–2.3	2 (0.8)	0.14–3.1	4 (1.2)	0.38–3.2	
U.S.	551 (93)	90-95	238 (94)	90-96	313 (92)	88-94	
Other countries	15 (2.5)	1.5–4.2	7 (2.8)	1.2–5.8	8 (2.3)	1.1–4.8	
Marital Status, No. (%)							0.387
Divorced	58 (10)	8.0-13	18 (7.5)	4.6-12	40 (13)	9.2-17	
Married or civil union	323 (58)	54-62	143 (60)	53-66	180 (57)	51-62	
Never married	159 (28)	25-32	72 (30)	24-36	87 (27)	23-33	
Separated	10 (1.8)	0.91–3.4	4 (1.7)	0.54–4.5	6 (1.9)	0.77–4.3	
Widowed	8 (1.4)	0.67–2.9	3 (1.3)	0.32–3.9	5 (1.6)	0.58–3.8	
Missing data	37		14		23		
Employed pre-pandemic, No. (%)	476 (86)	82-88	203 (85)	80-89	273 (86)	82-90	0.694
Missing data	39		15		24		
Pre-pandemic annual household income, No. (%)							0.402
\$10,000 to \$35,000	32 (5.8)	4.0–8.1	12 (5.0)	2.7–8.8	20 (6.3)	4.0–9.7	
\$35,000 to less than \$50,000	40 (7.2)	5.3–9.7	12 (5.0)	2.7–8.8	28 (8.8)	6.1-13	
\$50,000 to less than \$75,000	52 (9.4)	7.1-12	21 (8.8)	5.7-13	31 (9.8)	6.8-14	
\$75,000 or more	386 (69)	65-73	170 (71)	65-77	216 (68)	63-73	
Less than \$10,000	8 (1.4)	0.67–2.9	4 (1.7)	0.54–4.5	4 (1.3)	0.40–3.4	
Prefer not to answer	38 (6.8)	4.9–9.3	20 (8.4)	5.3-13	18 (5.7)	3.5–9.0	
Missing data	39		15		24		
Index SARS-CoV-2 infection time period, No. (%)							<0.001
Pre-Delta	215 (41)	37-46	72 (34)	28-41	143 (46)	41-52	
Delta	62 (12)	9.3-15	23 (11)	7.1-16	39 (13)	9.2-17	
Omicron	155 (30)	26-34	64 (30)	24-37	91 (29)	24-35	
Post-Omicron	90 (17)	14-21	54 (25)	20-32	36 (12)	8.4-16	
Missing data	73		41		32		
Hospitalized for COVID-related conditions, No. (%)	53 (8.9)	6.8-12	14 (5.5)	3.2–9.3	39 (11)	8.4-15	0.012
Number of weeks between infection and completing the symptom survey, median (IQR)	68, 36-112		59, 30-99		74, 42-121		<0.001
Missing data	75		42		33		
Financial difficulties caused by the pandemic, No. (%)							<0.001
Not at all	177 (32)	28-36	101 (42)	36-49	76 (24)	19-29	
A little	205 (37)	33-41	89 (37)	31-44	116 (37)	31-42	
Very much	84 (15)	12-18	21 (8.8)	5.7-13	63 (20)	16-25	
Quite a bit	90 (16)	13-20	28 (12)	8.1-17	62 (20)	15-24	
Missing data	39		15		24		
Do not have health insurance, No. (%)	19 (3.2)	2.0–5.0	6 (2.4)	0.96–5.3	13 (3.8)	2.1–6.6	0.320

(Continued)

**Table 1** (Continued).

Characteristic <sup>a</sup>	Overall, N = 595	95% CI <sup>a</sup>	No Ocular Symptoms <sup>b</sup> , N = 254	95% CI <sup>a</sup>	Has Ocular Symptoms <sup>b</sup> , N = 341	95% CI <sup>a</sup>	p-value <sup>c</sup>
Social support (someone around to help you if you need it), No. (%)							0.140
Never	30 (5.4)	3.7–7.7	9 (3.8)	1.8–7.2	21 (6.6)	4.2–10	
Rarely	47 (8.4)	6.3–11	19 (7.9)	5.0–12	28 (8.8)	6.0–13	
Sometimes	107 (19)	16–23	41 (17)	13–23	66 (21)	17–26	
Usually	205 (37)	33–41	86 (36)	30–42	119 (37)	32–43	
Always	169 (30)	27–34	85 (35)	29–42	84 (26)	22–32	
Missing data	37		14		23		
Social isolation (how often do you feel isolated from others?), No. (%)							0.001
Hardly ever or never	110 (20)	17–23	63 (26)	21–33	47 (15)	11–19	
Some of the time	225 (41)	37–45	96 (40)	34–47	129 (41)	35–46	
Often	219 (40)	35–44	79 (33)	27–40	140 (44)	39–50	
Missing data	41		16		25		
Housing, No. (%)							<0.001
I do not have a steady place to live	5 (0.9)	0.33–2.2	1 (0.4)	0.02–2.7	4 (1.3)	0.40–3.4	
I have a place to live today, but I am worried about losing it in the future	65 (12)	9.2–15	13 (5.4)	3.0–9.3	52 (16)	13–21	
I have a steady place to live	488 (87)	84–90	226 (94)	90–97	262 (82)	78–86	
Missing data	37		14		23		

**Notes:** <sup>a</sup> IQR, interquartile range; CI, Confidence Interval. <sup>b</sup> Ocular symptoms were analyzed as a composite outcome to reduce misclassification from overlapping self-reported symptom experiences. <sup>c</sup> Wilcoxon rank sum test; Fisher's exact test; Pearson's Chi-squared test.

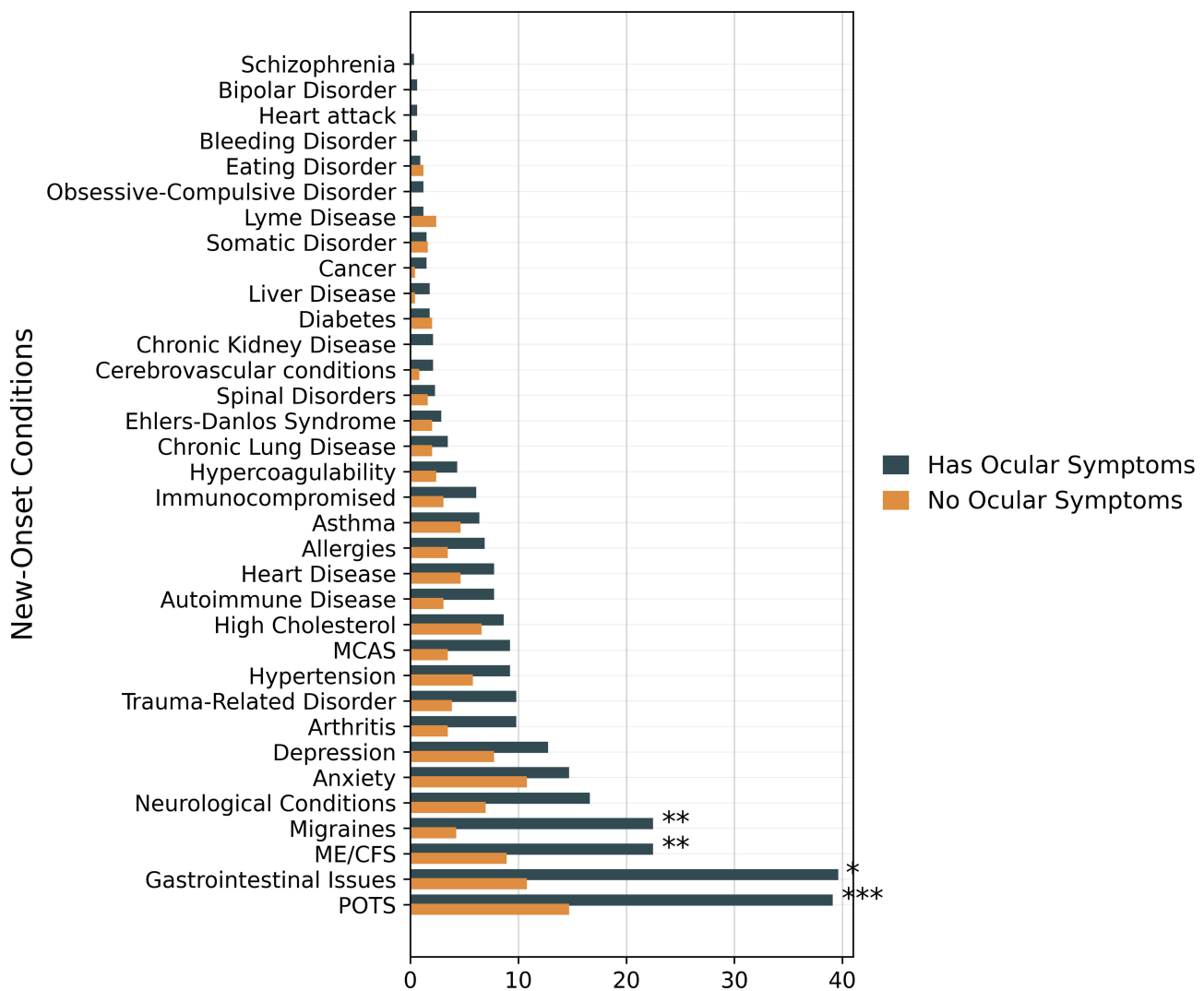
instability due to the pandemic (having a steady place to live, 82% [95% CI, 78–86] vs. 94% [90–97],  $P < 0.001$ ), and social isolation (hardly ever or never isolated, 15% [95% CI, 11–19] vs. 26% [21–33],  $P = 0.001$ ).

## Health Conditions Before the Pandemic

The most commonly reported health conditions before the pandemic ([Table S2](#)) included any allergies (49%), anxiety disorders (31%), depressive disorders (29%), and gastrointestinal issues (26%). Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) was more present in those with ocular symptoms compared to those without these symptoms before the pandemic (6.2% [95% CI, 3.9–9.4] vs. 0.8% [0.14–3.1],  $P < 0.001$ ). The proportion of all other pre-pandemic comorbidities surveyed did not differ between the two groups, including co-morbidities which may influence vision such as diabetes and hypertension. For readability, we highlight the most frequent and clinically relevant differences; full results are shown in [Table S2](#).

## New-Onset Conditions

In the entire study group, the most frequently newly emerging health conditions were postural orthostatic tachycardia syndrome (POTS) or other dysautonomia (28%), gastrointestinal issues (16%), and ME/CFS (16%) ([Table S3](#)). Those who experienced ocular symptoms, compared with those without, reported a significantly higher percentage of POTS or other dysautonomia (38% [95% CI, 33–43] vs. 15% [11–20],  $P < 0.001$ ), gastrointestinal issues (21% [95% CI, 17–26] vs. 11% [7.2–15],  $P = 0.03$ ), ME/CFS (21% [95% CI, 17–26] vs. 11% [7.2–15],  $P = 0.005$ ), and migraines (15% [95% CI, 11–19] vs. 4.3% [2.3–7.8],  $P < 0.001$ ; [Figure 2](#); [Table S3](#)). All other newly reported conditions did not differ significantly between groups after correction for multiple testing. The frequency of all surveyed new-onset conditions in the entire cohort, as well as in those with and without ocular symptoms, can be found in [Table S3](#).



**Figure 2** New-onset conditions. \*Bonferroni-adjusted  $p < 0.05$ . \*\*Bonferroni-adjusted  $p < 0.01$ . \*\*\*Bonferroni-adjusted  $p < 0.001$ .

**Abbreviations:** MCAS, mast cell activation syndrome; ME/CFS, myalgic encephalomyelitis/chronic fatigue syndrome; POTS, postural orthostatic tachycardia syndrome.

## Health Status

Participants who experienced ocular symptoms reported significantly worse current health status compared to those without ocular symptoms (median EQ-VAS: 40 [IQR, 30–59] vs. 51 [39–70],  $P < 0.001$ ; [Table 2](#)). Median EQ-VAS scores differed by 11 points between groups. Additionally, when rating the severity of their symptoms on their worst days using a visual sliding scale from 0 (representing a trivial illness) to 100 (representing an unbearable condition), those with ocular symptoms indicated a higher severity, with a median score of 80 [95% CI, 70–90] compared to a median of 75 [60–81] for those without ocular symptoms, also showing a significant difference ( $P < 0.001$ ; [Table 2](#)). The timing of the initial SARS-CoV-2 infection did not show a significant correlation with EQ-VAS scores in either group.

## Symptoms Differentiating Individuals with Ocular Symptoms from Those Without

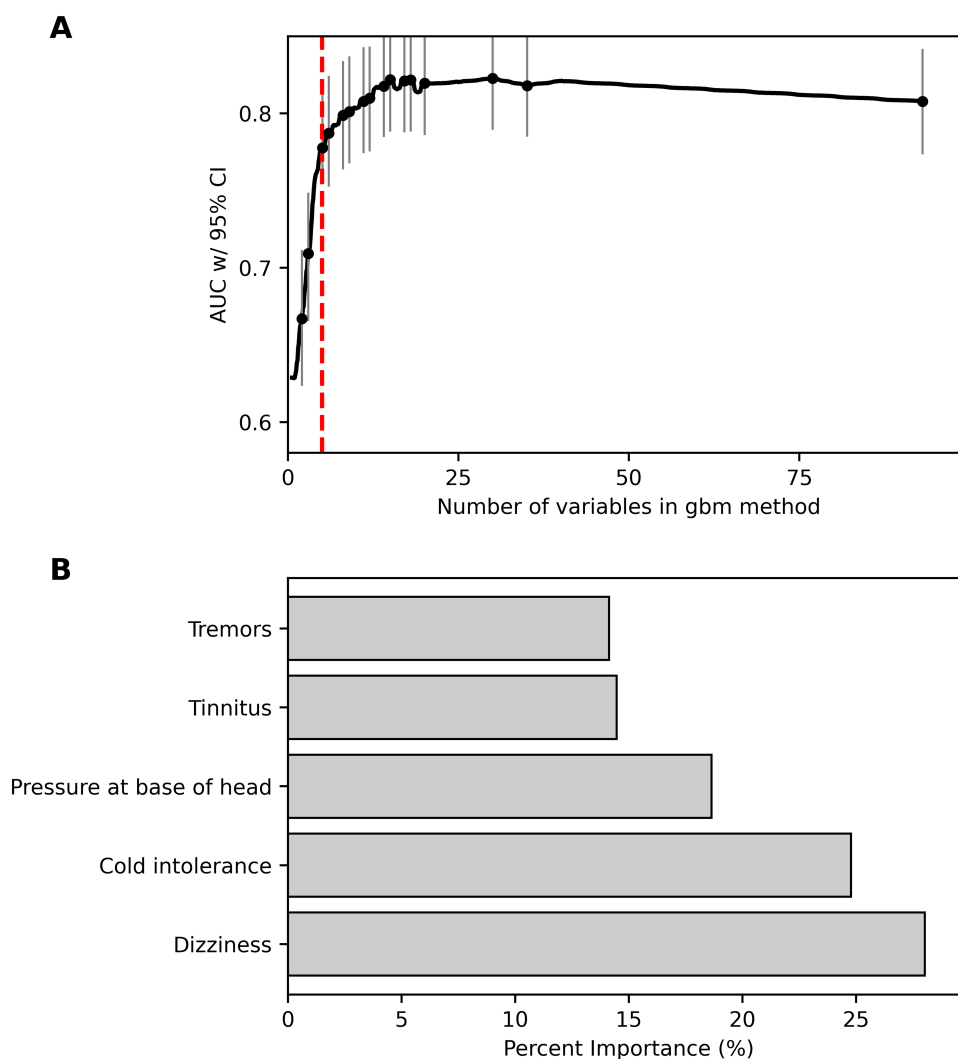
Individuals with ocular symptoms reported higher rates of other symptoms ([Table S4](#)). The gradient-boosted tree machine learning model that was developed to identify symptoms most important for differentiating participants with long COVID experiencing ocular symptoms from those that do not achieved an AUC of 0.77 [95% CI: 0.74–0.81] and found that the five most important symptoms in differentiating individuals with ocular symptoms vs those without were: dizziness, cold intolerance, pressure at base of head, tinnitus, and tremors ([Figure 3](#)). [Figure S2](#) illustrates model

**Table 2** Health Status and Symptom Severity

Characteristic <sup>a</sup>	Overall, N = 595	95% CI <sup>a</sup>	No Ocular Symptoms <sup>b</sup> , N = 254	95% CI <sup>a</sup>	Has Ocular Symptoms <sup>b</sup> , N = 341	95% CI <sup>a</sup>	p-value <sup>c</sup>
Euro-QoL visual analogue scale (0–100, 100 means best), median (IQR)	49 (31, 61)		51 (39, 70)		40 (30, 59)		<0.001
Symptom severity on worst days (0–100, 100 means unbearable), median (IQR)	80 (68, 88)		75 (60, 81)		80 (70, 90)		<0.001
Missing data	36		14		22		

**Notes:** <sup>a</sup> IQR, interquartile range; CI, Confidence Interval. <sup>b</sup> Ocular symptoms were analyzed as a composite outcome to reduce misclassification from overlapping self-reported symptom experiences. <sup>c</sup> Wilcoxon rank sum test; Pearson's Chi-squared test.

performance across iterative variable selection, demonstrating stability of discrimination. The model variations xgb gain and xgb shap agreed with the main model with a correlation of 0.79 and 0.813 respectively. All five of the most important differentiating symptoms identified in the main model were present in significantly higher proportions in the ocular symptoms group compared to the group without ocular symptoms: dizziness (73% [95% CI, 68–77] vs. 39% [33–46]),



**Figure 3** Results from gbm main model. **(A)** Relationship between AUC with 95% CI of gbm model with number of variables included. **(B)** Most important symptoms for differentiating participants with and without ocular symptoms based on percentage importance.

**Abbreviations:** AUC, area under the curve, w/, with, CI, confidence interval.

cold intolerance (43% [95% CI, 38–49] vs. 17% [12–22]), pressure at base of head (48% [95% CI, 42–53] vs. 17% [13–22]), tinnitus or humming in ears (56% [95% CI, 51–61] vs. 29% [24–35]), and tremors or shakiness (48% [95% CI, 43–54] vs. 20% [15–26]), with Bonferroni-adjusted  $P < 0.001$  for each. [Figure S3](#) shows concordance of symptom importance rankings across modeling approaches.

## Discussion

In this online decentralized study, over half of the individuals with long COVID reported ocular symptoms. Participants with ocular symptoms were more likely to be female and had a higher rate of ME/CFS as a pre-pandemic condition but were otherwise similar to those without symptoms. Despite these similarities before infection, participants experiencing ocular symptoms displayed worse health status and showed a greater rate of newly developed health conditions including POTS and ME/CFS. References to ME/CFS in the post-COVID context reflect new-onset diagnoses rather than pre-existing disease. Key symptoms distinguishing those with and without ocular symptoms included dizziness, cold intolerance, pressure at the base of the head, tinnitus, and tremors. From a socioeconomic perspective, those with ocular symptoms reported increased financial hardship and greater housing insecurity, which participants attributed to the impacts of long COVID. These findings highlight that ocular symptoms identified in long COVID may be more common among individuals with a higher overall symptom burden, warranting systematic assessment and support for other physical and mental dysfunctions associated with its manifestation.

Our study advances the field in three important ways. First, ocular symptoms clustered with systemic post-COVID conditions such as POTS and ME/CFS, suggesting a broader symptom constellation rather than isolated ophthalmic sequelae. Though previous studies have reported associations between individual conditions and ocular symptoms, they have not comprehensively explored these relationships.<sup>2,20</sup> POTS is known to cause vision problems, such as blurred vision, tunnel vision, and syncope, due to its systemic effects.<sup>21</sup> Symptoms that are associated with POTS also overlap with the long COVID symptoms distinguishing individuals with ocular symptoms from those without these symptoms identified by our machine learning models: dizziness, cold intolerance, pressure at the base of the head, tinnitus, and tremors. This further suggests a close association between POTS and ocular symptoms. New-onset ME/CFS was also reported at higher rates by individuals with ocular symptoms. Visual disturbances assessed in our study, such as blurred vision and dry eyes, are common symptoms of this condition.<sup>20</sup> While a symptom-level stratification was considered, such analyses are difficult to interpret in self-reported, cross-sectional data. Overlapping visual experiences may be variably labeled as dry eye or blurred vision, and systemic diagnoses such as POTS or ME/CFS may be assigned after symptom onset. Symptom-specific stratification could therefore introduce misleading specificity without establishing temporal or causal ordering. As a result, ocular symptoms were analyzed as a composite outcome to capture overall vision-related symptom burden. In addition, mast cell disorders, frequently seen in long COVID, can trigger systemic inflammation leading to ophthalmic sequelae and dysautonomia.<sup>22</sup> The interconnected nature of these symptoms is consistent with potential common pathophysiological mechanisms. Taken together, these findings suggest that ocular symptoms in long COVID may be interpreted as vision-related manifestations that cluster with systemic post-COVID conditions, rather than as independent ophthalmic sequelae. Our study offers a more comprehensive understanding of the specific conditions linked to ocular symptoms, emphasizing the immunological or inflammatory basis of these associations. Future studies should be conducted to identify potential treatments for ocular symptoms and their associated conditions in long COVID.

Secondly, we found that participants with long COVID-related ocular symptoms tend to have poorer general health and experience more severe peaks in long COVID symptom severity compared to those without such symptoms. In a multinational study of 82 individuals with long COVID recruited via social media, the mean EQ-VAS was 41.6, similar to our ocular symptom cohort.<sup>23</sup> However, this study did not investigate the association between individual symptoms and overall health status. The higher rate of hospitalization during acute SARS-CoV-2 infection among participants with ocular symptoms may also reflect greater initial disease severity, which could partially contribute to the more severe long COVID phenotype observed in this group. Our study suggests that ocular symptoms in long COVID may be associated with a higher overall disease burden, emphasizing the need for physicians to ask patients about these symptoms and for future studies to investigate the mechanism of ocular symptoms in long COVID. This comparison highlights the greater

health burden faced by those with ocular symptoms, offering valuable insights for healthcare providers to prioritize these patients for more comprehensive care.

Third, we found that participants with long COVID-related ocular symptoms report a greater financial burden and more difficulties in pursuing everyday life. A report from the COVID States Project, which recruited 15,308 US residents under the age of 70, showed that individuals with long COVID are less likely to be employed full-time, especially those experiencing cognitive symptoms.<sup>24</sup> However, this study only assessed a limited number of symptoms and did not include ocular symptoms. In contrast, our study included 96 symptoms, selected after multiple sessions with patient collaborators, and allowed for a more thorough characterization of long COVID symptoms. The high prevalence of ocular symptoms in our study (57%) and in the literature, ranging from 7% to 38.5%, indicates the importance of inquiring about ocular symptoms.<sup>5</sup> It is crucial to highlight that individuals with ocular symptoms reported greater overall symptom burden, financial difficulties, and challenges in pursuing everyday life due to these individuals' reduced ability to function at pre-pandemic levels.

The current study has several limitations. Participants were recruited from an online community of individuals experiencing long COVID and comprised of predominantly female and non-Hispanic White individuals. However, comparison with NHIS long COVID data suggests that this demographic skew is also present in population-based long COVID samples. Recruitment via an online community may have also preferentially captured individuals with more persistent symptoms, potentially inflating ocular symptom prevalence. These factors may limit generalizability of symptom prevalence estimates but are less likely to invalidate observed patterns of symptom co-occurrence. As well, the missing data from survey respondents may have influenced results. However, the sampling methodology of the LISTEN study allowed for participant input on the survey design, allowing for the study questions to represent what these individuals with long COVID thought were important to study. Another limitation of the study is the usage of "ocular symptoms" to refer to individuals who self-reported blurred/loss of vision, floaters, or dry eyes. This definition does not encompass all possible ocular symptoms, making it difficult to compare the prevalence of ocular symptoms in our study to others as various definitions have been used in the literature. As well, the use of a composite symptom, together with the high proportion of females in our study, make it challenging to determine if the results are being driven by sex-related differences. Although sex differences in clinically diagnosed dry eye disease are well established, symptom-specific analyses in self-reported data are difficult to interpret, as overlapping visual experiences may be variably labeled by participants. Separating individual ocular symptoms could therefore introduce misleading specificity driven by labeling rather than true clinical differences. Accordingly, ocular symptoms were analyzed as a composite outcome to capture overall vision-related symptom burden rather than infer symptom-specific mechanisms. In addition, these symptoms are heterogeneous and may reflect involvement of distinct ocular systems, including ocular surface disease, neurologic or refractive causes of blurred vision, and vitreoretinal phenomena such as floaters or flashes, which further limits symptom-specific interpretation. However, heterogeneity of ocular symptoms supports use of a composite outcome rather than symptom-specific inference. As well, the timing of the onset of ocular symptoms was not surveyed. Nonetheless, since participants were consulted in the creation of the survey, details related to disease course and symptomatology which were important to those in the online community were included. Additionally, there is poor characterization of the relationship between individual long COVID symptoms and overall health status in the literature, hence it is hard to compare our findings of lower health status among individuals with ocular symptoms to other studies. Moreover, the reliance on self-reported conditions and symptoms using a predetermined list could lead to recall bias, with the potential for both underreporting and overreporting, which is not clearly understood. Individuals with more severe long COVID symptoms may be more likely to report pre-COVID health issues. Even so, conducting a prospective study to address this concern would have been more difficult and taken longer to complete, delaying the recognition of ocular symptoms as an important long COVID symptom. Data on diagnosed ocular conditions, such as glaucoma and macular degeneration, were not collected and may have influenced the development of ocular symptoms attributed to long COVID. However, healthcare disruptions during the pandemic may have led to under-reporting of these conditions, which would have made it hard to interpret this data even if it were available.

## Conclusion

In conclusion, ocular symptoms were common among individuals with long COVID and were associated with greater symptom burden and poorer overall health status. Because symptom onset was assessed cross-sectionally, the precise temporal relationship between ocular symptoms and SARS-CoV-2 infection cannot be definitively established. These symptoms appear to cluster with systemic post-COVID conditions, suggesting that they may represent vision-related manifestations within a broader post-infectious phenotype rather than isolated ocular sequelae. Healthcare providers should recognize this presentation, inquire about ocular symptoms as part of comprehensive long COVID assessment, and consider associated systemic conditions when determining management strategies. Future studies should focus on detailed ophthalmic phenotyping, clarifying temporal relationships with systemic conditions, and identifying targeted treatments.

## Abbreviations

LISTEN, Listen to Immune, Symptom, and Treatment Experiences Now; EQ-VAS, EuroQoL visual analogue scale; COVID-19, coronavirus disease 2019; IQR, interquartile range; NHIS, National Health Institute Survey; AUC, area under the curve; xgb gain, XGBoost gain in accuracy; xgb shap, XGBoost Shapley; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology; ME/CFS, Myalgic encephalomyelitis/chronic fatigue syndrome; POTS, postural orthostatic tachycardia syndrome.

## Data Sharing Statement

The data used in this study is not publicly available due to participant privacy, but is accessible in a deidentified format upon reasonable request from the corresponding author, HMK.

## Ethics Approval and Consent to Participate

The Yale University Institutional Review Board granted approval for the LISTEN study on April 1, 2022. Participants consented to the study through electronic forms. The conduct of LISTEN adheres to the principles outlined in the Declaration of Helsinki and follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines for observational studies.

## Consent for Publication

All authors have read and approved the final manuscript and consent to its publication.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## References

- Nalbandian A, Sehgal K, Gupta A, et al. Post-acute COVID-19 syndrome. *Nat Med*. 2021;27(4):601–615. doi:10.1038/s41591-021-01283-z
- Ali ST, Kang AK, Patel TR, et al. Evolution of neurologic symptoms in non-hospitalized COVID-19 “long haulers”. *Ann Clin Transl Neurol*. 2022;9(7):950–961. doi:10.1002/acn3.51570
- Johansson J, Levi R, Jakobsson M, Gunnarsson S, Samuelsson K. Multiprofessional neurorehabilitation after COVID-19 infection should include assessment of visual function. *Arch Rehabil Res Clin Transl*. 2022;4(2):100184. doi:10.1016/j.arrct.2022.100184
- Tohamy D, Sharaf M, Abdelazeem K, et al. Ocular manifestations of post-acute COVID-19 syndrome, upper Egypt early report. *J Multidiscip Healthc*. 2021;14:1935–1944. doi:10.2147/JMDH.S323582
- Trott M, Driscoll R, Pardhan S. The prevalence of sensory changes in post-COVID syndrome: a systematic review and meta-analysis. *Front Med*. 2022;9:980253. doi:10.3389/fmed.2022.980253
- Parmar UP, Surico PL, Singh RB, et al. Ocular Implications of COVID-19 infection and vaccine-related adverse events. *J Pers Med*. 2024;14(8):780. doi:10.3390/jpm14080780
- SeyedAlinaghi S, Mehraeen E, Afzalian A, et al. Ocular manifestations of COVID-19: a systematic review of current evidence. *Prev Med Rep*. 2024;38:102608. doi:10.1016/j.pmedr.2024.102608
- Monu M, Ahmad F, Olson RM, Balendiran V, Singh PK. SARS-CoV-2 infects cells lining the blood-retinal barrier and induces a hyperinflammatory immune response in the retina via systemic exposure. *PLoS Pathog*. 2024;20(4):e1012156. doi:10.1371/journal.ppat.1012156
- Kuchler T, Günthner R, Ribeiro A, et al. Persistent endothelial dysfunction in post-COVID-19 syndrome and its associations with symptom severity and chronic inflammation. *Angiogenesis*. 2023;26(4):547–563. doi:10.1007/s10456-023-09885-6
- Al-Sharif E, Strianese D, AlMadhi NH, et al. Ocular tropism of coronavirus (CoVs): a comparison of the interaction between the animal-to-human transmitted coronaviruses (SARS-CoV-1, SARS-CoV-2, MERS-CoV, CoV-229E, NL63, OC43, HKU1) and the eye. *Int Ophthalmol*. 2021;41(1):349–362. doi:10.1007/s10792-020-01575-2
- Zhou T, Sawano M, Arun AS, et al. Internal tremors and vibrations in long COVID: a cross-sectional study. *Am J Med*. 2024. doi:10.1016/j.amjmed.2024.07.008

12. Gottlieb M, Wang RC, Yu H, et al. Severe Fatigue and Persistent Symptoms at 3 months following severe acute respiratory syndrome Coronavirus 2 infections during the Pre-Delta, Delta, and Omicron time periods: a multicenter prospective cohort study. *Clin Infect Dis.* 2023;76(11):1930–1941. doi:10.1093/cid/ciad045
13. EuroQol Group. EuroQol - a new facility for the measurement of health-related quality of life. *Health Policy.* 1990;16(3):199–208. doi:10.1016/0168-8510(90)90421-9
14. Jiang R, Janssen MFB, Pickard AS. US population norms for the EQ-5D-5L and comparison of norms from face-to-face and online samples. *Qual Life Res.* 2021;30(3):803–816. doi:10.1007/s11136-020-02650-y
15. Kuhn M. Building predictive models in R using the caret package. *J Stat Softw.* 2008;28:1–26. doi:10.18637/jss.v028.i05
16. Friedman JH. Greedy function approximation: a gradient boosting machine. *Ann Stat.* 2001;29(5):1189–1232. doi:10.1214/aos/1013203451
17. Breiman L. Random Forests. *Mach Lang.* 2001;45(1):5–32. doi:10.1023/A:1010933404324
18. Chen T, Guestrin C. XGBoost: a scalable tree boosting system. In: *Proceedings of the 22nd ACM SIGKDD International Conference on Knowledge Discovery and Data Mining*. KDD '16. Association for Computing Machinery; 2016:785–794. doi:10.1145/2939672.2939785.
19. Lundberg SM, Lee SI. A unified approach to interpreting model predictions. In: *Advances in Neural Information Processing Systems*. Vol. 30. Curran Associates, Inc; 2017. [https://papers.nips.cc/paper\\_files/paper/2017/hash/8a20a8621978632d76c43dfd28b67767-Abstract.html](https://papers.nips.cc/paper_files/paper/2017/hash/8a20a8621978632d76c43dfd28b67767-Abstract.html).
20. Weinstock LB, Nelson RM, Blitshteyn S. Neuropsychiatric manifestations of mast cell activation syndrome and response to mast-cell-directed treatment: a case series. *J Pers Med.* 2023;13(11):1562. doi:10.3390/jpm13111562
21. Garland EM, Celedonio JE, Raj SR. Postural Tachycardia Syndrome: beyond orthostatic intolerance. *Curr Neurol Neurosci Rep.* 2015;15(9):60. doi:10.1007/s11910-015-0583-8
22. Johansson J, Möller M, Markovic G, Borg K. Vision impairment is common in non-hospitalised patients with post-COVID-19 syndrome. *Clin Exp Optom.* 2023;106:1–8. doi:10.1080/08164622.2023.2213826
23. Tak CR. The health impact of long COVID: a cross-sectional examination of health-related quality of life, disability, and health status among individuals with self-reported post-acute sequelae of SARS CoV-2 infection at various points of recovery. *J Patient-Rep Outcomes.* 2023;7(1):31. doi:10.1186/s41687-023-00572-0
24. Perlis RH, Lunz Trujillo K, Safarpour A, et al. Association of Post-COVID-19 condition symptoms and employment status. *JAMA Netw Open.* 2023;6(2):e2256152. doi:10.1001/jamanetworkopen.2022.56152

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