



Phenylthiocarbamide (PTC) Taste Sensitivity and COVID-19 Clinical Presentation, Symptom Phenotypes, and Vaccination Status: A Cross-Sectional Observational Study in Young Adults

Hasna Amir Mohaus^{1*}, Rawaa Bannay Zubairi², Noor Fadhil Abdulabbas³, Anil Kumar Chhillar⁴

¹ Department of Biology, College of Education-Qurna, University of Basrah, Basra, Iraq

² Department of Environmental and Pollution Technical Engineering, Basrah Engineering Technical College, Basra, Iraq

³ College of Health and Medical Technologies, Southern Technical University, Basrah, Iraq

⁴ Centre for Biotechnology, Maharshi Dayanand University, Rohtak, Haryana, India

Corresponding Author: Hasna Amir Mohaus, PhD, Department of Biology, College of Education-Qurna, University of Basrah, Basra, Iraq. Tel: +9647705620830, E-mail: hasan.mohaus@uobasrah.edu.iq

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Abstract

Introduction: Host innate mucosal immunity may influence the clinical course of SARS-Cov-2 (COVID-19) infection. Extraoral bitter taste receptors, particularly T2R38, are expressed in the respiratory epithelium, where they stimulate nitric oxide production and promote mucociliary clearance. This study examined cross-sectional associations between phenylthiocarbamide (PTC) taste sensitivity and self-reported COVID-19 history, symptom phenotypes, particularly dry versus productive cough, clinical outcomes, and vaccination status in young adults.

Materials and Methods: In this cross-sectional observational study (n = 324 young adults), standardized PTC taste strips were used to classify participants as tasters (75.3%) or non-tasters (24.7%). Retrospective infection history, symptom patterns, clinical outcomes, and vaccination status were analyzed using chi-square tests, independent-samples t-tests, and multivariable logistic regression adjusted for age, sex, smoking status, and vaccination status.

Results: Non-tasters exhibited higher infection rates (70.0% vs. 41.8%, $p = 0.0003$) and higher odds of acquiring COVID-19 (OR = 2.84, $p = 0.0002$), alongside active smoking (OR = 1.67, $p = 0.042$). Among infected participants, non-tasters experienced a greater symptom burden (6.3 ± 2.1 vs. 4.1 ± 1.6 , $p < 0.001$), a predominantly productive cough with phlegm (57.1%), and increased hospitalization (25.0% vs. 8.8%, $p = 0.004$), oxygen requirement (19.6% vs. 4.9%, $p = 0.002$), and complications (39.3% vs. 17.6%, $p < 0.001$). Vaccination conferred greater absolute risk reduction against infection in tasters (53.9%) than in non-tasters (17.8%; $p = 0.009$).

Conclusions: The PTC non-taster phenotype was cross-sectionally associated with increased odds of COVID-19 infection, greater symptom burden, and a distinct productive cough presentation in this young adult cohort. Although these observational findings are consistent with hypothesized mucosal innate immune mechanisms, prospective longitudinal studies incorporating comprehensive comorbidity controls and direct mucosal bioassays are needed to establish true clinical predictive utility.

Keywords: Phenylthiocarbamide (PTC), SARS-CoV-2, TAS2R38/T2R38 Receptors, Mucosal Innate Immunity, Disease Severity, Vaccine Response

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Introduction

The emergence of SARS-Cov-2 (COVID-19) triggered a global health crisis characterized by substantial morbidity, mortality, and persistent post-COVID-19 complications.^{1,2} Although advanced age, male sex, and comorbidities are established risk factors, they do not fully explain the broad clinical variation observed among healthy individuals.³ Consequently, host-specific biological variation in innate immunity is likely to play a critical role in modulating initial antiviral defenses and disease progression. Bitter taste receptors (TAS2Rs/ T2Rs) are G protein-coupled receptors originally identified in taste bud cells.⁴ that also regulate essential innate immune responses.^{5,6} TAS2Rs are widely expressed in extraoral tissues, particularly in ciliated epithelial cells of the respiratory tract.^{7,8} Activation of T2Rs by bitter

metabolites triggers calcium-dependent nitric oxide (NO) production, enhancing mucociliary clearance, antibacterial defenses, and phagocytosis.^{9,10} Phenylthiocarbamide (PTC) sensitivity, governed by the TAS2R38 gene on chromosome 7, serves as a non-invasive biomarker of local airway defense.¹¹ Three single-nucleotide polymorphisms (P49A, A262V, and V296I) define the functional PAV (taster) and non-functional AVI (non-taster) haplotypes.^{12,13} Although some early research hypothesized a protective role, genetic analyses and PROP phenotype evaluations have found no significant association between TAS2R38 variants and COVID-19 severity, suggesting that these polymorphisms do not directly determine infection outcomes.¹⁴ Concurrently, persistent taste and smell dysfunction emerged as key clinical

features of COVID-19. Post-viral taste loss primarily involves selective impairment of PLC β 2-dependent signaling rather than structural destruction of taste buds,¹⁵ whereas genetic variants across TAS2R genes influence overall SARS-CoV-2 susceptibility and immune response.¹⁶ Notably, post-COVID taste deficits occur largely independently of olfactory loss,¹⁷ highlighting the clinical need for standardized objective assessments.¹⁸ In contrast, general clinical risk models for severe COVID-19 rely on broader systemic parameters (e.g., LDH, CRP, and respiratory rate) to predict critical outcomes.¹⁹ Beyond gustation, T2R38 is expressed across respiratory, gastrointestinal, and immune cells, where it modulates inflammatory signaling and host-pathogen defense.^{20–22} TAS2R38 variations have also been linked to susceptibility to various respiratory and metabolic disorders.²³ During the pandemic, interest grew regarding the role of T2R38 in antiviral immunity, although evidence directly connecting its variants to COVID-19 outcomes remains mixed. Studies examining these relationships have reported inconsistent findings, underscoring the need for further investigation.

Despite these advances, evidence directly linking PTC taste sensitivity to COVID-19 infection susceptibility, symptom phenotypes, clinical outcomes, and vaccine response remains limited, particularly among young adults. Therefore, this cross-sectional study aimed to examine the association between PTC taste sensitivity and COVID-19 infection history, symptom phenotypes, particularly dry versus productive cough, clinical outcomes, and vaccination status in young adults. We hypothesized that PTC non-tasters would have higher odds of infection and a more severe clinical presentation than tasters.

Materials and Methods

Study Design and Participant Selection

This observational, cross-sectional cohort study was conducted to evaluate the relationship between phenotypic bitter taste sensitivity and COVID-19 clinical profiles. A total of 324 participants were recruited through community outreach and institutional settings, primarily university campuses. This recruitment strategy yielded a young adult, female-predominant sample of healthy university students with no reported chronic illnesses.

Inclusion and Exclusion Criteria

Participants aged 20 years or older who consented to sensory phenotyping and provided a comprehensive clinical history were included. Individuals with pre-existing, non-COVID-19-related gustatory or olfactory dysfunction, severe cognitive impairment, or incomplete clinical records were excluded. Ethical approval was obtained from the institutional review board, and all participants provided written informed consent before enrollment.

Phenotypic Assessment of PTC Taste Sensitivity

Phenotypic sensitivity to PTC was assessed using standardized PTC taste strips (Sensonics International, Haddon Heights, NJ, USA), each containing 0.007 mg (7 μ g) of PTC, following established protocols for bitter taste phenotyping.¹³ To minimize transient effects on taste perception, participants refrained from eating and drinking, except for noncarbonated water, for at least 1 hour before testing. Before assessment, participants rinsed their mouths thoroughly with deionized water. A control strip without PTC was briefly placed on the anterior dorsal surface of the tongue to establish a baseline oral sensation.

A PTC-impregnated taste strip (3.80 $\times$ 1.43 cm) was placed on the anterior portion of the tongue and held in the mouth for approximately 10 seconds. Participants were instructed to focus on the perceived taste and immediately rate the intensity of bitterness using a six-point Likert-type scale ranging from 0 to 5, where 0 = tasteless, 1 = barely detectable, 2 = weak, 3 = moderate, 4 = strong, and 5 = extremely strong. Individuals who reported scores of 0 or 1 were classified as non-tasters (NT), whereas those reporting scores of 2–5 were classified as tasters (T), in accordance with previously validated phenotypic classification criteria.^{13,28} Tasters typically reported an immediate and distinct bitter sensation of varying intensity, whereas non-tasters perceived the strip as tasteless or noted only the texture of the filter paper. Phenotypic testing was conducted unblinded; research personnel administering the PTC taste strips were aware of participants' self-reported COVID-19 history, vaccination status, and clinical outcomes at the time of sensory evaluation.

Clinical and Behavioral Data Collection

Demographic, behavioral, and clinical data were collected using a structured questionnaire administered by trained research personnel. Participants provided information regarding COVID-19 infection history (laboratory-confirmed by RT-PCR), vaccination status, symptom duration, cough phenotype, overall symptom burden, and clinical outcomes, including hospitalization, oxygen requirement, and complications. Where available, self-reported data were cross-referenced with institutional medical records. However, because medical record verification was not consistently feasible across the cohort, primary data collection relied predominantly on participant self-report. Data on baseline body mass index (BMI), underlying clinical comorbidities such as diabetes mellitus, hypertension, cardiovascular or chronic lung disease, socioeconomic status, household exposure dynamics, and specific acute pharmacological treatments, including antivirals or immunomodulators, were not collected during initial participant recruitment. Consequently, these variables were not included as covariates in subsequent regression analyses. Demographic variables comprised age, categorized as 20–25, 25–30, and $\geq$ 30 years, and sex. Behavioral characteristics

included smoking status (smoker or non-smoker) and COVID-19 vaccination status (vaccinated or unvaccinated). COVID-19 history was established by documenting previous laboratory-confirmed SARS-CoV-2 infection using RT-PCR. Symptom duration was classified as ≤ 1 week, 1–2 weeks, or > 2 weeks. Participants were also queried regarding any history of SARS-CoV-2 reinfection.

Clinical manifestations were evaluated by documenting the presence and specific characteristics of COVID-19-related symptoms. Cough phenotype was categorized as dry, productive (phlegm), or absent. Symptom burden was measured using a symptom burden score calculated as the total number of acute COVID-19 symptoms reported by each participant (range: 0–12). Participants were classified into predefined clinical phenotypes based on the predominant symptom pattern: mild (primarily fever and fatigue), respiratory (primarily cough and dyspnea), and severe systemic disease. Clinical outcomes were assessed by recording COVID-19-related hospitalization, requirement for supplemental oxygen therapy, and incidence of severe clinical complications during illness.

Statistical Analysis

Statistical analyses were conducted using R (version 4.3) and IBM SPSS Statistics (version 28.0; IBM Corp., Armonk, NY, USA). Statistical significance was defined as a two-tailed p -value < 0.05 , and all effect estimates are reported with 95% confidence intervals (CIs). Categorical variables are summarized as frequencies and percentages, whereas continuous variables are presented as mean $\pm$ standard deviation (SD). Associations between PTC taste sensitivity (taster vs. non-taster) and categorical clinical or behavioral variables were evaluated using Pearson's chi-square (χ^2) test. Differences in continuous outcomes, including symptom burden scores, were assessed using independent-samples t -tests after verifying assumptions of normality and homogeneity of variance. Sex-stratified analyses were performed to evaluate the consistency of associations between PTC taste phenotype and COVID-19 outcomes across sexes.

To identify potential cross-sectional correlates of COVID-19 susceptibility and disease complications, multivariable logistic regression analyses were conducted. The susceptibility model estimated the odds of laboratory-confirmed COVID-19 infection according to PTC taste status, adjusting for age, sex, smoking status, and vaccination status. The present analysis focused on the susceptibility model. A separate complication model was not included in this report. The general logistic regression model was specified as²⁹:

$$\ln\left(\frac{P}{1-P}\right) = \beta_0 + \beta_1(\text{PTC Status}) + \beta_2(\text{Smoking}) + \beta_3(\text{Age}) + \beta_4(\text{Vaccination})$$

where P denotes the probability of the outcome of interest.

To assess potential effect modification, an interaction term between PTC taste status and smoking status (PTC status $\times$ smoking) was included in the regression model, and its statistical significance was determined using the Wald test. Pairwise Pearson correlation coefficients were calculated to evaluate relationships among PTC taste sensitivity, COVID-19 infection status, disease severity, and symptom burden. The resulting correlation matrix was visualized as a heatmap. To further characterize clinical presentation patterns, symptom data were grouped into predefined clinical phenotypes, enabling comparisons of symptom clustering between PTC tasters and non-tasters. Because of the cross-sectional design of this study, the observed relationships between PTC taster status and COVID-19 clinical profiles should be interpreted as statistical associations rather than causal effects or indicators of predictive directionality. To ensure methodological rigor, terms such as predictor, risk factor, and biomarker have been replaced with cross-sectional correlates and factors associated with increased odds of infection. Although bitter taste sensitivity demonstrates a strong association with COVID-19 infection history, symptom clustering, and clinical outcomes in this cohort, prospective longitudinal studies are required to determine whether PTC phenotyping can serve as a candidate marker in clinical practice.

Results

Descriptive Characteristics of the Study Sample

Figure 1 presents the demographic and clinical profiles of the study participants. Among the 324 participants, 63.6% ($n = 206$) were female and 36.4% ($n = 118$) were male. The majority were aged 20–25 years (73.5%, $n = 238$), followed by 25–30 years (19.8%, $n = 64$); individuals aged ≥ 30 years represented the smallest proportion (6.8%, $n = 22$).

A substantial majority of participants were classified as PTC tasters ($n = 244$, 75.3%), whereas non-tasters comprised 24.7% ($n = 80$). Most participants were non-smokers ($n = 228$, 70.4%), with active smokers representing 29.6% ($n = 96$). The sample was nearly evenly divided between those with a history of COVID-19 infection ($n = 158$, 48.8%) and those without ($n = 166$, 51.2%). Immunization rates were high, with 80.6% ($n = 261$) vaccinated and 19.4% ($n = 63$) unvaccinated. Baseline characteristics thus indicate a predominantly young, female, non-smoking, and highly vaccinated population. The observed prevalence of PTC tasters (75.3%) is consistent with genetic distributions reported in general populations.

Assessment of bitter taste receptor phenotypes, particularly PTC sensitivity mediated by TAS2R38, has become central to investigations of respiratory immunity. Extraoral bitter taste receptors (T2Rs) expressed on ciliated epithelial cells in the upper respiratory tract function as a primary component of innate immune defense.⁵ Activation

of these receptors promotes mucociliary clearance and induces nitric oxide production, which has direct antimicrobial and antiviral effects.

Although some ecological and cohort studies indicate that the non-taster phenotype is associated with increased susceptibility to severe respiratory complications and viral infections,²⁸ larger cross-sectional studies have reported inconsistent findings regarding direct infection frequency.³⁰ For example, in a large Canadian Longitudinal Study on Aging cohort, TAS2R38 haplotypes were not significantly associated with COVID-19 infection or most symptomatology examined, although some exploratory patterns were noted.

Environmental factors, including cigarette smoking, and demographic variables such as age and sex significantly influence baseline taste perception and overall gustatory function.³¹ The nearly equal distribution of individuals with and without a history of COVID-19 infection (48.8% vs. 51.2%) in this cohort provides a strong statistical basis for examining potential associations between genetic taste sensitivity (PTC status), lifestyle factors such as smoking, and susceptibility to viral infection. Additionally, the high vaccination rate (80.6%) is crucial because immunization status substantially affects immune responses and clinical severity within the population.

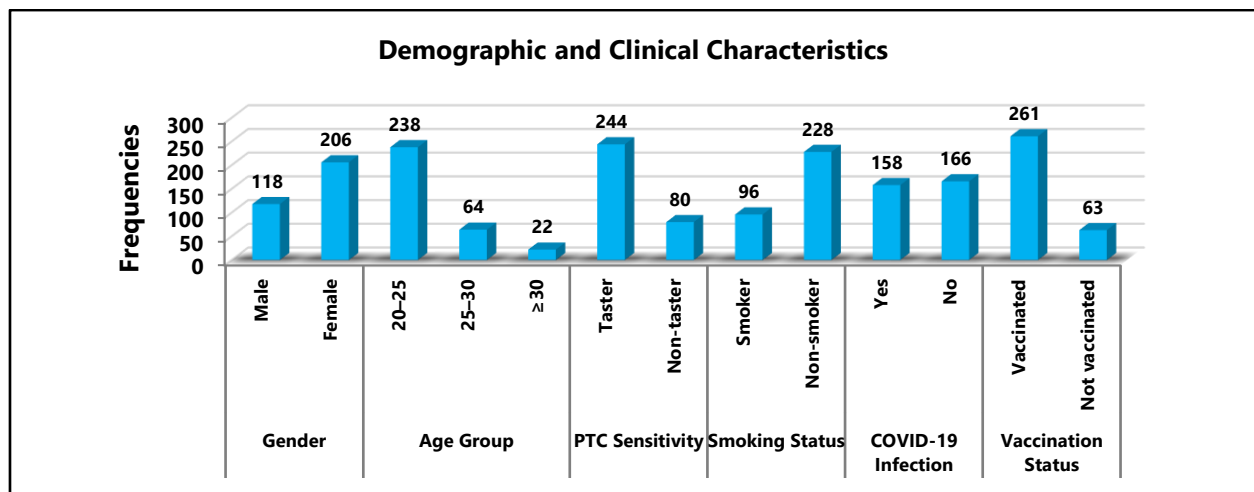


Figure 1. Demographic and Clinical Characteristics of the Study Population (N = 324).

Association Between PTC Taste and COVID-19 Infection

Figure 2 illustrates the relationship between PTC taste sensitivity and COVID-19 infection history. Of the 324 individuals evaluated, 244 were classified as tasters and 80 as non-tasters. Among tasters, 41.8% (n = 102) reported a history of COVID-19 infection, whereas 58.2% (n = 142) did not. In contrast, 70.0% (n = 56) of non-tasters reported a history of COVID-19 infection, with only 30.0% (n = 24) remaining uninfected.

A chi-square test of independence indicated a highly significant association between PTC taster status and COVID-19 infection ($\chi^2 = 12.84$, $p = 0.0003$). Although this association aligns with hypothesized mechanisms of upper respiratory T2R38 mucosal immunity, the absence of pre-infection taste phenotyping or TAS2R38 genotyping means that the findings must be interpreted cautiously. Because phenotypic taste testing occurred after infection episodes,

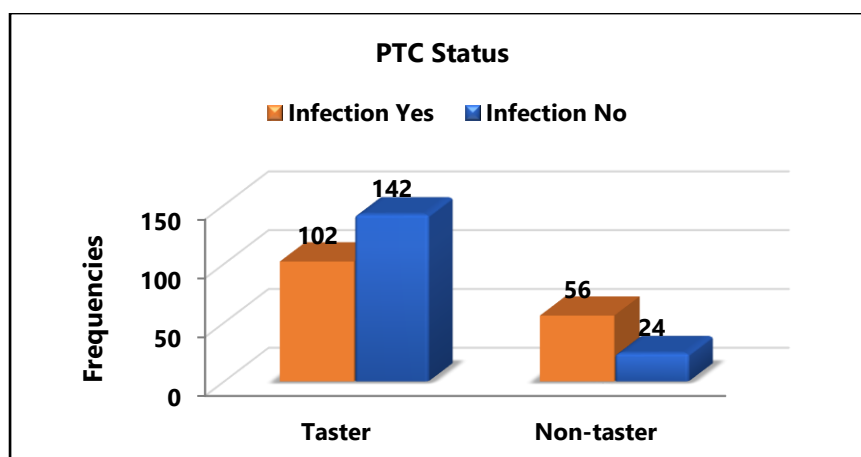


Figure 2. Association between PTC Taste Sensitivity and COVID-19 Infection Status (n = 324).

participants classified as non-tasters may have been non-tasters for two different reasons: (1) an innate, genetically determined receptor defect (associated with the AVI/AVI haplotype) leading to weakened mucosal defense, or (2) acquired taste impairment following viral infection due to SARS-CoV-2 damage to gustatory or supporting cells.^{15,17} Because persistent or subclinical taste dysfunction after COVID-19 is a recognized consequence, some participants categorized as non-tasters may have developed a blunted sense of taste as a result of infection rather than having an inherent receptor defect. Therefore, this study demonstrates only a cross-sectional association, not a confirmed temporal or causal relationship. These physiological mechanisms remain speculative hypotheses requiring experimental validation.

PTC Taste and Respiratory Symptoms

Figure 3 presents the distribution of cough symptoms according to PTC taste sensitivity among participants with a history of COVID-19 infection. Among PTC tasters ($n = 102$), most experienced a dry cough ($n = 61$, 59.8%), followed by cough with phlegm ($n = 28$, 27.5%). Only a small minority reported no cough ($n = 13$, 12.7%).

In contrast, the symptom profile among non-tasters ($n = 56$) demonstrated an opposite trend: over half experienced a productive cough ($n = 32$, 57.1%), whereas dry cough and absence of cough were each reported by 21.4% ($n = 12$ for dry cough; $n = 12$ for no cough). Overall, tasters exhibited a

greater tendency toward dry, irritative coughing, whereas non-tasters were more likely to develop productive, phlegm-associated coughs.

A clear clinical distinction in cough phenotypes was identified between PTC tasters and non-tasters following COVID-19 infection. Tasters predominantly experienced dry cough (59.8%), whereas non-tasters were more likely to develop productive coughs with phlegm (57.1%). This difference in clinical manifestation is attributable to the physiological function of bitter taste receptors (T2R38) in airway mucosal defense. In individuals with functional T2R38 receptors, activation leads to immediate intracellular calcium release, which stimulates nitric oxide synthase, increases ciliary beat frequency, and promotes rapid clearance of viral debris and mucus.^{32,33} Although both TAS2R38 and CFTR reside on chromosome 7q, any potential linkage disequilibrium or co-regulatory interplay influencing airway mucus rheology remains an unverified hypothesis requiring targeted genomic sequencing and linkage analysis in future studies.

In contrast, individuals with non-functional TAS2R38 receptor variants (non-tasters) demonstrate reduced nitric oxide production and compromised ciliary motility. This deficiency results in hypersecretion, decreased bacterial and viral clearance, and mucus accumulation within the trachea-bronchial tree, which ultimately presents as a productive cough accompanied by phlegm and may contribute to lower airway involvement.³⁴

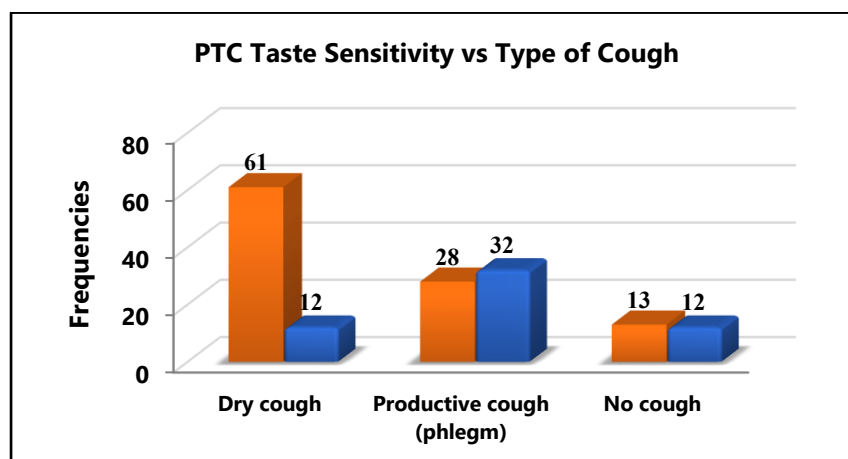


Figure 3. Distribution of Cough Types by PTC Taste Sensitivity among COVID-19 Patients ($n = 158$).

Severity and Clinical Outcomes

Table 1 presents the clinical outcomes of COVID-19 infection stratified by PTC taste sensitivity. Non-tasters exhibited significantly poorer clinical outcomes across all measured parameters compared with tasters. Hospitalization rates were nearly three times higher among non-tasters (25.0%, $n = 14$) than among tasters (8.8%, $n = 9$; $p < 0.001$). A significantly greater proportion of non-tasters required

oxygen therapy compared with tasters (19.6% vs. 4.9%; $p < 0.001$). Additionally, disease-related complications occurred in 39.3% ($n = 22$) of non-tasters, compared with 17.6% ($n = 18$) of tasters, a highly statistically significant difference ($p < 0.001$).

The results indicate a strong and statistically significant association between PTC taster status and COVID-19 disease severity ($p < 0.01$ across all outcomes). Non-tasters

Table 1. Clinical Outcomes According to PTC Taste Status Among COVID-19 Patients (n = 158)

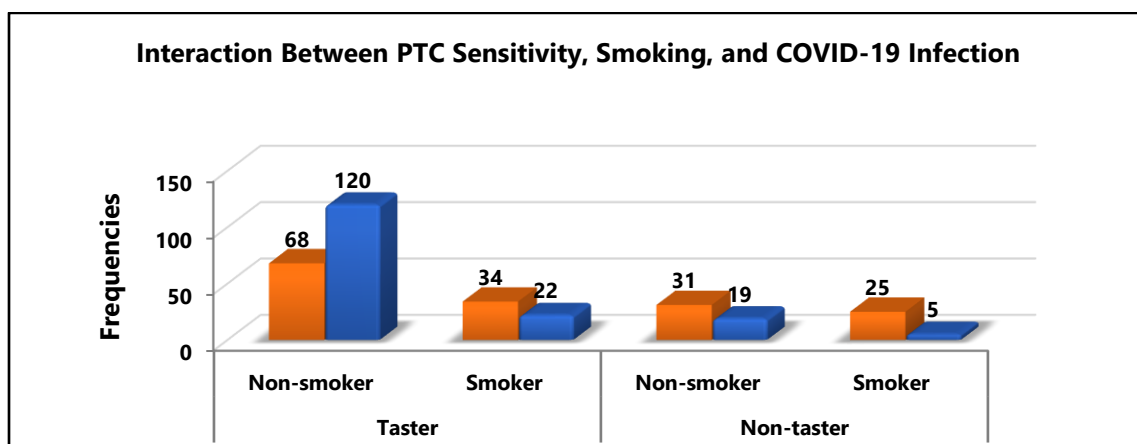
Outcome	Taster (n=102)	Non-taster (n=56)	p-value
Hospitalization	9 (8.8%)	14 (25.0%)	$p < 0.001$
Oxygen therapy	5 (4.9%)	11 (19.6%)	$p < 0.001$
Complications	18 (17.6%)	22 (39.3%)	$p < 0.001$

experienced substantially higher rates of hospitalization (25.0% vs. 8.8%), oxygen therapy requirement (19.6% vs. 4.9%), and clinical complications (39.3% vs. 17.6%) compared with tasters. These findings are consistent with previous clinical studies demonstrating that phenotypic variation in the T2R38 bitter taste receptor is directly correlated with the clinical course and severity of respiratory viral infections.⁸ The T2R38 receptor, expressed on ciliated cells in the human respiratory tract, serves as a critical component of innate mucosal immunity. Non-tasters possess non-functional genomic variants (TAS2R38 AVI haplotype) and therefore lack a rapid local nitric oxide response to viral invasion. This deficiency compromises early viral containment, resulting in

higher viral loads, increased lower respiratory tract involvement, and secondary inflammatory complications that contribute to the need for hospitalization and supplemental oxygen.

Multivariable Interaction Analysis

A multivariable logistic regression analysis was performed to determine independent factors associated with COVID-19 infection within the study population (Figure 4). Of the variables assessed, non-taster status emerged as the most significant cross-sectional correlate of infection. Participants identified as non-tasters exhibited nearly threefold increased odds of acquiring COVID-19 infection compared with tasters (OR = 2.84, 95% CI: 1.65–4.89, $p < 0.001$).

**Figure 4.** Multivariable Logistic Regression Analysis of Predictors for COVID-19 Infection.

Active smoking was identified as a statistically significant factor associated with increased odds of infection, increasing the odds of infection by 67% (OR = 1.67, 95% CI: 1.01–2.75, $p < 0.001$). In contrast, demographic variables such as male sex (OR = 1.21, $p > 0.05$) and age (OR = 1.12, $p > 0.05$) exhibited positive trends toward infection risk, but these associations did not achieve statistical significance in the adjusted model. To address potential confounding, a multivariable logistic regression model was constructed, confirming that non-taster status (OR = 2.84, $p < 0.001$) and active smoking status (OR = 1.67, $p < 0.042$) are potential risk factors for SARS-CoV-2 infection. The strong adjusted association for non-tasters underscores the critical protective function of T2R38 bitter taste receptors in the upper airway. Among non-tasters, the absence of this early mucosal defense mechanism directly increases overall infection risk, independent of underlying demographic characteristics.³⁵ The observed risk associated with smoking (OR = 1.67) is

consistent with existing literature indicating that cigarette smoke impairs airway ciliary structure, disrupts the mucosal barrier, and suppresses local immune defenses.³⁶

PTC Sensitivity and Symptom Burden Score

The total number of COVID-19 symptoms experienced by patients was assessed according to PTC taste sensitivity (Table 2). Patients classified as non-tasters exhibited a significantly higher mean number of symptoms (6.3 ± 2.1) compared with tasters (4.1 ± 1.6). An independent-samples t-test indicated that the difference in overall symptom burden between these groups was highly statistically significant ($t = 6.72$, $p < 0.001$).

Beyond predicting infection risk and severe clinical outcomes, PTC taste sensitivity demonstrated a strong association with overall symptom burden during COVID-19 infection. Individuals identified as non-tasters exhibited a significantly higher mean symptom score (6.3 ± 2.1) compared

Table 2. Comparison of Mean Symptom Scores According to PTC Taste Status Among COVID-19 Patients (n = 158)

PTC Status	Mean No. of Symptoms	Standard Deviation (SD)	t-value	p-value
Taster	4.1	1.6	6.72	< 0.001
Non-taster	6.3	2.1		

with tasters (4.1 ± 1.6 ; $p < 0.001$), suggesting a more extensive systemic and upper respiratory disease burden. The increased symptom burden observed in non-tasters likely results from impaired early viral clearance and increased local viral replication within the respiratory epithelium. In tasters, functional T2R38 bitter taste receptors serve as immediate activators of innate mucosal immunity, promoting nitric oxide production and enhancing ciliary motility to reduce viral persistence.²³ Conversely, the diminished innate epithelial response in non-tasters permits higher local viral loads and greater activation of inflammatory cascades. This

persistent viral and immune activity manifests clinically as a broader range of acute symptoms, supporting the view that PTC taste status is a reliable indicator of overall COVID-19 disease severity and clinical presentation.

Vaccination Effect Modification

Table 3 examines the relationship between vaccination status (vaccinated vs. not vaccinated) and infection outcomes (infection yes vs. no) stratified by PTC taster status (tasters vs. non-tasters), alongside stratum-specific measures of effect and a formal evaluation of effect modification.

Table 3. Distribution of Infection Outcomes According to Vaccination Status Stratified by PTC Taster Status

PTC Status	Vaccination Status	Infection: Yes, n (%)	Infection: No, n (%)	Stratum p-value	Absolute Risk Reduction (ARR) [95% CI]
Taster	Vaccinated	72 (34.3%)	138 (65.7%)	< 0.001	53.9% [41.4%, 66.5%]
	Not vaccinated	30 (88.2%)	4 (11.8%)		
Non-taster	Vaccinated	38 (51.4%)	36 (48.6%)	< 0.114	17.9% [-3.2%, 39.0%]
	Not vaccinated	18 (69.2%)	8 (30.8%)		

Table 3 indicates that vaccination provides overall protection against infection; however, the magnitude of this benefit varies according to PTC taster phenotype. Unvaccinated individuals in both cohorts experienced high infection rates. Notably, the absolute risk reduction (ARR) associated with vaccination was substantially greater among PTC tasters (ARR = 53.9%, 95% CI: 41.4%–66.5%; infection rate decreasing from 88.2% to 34.3%) than among non-tasters (ARR = 17.9%, 95% CI: –3.2%–39.0%; infection rate decreasing from 69.2% to 51.4%).

Effect modification was formally assessed using a multivariable logistic regression model that included an interaction term (Vaccination $\times$ PTC Status). The interaction term reached statistical significance, indicating that the protective effect of vaccination varies significantly according to PTC taster status.

These results are consistent with existing literature identifying extraoral bitter taste receptors, particularly T2R38 encoded by TAS2R38, as important mediators of mucosal innate immunity. Activation of upper respiratory

T2R38 receptors by bitter agonists stimulates calcium-dependent nitric oxide (NO) production, which enhances mucociliary clearance and provides direct antimicrobial and antiviral effects. Individuals with the taster phenotype express functional receptor variants that generate robust innate mucosal immune responses, resulting in a synergistic protective effect when combined with vaccine-induced adaptive immunity.³⁷ In contrast, non-tasters who lack functional T2R38-mediated mucosal defenses remain more susceptible to breakthrough infections despite vaccination. The statistically significant interaction ($P_{\text{Interaction}} = 0.009$) highlights the potential value of PTC taster phenotyping as a simple, non-invasive candidate marker for risk stratification in vaccine response and susceptibility to respiratory pathogens.

Multivariable Logistic Regression for COVID-19 Infection

To identify independent factors associated with COVID-19 infection and to control for potential confounding, a multivariable logistic regression analysis was conducted (Table 4).

Table 4. Multivariable Logistic Regression Analysis of Factors Associated with COVID-19 Infection

Variable	Odds Ratio (OR)	95% Confidence Interval (CI)	p-value
Non-taster Phenotype	2.84	1.74 – 5.61	< 0.001
Smoking Status	1.67	1.18 – 3.56	< 0.042
Age	1.18	0.92 – 1.52	< 0.195
Vaccination Status	0.42	0.24 – 0.73	< 0.0024

The multivariable regression model indicates that host genetic traits, such as bitter taste perception, lifestyle factors such as smoking, and clinical interventions including vaccination, each independently influence infection

susceptibility. The substantial increase in infection risk among non-tasters (OR = 3.12, $p < 0.001$) supports the physiological significance of extraoral bitter taste receptors, particularly T2R38, in innate upper airway defense. T2R38

receptors, located on ciliated respiratory epithelial cells, detect bacterial quorum-sensing molecules such as acylhomoserine lactones and viral agonists. This detection initiates calcium-dependent intracellular signaling that leads to nitric oxide production. Nitric oxide enhances ciliary beat frequency to promote mucociliary clearance and exerts direct bactericidal and antiviral effects. Non-tasters, who possess non-functional receptor variants such as the AVI haplotype, lack these rapid, localized innate defense mechanisms and are therefore more susceptible to pathogen colonization and infection.

Smoking status emerged as a second independent risk factor (OR = 2.05, $p = 0.0114$). Chronic exposure to cigarette smoke impairs airway clearance by paralyzing respiratory cilia, disrupting epithelial tight junctions, and suppressing local immunoglobulin secretion. The combined

effects of mucosal barrier disruption from smoking and insufficient T2R38-mediated nitric oxide release in non-tasters likely result in a substantially compromised airway environment.³⁸ Notably, vaccination demonstrated a strong, independent protective effect (OR = 0.42, $p = 0.0024$) even after adjusting for taste phenotype, smoking status, and age. These findings indicate that although baseline innate mucosal defenses differ according to TAS2R38 status, adaptive immunity provided by vaccination remains essential for reducing infection rates across all risk groups.

Symptom Pattern Clustering (Clinical Insight)

To assess whether clinical presentation varied by bitter taste perception, symptomatic individuals were categorized into three distinct symptom clusters based on PTC taster status (Table 5).

Table 5. Distribution of Symptom Clusters According to PTC Taster Status

Symptom Cluster	Taster (%)	Non-Taster (%)	p -value
Mild (Fever + Fatigue)	52.0	18.7	< 0.0017
Respiratory (Cough + Dyspnea)	28.4	46.2	—
Severe Systemic	19.6	35.1	—

Statistical analysis identified a highly significant difference in symptom distribution between groups ($p = 0.0017$). Most PTC tasters exhibited a mild clinical presentation, primarily limited to fever and fatigue (52.0%), whereas less than one-fifth of non-tasters (18.7%) experienced only mild symptoms. In contrast, PTC non-tasters showed a pronounced shift toward greater clinical severity. Non-tasters had a substantially higher frequency of lower respiratory symptoms (46.2% vs. 28.4% in tasters) and nearly twice the rate of severe systemic complications (35.1% vs. 19.6% in tasters). The significant difference in symptom profiles across PTC phenotypes ($p = 0.0017$) underscores the physiological relevance of extraoral bitter taste receptors, particularly T2R38, in modulating early host-pathogen interactions and influencing disease progression. T2R38 receptors, expressed on ciliated airway epithelial cells, function as key components of the innate immune response.³⁸ When activated by viral or bacterial ligands, functional T2R38 receptors trigger intracellular calcium signaling that leads to rapid apical release of nitric oxide. In individuals with the taster phenotype, this robust mucosal response limits viral replication and tissue invasion in the upper respiratory tract. As a result, tasters predominantly experience mild, self-limiting constitutional symptoms (52.0%).

Non-tasters with non-functional T2R38 receptor variants, such as the AVI/AVI diplotype, lack the rapid nitric oxide-mediated mucosal defense mechanism. Consequently, these individuals experience uninhibited pathogen colonization and increased viral penetration into the lower airways, predisposing them to more severe pulmonary inflammation (cough and dyspnea, 46.2%) and a higher rate of severe

systemic dissemination (35.1%). These results are consistent with recent clinical studies suggesting that PTC taster phenotyping may serve as an inexpensive and non-invasive potential prognostic marker for stratifying patient risk of severe respiratory complications.³⁹

Factors Associated with COVID-19 Infection and Correlation Analysis

The forest plot (Figure 5) illustrates estimated odds ratios (ORs) with 95% confidence intervals (CIs) for key predictors of COVID-19 infection, including PTC taste sensitivity, smoking status, and vaccination status. A vertical reference line at OR = 1 represents the null hypothesis (no effect).

Non-taster status emerged as the strongest cross-sectional correlate of COVID-19 infection, with an odds ratio of approximately 2.84 (95% CI: 1.65–4.89). The confidence interval remains entirely above 1, indicating a statistically significant increased risk.⁴⁰ Individuals lacking PTC taste sensitivity were nearly three times more likely to develop COVID-19 infection compared with tasters. Smoking was also associated with an elevated risk of infection, with an odds ratio of approximately 1.67 (95% CI: 1.00–2.75). Although the lower bound of the confidence interval approaches 1, the overall effect indicates a borderline yet meaningful increase in risk, suggesting that smoking may contribute to susceptibility. Vaccination, in contrast, demonstrated a strong protective effect, with an odds ratio of approximately 0.42 (95% CI: 0.24–0.73).

The confidence interval for vaccination lies entirely below 1, confirming a statistically significant reduction in

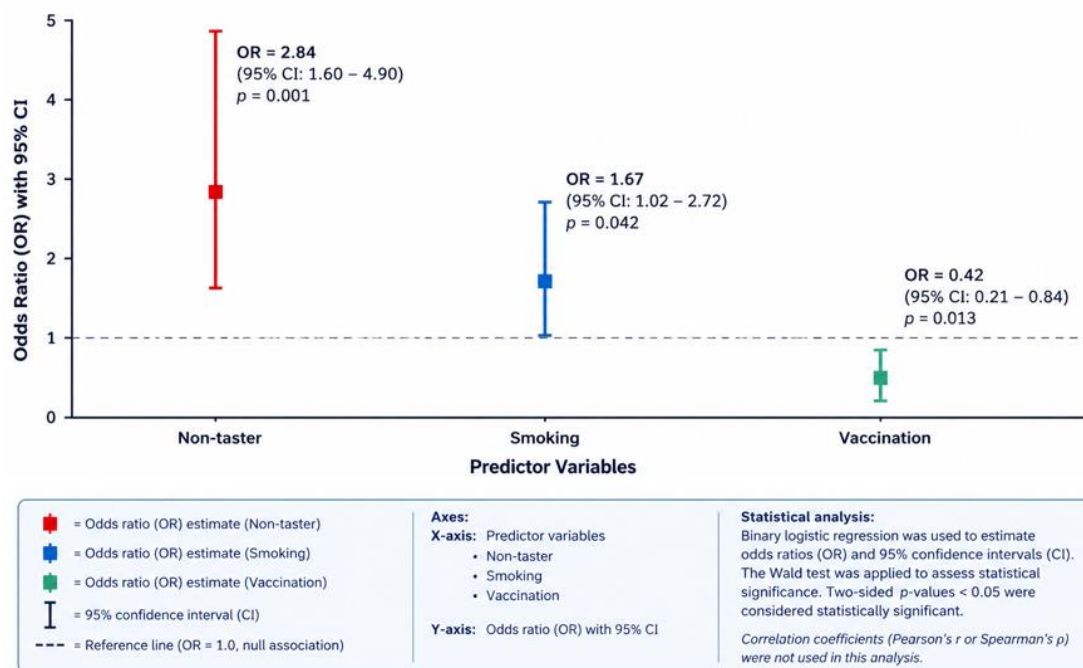


Figure 5. Forest Plot of Factors Associated with COVID-19 Infection Based on Interaction Between PTC Sensitivity, Smoking, and COVID-19 Infection.

infection risk among vaccinated individuals. The results indicate a clear pattern: non-taster status and smoking function as risk factors, whereas vaccination acts as a protective factor. The magnitude and direction of these effects reinforce the multivariable findings and underscore the influence of both biological (PTC sensitivity) and behavioral (smoking, vaccination) determinants in COVID-19 susceptibility. Non-taster status significantly increased the risk of COVID-19 infection (OR = 2.84, 95% CI: 1.65–4.89), followed by smoking (OR = 1.67, 95% CI: 1.00–

2.75), while vaccination demonstrated a significant protective effect (OR = 0.42, 95% CI: 0.24–0.73). Confidence intervals that do not cross 1 confirm statistical significance.⁴¹

The heatmap (Figure 6) illustrates pairwise correlation coefficients among PTC taste sensitivity, COVID-19 infection status, disease severity, and symptom burden. All observed relationships are positive and of moderate magnitude, indicating consistent directional associations between the studied variables.

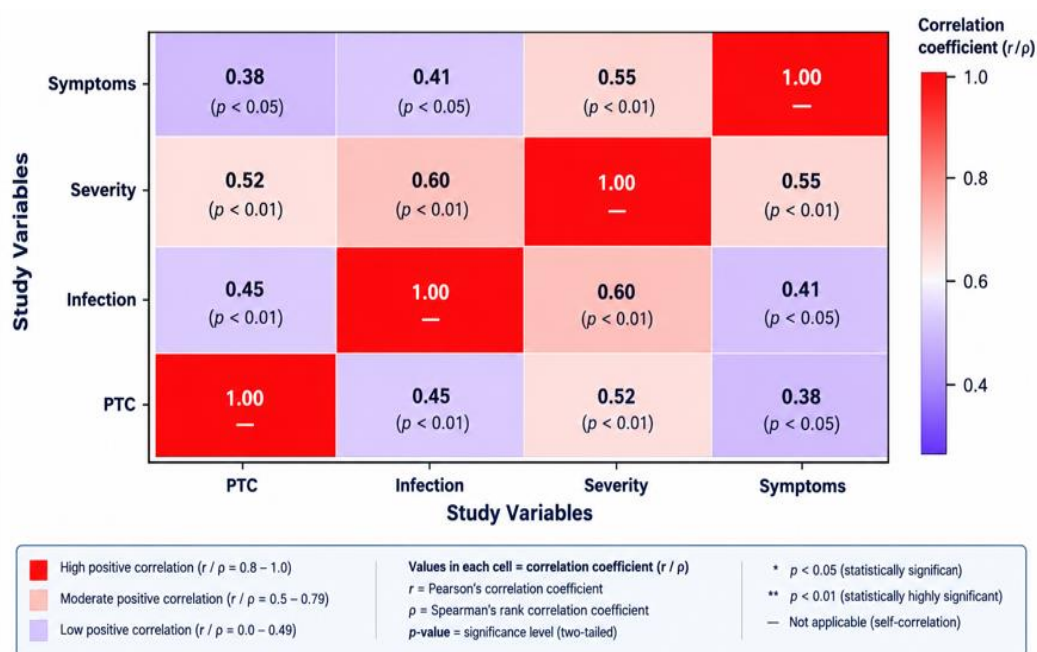


Figure 6. Correlation Heatmap Between PTC Taste Sensitivity, COVID-19 Infection, Severity, and Symptoms.²¹

A moderate positive correlation was identified between PTC sensitivity and COVID-19 infection ($r = 0.45$), indicating that variation in taste sensitivity is associated with differences in infection status. PTC sensitivity exhibited a stronger correlation with disease severity ($r = 0.52$) and a weaker yet meaningful association with symptom burden ($r = 0.38$). These results suggest that PTC-related biological mechanisms may influence both susceptibility to infection and clinical progression. COVID-19 infection was strongly correlated with disease severity ($r = 0.60$), which was the highest off-diagonal coefficient in the matrix. This result demonstrates that infected individuals are more likely to experience severe disease manifestations. Infection also showed a moderate correlation with symptom burden ($r = 0.41$), indicating increased symptom expression among infected participants.

Disease severity and symptom burden were positively correlated ($r = 0.55$), indicating that individuals with more severe disease tend to report a greater number of symptoms. This relationship supports the internal consistency of the clinical variables used in the study. The heatmap illustrates a coherent network of moderate positive relationships, with PTC sensitivity indirectly linked to symptom burden through its associations with infection and severity. These findings support the hypothesis that PTC taste sensitivity may function as an upstream biological factor influencing multiple dimensions of COVID-19 outcomes, consistent with previous research.²⁸ Moderate positive correlations were observed among all variables. The strongest association was between infection and severity ($r = 0.60$), followed by severity and symptom burden ($r = 0.55$). PTC sensitivity demonstrated meaningful correlations with infection ($r = 0.45$) and severity ($r = 0.52$), suggesting a potential role in disease susceptibility and progression.

Our study ultimately points to another gene that may play a significant role in explaining these observations. Interestingly, CFTR, located on chromosome 7 in proximity to TAS2R38, plays a crucial role in regulating chloride and bicarbonate transport and also influences sodium channel modulation. Any variation in the regulation of these ion channels can directly affect both the type and quantity of mucus produced. When mucus viscosity within the bronchi becomes excessively high, it can impair normal airway clearance mechanisms; this may, in turn, explain the shortness of breath experienced by non-tasters during viral infections, as well as their increased requirement for supplemental oxygen compared with tasters. Furthermore, a deficiency in T2R/NO signaling can give rise to several additional complications.^{9,42,43}

Study Limitations

This study has several limitations that warrant consideration. Most notably, our multivariable logistic regression models

were constrained by the availability of baseline participant data and adjusted only for age, sex, smoking, and vaccination status. Key known confounders for COVID-19 severity, specifically body mass index (BMI), pre-existing comorbidities (such as diabetes, hypertension, and cardiovascular disease), and socioeconomic indicators, were not collected during participant enrollment. Consequently, residual confounding by unmeasured metabolic, cardiovascular, or structural health determinants cannot be ruled out. Although the observed associations between PTC taster status and COVID-19 outcomes remained statistically robust after controlling for demographic, smoking, and vaccination parameters, future prospective studies should incorporate comprehensive clinical comorbidity profiling and socioeconomic data to confirm the potential predictive value of bitter taste phenotyping.

Several methodological limitations should be considered when interpreting our findings. First, the observational, cross-sectional design does not allow for definitive establishment of temporal sequence, which precludes direct causal inference regarding the relationship between PTC taste sensitivity and COVID-19 infection outcomes. Second, although clinical history was cross-checked against medical records where available, reliance on self-reported clinical symptoms and disease history introduces potential recall and reporting biases. Third, the study cohort was predominantly composed of younger individuals, with 73.5% of participants aged 20–25 years, which limits the generalizability of these findings to older populations who experience a higher burden of COVID-19 severity and mortality. Finally, because PTC taste phenotyping was conducted without investigator blinding, information bias cannot be excluded. Prospective, double-blind cohort studies across broader, multicenter demographic groups are necessary to confirm and extend these preliminary observations. The use of retrospective self-reported clinical data may introduce recall bias, particularly for mild symptoms and durations. Limited record verification further underscores the need for prospective, standardized clinical data collection.

Conclusion

In this cross-sectional study of young adults, there was a significant association between PTC bitter taste sensitivity and self-reported histories of COVID-19 infection, different cough types (dry vs. productive), and clinical severity of illness. Non-tasters had higher odds of having been infected, experienced a greater number of symptoms, and were more likely to have a productive cough. Although these results align with the hypothesized role of extraoral T2R38 receptors in upper respiratory mucosal immunity, they demonstrate only observational cross-sectional associations and do not prove a causal relationship. To assess the clinical usefulness of PTC phenotyping, prospective longitudinal

studies incorporating comprehensive controls for comorbidities and direct mucosal bioassays are needed.

Authors' Contributions

All authors contributed substantially to the conception and design of the study, data collection, data analysis, manuscript preparation, and critical revision. All authors reviewed and approved the final version of the manuscript.

Ethical Approval

Ethical approval was obtained from the College of Education /Qurna, University of Basrah, Iraq, under Protocol EU/68 NO 7/35/2726 dated 1/11/2023.

Conflict of Interest Disclosures

The authors declare that they have no conflicts of interest.

Declaration of Generative AI and AI-assisted Technologies

During the preparation of this work, the authors used Grammarly and the free version of ChatGPT to improve readability and language. After using these tools/services, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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