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Long COVID's Gender-Specific Determinants: 3- and 6-Month Evidence from Thai Females During the Delta and Omicron Waves

Chonlawat Chaichan MSc[1,2], Thammanard Charernboon MD, PhD[3,4], Paskorn Sritipsukho MD, MSc[3,4],

[1] *Department of Clinical Epidemiology, Faculty of Medicine, Thammasat University, Pathumthani 12120, Thailand*

[2] *Department of Research and Medical Innovation, Faculty of Medicine Vajira Hospital, Navamindradhiraj University, Bangkok 10300, Thailand*

[3] *Center of Excellence in Applied Epidemiology, Thammasat University, Pathumthani 12120, Thailand*

[4] *Research Group in Clinical Epidemiology, Faculty of Medicine, Thammasat University, Pathumthani 12120, Thailand*

Corresponding author
Paskorn Sritipsukho
paskorn100@yahoo.com
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ABSTRACT

Objectives: To prospectively identify determinants of Long COVID in Thai females and compare outcomes across the Delta and Omicron periods through structured follow-up assessments at 3 and 6 months post-infection.

Materials and Methods: From May 2021 through June 2022, this prospective cohort study was conducted in Thailand at Thammasat University Hospital and its field hospital. We enrolled 1,484 females aged 18 and older with laboratory-confirmed SARS-CoV-2 infection. Using a standardized questionnaire and trained interviewers to assess Long COVID symptoms, we followed up with participants via telephone interviews at 3- and 6-months post-diagnosis. Multivariable logistic regression was used to identify independent risk factors for Long COVID.

Results: At the 3-month follow-up, 806 participants (54.3%) reported Long COVID symptoms, which persisted in 418 (38.6%) at 6 months. At 3 months, infection during the Omicron-dominant wave (adjusted odds ratio (OR) 1.75, 95% confidenc interval (CI): 1.26–2.43) and acute myalgia (adjusted OR 1.52, 95% CI: 1.04–2.22) were significant predictors. At the 6-month follow-up, moderate-to-critical initial illness severity (adjusted OR 2.17, 95% CI: 1.01–4.69) and loss of smell during the acute phase (adjusted OR 1.61, 95% CI: 1.04–2.49) were significant predictors of persistent Long COVID.

Conclusion: In Thai females, determinants for Long COVID shift between 3 and 6 months post-infection. While acute myalgia and the Omicron variant are early predictors, initial illness severity and loss of smell better indicate symptom persistence at 6 months. These findings highlight Long COVID's dynamic nature and can help identify female patients at higher risk for prolonged symptoms.

Keywords: associated factor, female, long COVID, point prevalence, Thai

INTRODUCTION

Since its emergence in late 2019, COVID-19 has profoundly impacted global health over the past 5 years. Clinical presentation of acute SARS-CoV-2 infection demonstrates remarkable heterogeneity, ranging from asymptomatic to severe, life-threatening cases. Beyond the acute phase, a substantial proportion of infected individuals—estimated at 65 million globally—develop persistent symptoms lasting more than 3 months, a condition the World Health Organization and the Centers for Disease Control and Prevention formally recognize as Long COVID.[1-3]

In the post-pandemic era, Long COVID has evolved into a major public health challenge because this complex, multi-system disorder presents with debilitating symptoms that compromise individual quality of life, reduce workforce productivity, and strain healthcare infrastructure.[4] Recognizing Long COVID's substantial burden, health authorities and governments increasingly acknowledge the disease as requiring—rather than individualized management alone—coordinated, sustained public health interventions.

Current therapeutic approaches remain largely empirical. As new evidence emerges, approaches rely on trial-and-error methodologies and personalized-management strategies. Critically, standardized care protocols for high-risk populations remain underdeveloped, representing a significant limitation, particularly given consistent evidence that Long COVID disproportionately affects females.[4] Multiple large-scale studies and meta-analyses have identified being female as a primary risk factor for developing Long COVID, creating a clinical paradox. Although compared to males, females typically exhibit more robust immune responses during acute COVID-19 infection, paradoxically they experience higher rates of persistent symptoms.[5]

Leading hypotheses propose that female immunological advantages during acute infection may predispose them to Long COVID through immunological hyperactivation. The enhanced immune response that provides initial protection may subsequently trigger sustained infl mmatory cascades and autoimmune-like processes, wherein immune mechanisms inappropriately target host tissues, perpetuating Long COVID's multi-systemic symptomatology.[6]

Females' risk of Long COVID extends beyond biological sex to combine with multiple interacting determinants. Key predisposing factors include: perimenopausal status, particularly from age 40 to 55, when hormonal fluctuations alter immune regulation and elevated body mass index is associated with chronic inflammatory states, specifi SARS-CoV-2 variants with differential risk profil s between Delta and Omicron waves, vaccination status, and acute infection symptom severity.

Complex interactions among these predisposing factors across viral variant periods remain inadequately characterized, particularly within Thai populations. Therefore, this prospective study aimed to identify Long COVID's gender-specific determinants among Thai females by employing systematic follow-up assessments at 3 and 6 months post-infection during both the Delta and Omicron variant periods.

Furthermore, variations in genetic phenotypes affecting host immune responses, differences in vaccine types and completeness of vaccination regimens among Thai populations, together with other contextual and sociocultural factors, preclude the direct generalization of evidence from previous studies to this setting. Consequently, population-specific investigation is essential to accurately characterize Long COVID determinants among Thai females.

This study prospectively aimed to identify gender-specific determinants of Long COVID in Thai females using structured follow-up assessments at 3 and 6 months post-infection, comparing outcomes across Delta and Omicron variant periods.

MATERIALS AND METHODS

This study was approved by the Human Research Ethics Committee of Thammasat University (Medicine, MTU-EC-PE-1-280/65).To investigate Long COVID's risk factors among Thai females, this prospective cohort study was conducted at Thammasat University Hospital (TUH) and its affiliated Thammasat Field Hospital (TFH). Recruitment occurred from May 2021 to June 2022, spanning Thailand's Delta- and Omicron-variant dominant waves. TUH is a 700-bed tertiary-care academic medical center, providing comprehensive healthcare services to populations across northern Bangkok and central Thailand. The facility maintains established infectious disease protocols and electronic health records system essential for longitudinal patient tracking. TFH operates as a 490-bed specialized facility for patients with asymptomatic-to-mild COVID-19, allowing capture of the full spectrum of disease severity in the study population.

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The investigation employed a gender-focused approach, targeting female participants to address knowledge gaps on gender-specifi Long COVID patterns. Participants were monitored via telephone interviews at 3 and 6 months post SARS-CoV-2 diagnosis, enabling comprehensive assessment of symptom evolution and persistence. Participants were monitored via telephone interviews at 3 and 6 months after recovery from acute SARS-CoV-2 infection to assess symptom evolution and persistence. Nonetheless, the study did not employ a longitudinal design; data at each time point were collected independently, and individual-level follow-up across assessments was not performed.

Eligibility included female patients aged 18 and older with laboratory confirm d SARS-CoV-2 infection via nasopharyngeal reverse transcription polymerase chain reaction performed at either facility. This molecular approach ensured accurate case identification and standardized detection criteria across hospitals.

Participants were identified systematically through hospital databases and contacted by telephone for follow-up interviews. The recruitment strategy captured diverse clinical presentations, ranging from asymptomatic infections at the field hospital to severe cases at the tertiary center. All participants provided written informed consent at initial presentation and additional verbal consent was obtained for telephone interviews.

The study protocol received approval from both hospitals' institutional review boards, and participant confidentiality was maintained through coded identification systems in compliance with privacy standards.

Sample size determination followed a feasibility-based cohort design, with cohort size defined by real-world case accrual rather than an a prior power calculation, corresponding to the number of eligible female patients with laboratory-confirme SARS-CoV-2 infection presenting to the participating hospitals during the study period. A post-hoc assessment of statistical precision indicated that the achieved sample size was sufficien for descriptive and exploratory analyses, sufficient to achieve acceptable precision of parameter estimates, as reflect d by the width of corresponding confidenc intervals, permitting estimation of key epidemiological parameters and hypothesis generation within an observational epidemiological framework.

Long COVID was assessed using a standardized, symptom-based questionnaire developed by the Thai Ministry of Public Health and validated for telephonic administration. This instrument was generated through rigorous developmental processes, incorporating international Long COVID diagnostic criteria and also adapting to local linguistic and cultural considerations. Trained interviewers conducted structured telephone interviews at 3 and 6 months post-diagnosis evaluating symptom presence, functional status evaluation, and healthcare utilization. Interviewers followed standardized questioning techniques, symptom severity grading, and quality assurance procedures.

To ensure complete characterization of potential Long COVID determinants, comprehensive data collection integrated information from multiple sources. Primary data extraction was from the TUH electronic health record system, supplemented by structured interviews to capture variables not routinely documented in clinical records.

Demographic variables included chronological age, educational attainment categorized according to Thai educational system standards, and smoking history with detailed quantification of exposure duration and intensity. During the study period, vaccination status was recorded based on manufacturer specifications dose timing relative to infection, and completion status according to recommended schedules.

Comorbidities were assessed through systematic review of documented medical conditions, including coronary artery disease, heart failure, arrhythmias, chronic pulmonary conditions including asthma and chronic obstructive pulmonary disease, diabetes mellitus with glycemic control status, chronic kidney disease staged according to estimated glomerular filtration rate, cerebrovascular disease history, and active or prior malignancy.

Initial COVID-19 illness severity classificatio followed the National Institute for Health and Care Excellence guidelines, providing standardized frameworks for symptom categorization and severity grading. Symptom documentation employed systematic organ system classification, including respiratory manifestations such as cough, dyspnea, and chest discomfort; neurological symptoms such as headache and altered consciousness; musculoskeletal complaints including myalgia and arthralgia; gastrointestinal symptoms such as diarrhea, nausea, and abdominal pain; and constitutional symptoms including fever, fatigue, and anorexia.

Overall illness severity was classified according to World Health Organization criteria, ranging from

asymptomatic infection to mild illness not requiring hospitalization, moderate illness requiring medical intervention, severe illness necessitating intensive monitoring, and critical illness requiring life support measures. This classificatio enabled systematic comparison across severity categories and their associated Long COVID risks.

Comprehensive symptom evaluation included 21 distinct manifestations identified through literature review and clinical expertise as commonly associated with Long COVID. Respiratory symptoms included persistent dyspnea, chronic cough, and chest tightness or discomfort; cardiovascular manifestations included palpitations and exercise intolerance; neurological symptoms included headache, attention defici s, memory impairment, and sleep disturbances. Gastrointestinal assessment focused on persistent diarrhea and appetite changes. Musculoskeletal evaluation included ongoing myalgia and arthralgia. Sensory symptoms encompassed anosmia and ageusia, representing persistent chemosensory dysfunction. Dermatological manifestations included skin rash and alopecia. Psychological symptoms comprised depression and stress responses, while constitutional symptoms included persistent exhaustion, generalized weakness, and dizziness.

Each symptom was systematically assessed for onset, duration, severity impact on daily functioning, and relationship to initial acute infection. Participants reported both new onset symptoms not present before COVID-19 and persistent symptoms continuing from the acute phase beyond the 3-month diagnostic threshold.

Patient characteristics were summarized through comprehensive descriptive statistics appropriate for variable types and distributions. Categorical variables were presented as absolute frequencies with corresponding percentages, enabling clarity of demographics and clinical profiles. Continuous variables were assessed for distribution normality, with appropriate measures of central tendency and variability selected accordingly. Categorical variable associations were analyzed using Chi-square testing for variables meeting expected frequency assumptions, with Fisher's exact testing applied for sparse data scenarios. These analytical approaches identifie statistically significan relationships among potential determinants and Long COVID development.

For prognostic modeling, acute-phase symptom inclusion required prevalence exceeding 5% in the study population, ensuring adequate statistical power for meaningful effect estimation. This threshold prevented analytical instability associated with rare exposures while also maintaining clinical relevance for commonly occurring symptoms.

Univariate logistic regression analysis assessed individual relationships between each potential determinant and Long COVID development. Results were presented as crude odds ratios (ORs) with corresponding 95% confidence intervals, providing effect magnitude estimates and statistical significance assessment for each variable. Independent prognostic factor identification employed multivariable logistic regression modeling with systematic variable selection procedures. The initial model included all variables demonstrating univariate associations with $p < 0.20$, thus providing a sufficiently liberal threshold to capture potential confounding relationships while also maintaining analytical feasibility. Final model development utilized backward elimination procedures, systematically removing variables that failed to demonstrate independent associations while maintaining overall model performance and clinical interpretability. This approach balanced statistical significance with practical clinical relevance, ensuring that final models provided meaningful prognostic information for Long COVID risk assessment. In the presence of missing data, analyses were conducted using a complete case approach, whereby only observations with complete data for all variables included in each specific analysis were retained. No data imputation procedures were performed.

All statistical analyses employed STATA version 14.2 software, which provides robust analytical capabilities for complex epidemiological data analysis. Statistical significance was established at $p < 0.05$, with confidence interval calculated at 95%.

RESULTS

A total of 1,484 female participants were enrolled and prospectively followed after hospital discharge to assess Long COVID outcomes during the Delta- and Omicron-dominant waves. At the 3-month follow-up, 806 participants (54.3%) reported persistent symptoms consistent with Long COVID, while 678 (45.7%) reported no persistent symptoms. At 6 months, 418 (38.6%) continued to experience Long COVID, while 664 (61.4%) had recovered. Fluctuating immune responses among participants aged 40-55 did not differ significantly between groups at either time point.

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Baseline characteristics further indicated that obesity (body mass index (BMI) ≥ 30.0) was more prevalent among those with Long COVID at 3 months, while vaccination status and acute disease severity showed differential distributions across groups, particularly during the Delta-dominant wave. These findings provide the foundation for examining Long COVID's female-specifi determinants across distinct viral variants and follow-up intervals. (Table 1)

Significant differences in baseline characteristics were observed between females with and without Long COVID. At 3 months, Long COVID occurred more frequently following Omicron infections (60.0% vs. 47.0%, p < 0.001). Vaccination status showed a marked association at 3 months: individuals with incomplete or no vaccination and those without booster doses, were overrepresented in the Long COVID group (p < 0.001). At 6 months, although obesity and overall comorbidity prevalence did not differ significantl between groups, disease severity demonstrated an association, with moderate-to-severe acute illness more frequently reported among those with Long COVID (19.6% vs. 16.3%, p = 0.044). Collectively, these findings highlight the roles of obesity, vaccination coverage, variant type, and acute illness severity as determinants of Long COVID persistence in Thai females. (Table 1)

Regarding acute symptomatology, several clinical manifestations during initial infection were significa tly associated with subsequent Long COVID among females. At 3 months, compared with those without persistent symptoms, myalgia was more

Table 1 Patient Characteristics of Females for Long COVID at 3- and 6-Month Follow-Up after the Delta and Omicron Variant COVID Infections

	3 Months (n = 1484)			6 Months (n = 1082)		
	Long COVID (n = 806)	Without Long COVID (n = 678)	P-value[a]	Long COVID (n = 418)	Without Long COVID (n = 664)	P-value[b]
Age between 40 and 55 years – no (%)	207 (25.7)	148 (21.8)	0.083	111 (26.6)	153 (23.0)	0.190
Obesity – no (%)						
Normal Weight (BMI ≤ 24.9 kg/m^2)	379 (47.0)	348 (51.3)	0.228	201 (48.1)	320 (48.2)	0.883
Overweight (BMI ≥ 25.0-29.9 kg/m^2)	111 (13.8)	91 (13.4)		49 (11.7)	84 (12.7)	
Obesity (BMI 30.0 kg/m^2)	316 (39.2)	239 (35.3)		168 (40.2)	260 (39.2)	
Comorbidities – no (%)						
CVD	127 (15.8)	111 (16.4)	0.748	59 (14.1)	91 (13.7)	0.849
COPD	31 (3.9)	25 (3.7)	0.873	17 (4.1)	23 (3.5)	0.609
DM	79 (9.8)	69 (10.2)	0.810	29 (6.9)	57 (8.6)	0.330
CKD	17 (2.1)	8 (1.2)	0.224	4 (0.96)	5 (0.75)	0.740
Stroke	11 (1.4)	8 (1.2)	0.752	2 (0.48)	4 (0.60)	1.000
Cancer	16 (2.0)	12 (1.8)	0.761	6 (1.4)	14 (2.1)	0.424
Variant of Concern – no (%)[c]						
Delta	303 (47.0)	342 (53.0)	< 0.001*	229 (41.1)	328 (58.9)	0.084
Omicron	503 (60.0)	336 (40.0)		189 (36.0)	336 (64.0)	

Table 1 Patient Characteristics of Females for Long COVID at 3- and 6-Month Follow-Up after the Delta and Omicron Variant COVID Infections (cont.)

	3 Months (n = 1484)			6 Months (n = 1082)		
	Long COVID (n = 806)	Without Long COVID (n = 678)	P-value[a]	Long COVID (n = 418)	Without Long COVID (n = 664)	P-value[b]
Vaccine History – no (%)						
Not Complete	265 (32.9)	262 (38.6)	< 0.001*	252 (38.0)	182 (43.5)	0.170
Complete	217 (26.9)	229 (33.8)		228 (34.3)	135 (32.3)	
Booster	324 (40.2)	187 (27.6)		184 (27.7)	101 (24.2)	
Severity at Acute Illness – no (%)						
Asymptomatic	25 (3.1)	35 (5.2)	0.102	11 (2.6)	36 (5.4)	0.044*
Mild	632 (78.4)	530 (78.2)		325 (77.8)	520 (78.3)	
Moderate-to-Critical	149 (18.5)	113 (16.7)		82 (19.6)	108 (16.3)	
Symptoms during Acute Illness – no (%)						
At Least 1 Symptom	677 (84.0)	547 (80.7)	0.094	352 (84.2)	534 (80.4)	0.115
Cough	465 (57.7)	358 (52.8)	0.059	231 (55.3)	344 (51.8)	0.267
Sore Throat	404 (50.1)	312 (46.0)	0.115	180 (43.1)	318 (47.9)	0.121
Myalgia	84 (10.4)	50 (7.4)	0.041*	41 (9.8)	58 (8.7)	0.551
Rhinorrhea	178 (22.1)	152 (22.4)	0.877	85 (20.3)	144 (21.7)	0.596
Sputum Production	96 (11.9)	63 (9.3)	0.104	41 (9.8)	71 (10.7)	0.642
Dyspnea	63 (7.8)	49 (7.2)	0.669	38 (9.1)	48 (7.2)	0.270
Headache	163 (20.2)	123 (18.1)	0.311	87 (20.8)	117 (17.6)	0.191
Diarrhea	19 (2.4)	13 (1.9)	0.561	15 (3.59)	10 (1.51)	0.026*
Loss of Smell	59 (7.3)	50 (7.4)	0.968	52 (12.4)	48 (7.2)	0.004*
Loss of Taste	21 (2.6)	19 (2.8)	0.816	21 (5.0)	17 (2.6)	0.032*

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; COVID, coronavirus disease; CVD, cardiovascular diseases; DM, diabetes mellitus; kg, kilogram m^2, square metre; n, number

[a] Comparison between long COVID and without long COVID at 3 months

[b] Comparison between long COVID and without long COVID at 6 months

[c] Row percentage

* Statistical significan e

Note: Data are numbers (%).

frequently reported in the Long COVID group (10.4% vs. 7.4%, p = 0.041). By 6 months, gastrointestinal and sensory symptoms emerged as notable determinants: diarrhea (3.6% vs. 1.5%, p = 0.026), loss of smell (12.4% vs. 7.2%, p = 0.004), and loss of taste (5.0% vs. 2.6%, p = 0.032) were significantly more common among individuals with ongoing Long COVID. These finding suggest that the presence of systemic and sensory disturbances during the acute phase may predispose female patients to prolonged symptoms, highlighting the need for early clinical indicators to identify those at elevated risk.

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As shown in **Table 2**, the point prevalence of Long COVID symptoms was evaluated at 3 months (n = 1484) and 6 months (n = 1082) post-infection. At 3 months, 54.3% (n = 806) reported at least one symptom. This proportion decreased by 6 months, with 38.6% (n = 418) reporting at least one symptom.

At 3 months, the most frequently reported symptom category was fatigue and weakness, affecting 31.9% (n = 474). Within this category, weakness was the most common individual symptom (30.3%, n = 449). Neurological symptoms were also prevalent (30.1%, n = 447), with memory loss the most frequent (20.3%, n = 299), followed by insomnia (14.1%, n = 209) and attention deficit (11.5%, n = 171). Dermatological symptoms were reported by 24.7% (n = 366), driven primarily by alopecia (21.5%, n = 319). Respiratory symptoms were present in 23.9% (n = 354), with dyspnea (15.7%, n = 233) more common than cough (13.2%, n = 196).

By 6 months, the prevalence of all symptom categories had declined. Fatigue and weakness remained the most common category but decreased to 21.0% (n = 224). The prevalence of weakness specifically fell to 18.5% (n = 200). Neurological symptoms decreased to 17.3% (n = 187), with memory loss reducing to 9.0% (n = 97). Dermatological symptoms reduced to 15.9% (n = 172), with alopecia dropping to 13.9% (n = 150). Respiratory symptoms also declined to 12.4% (n = 134).

As shown in **Table 3 and 4**, this study investigated associations between various factors and individual Long COVID symptoms in females at 3 and 6 months—including both Delta and Omicron variants—by selecting only determinants with a prevalence greater than 5% for each variable. Analysis at each time point was conducted in two stages. First, unadjusted ORs were calculated, followed by multivariable adjusted ORs including factors with a $p < 0.2$ in the unadjusted analysis.

At 3 months, several factors demonstrated significant association with Long COVID symptoms after adjustment. Infection during the Omicron-dominant wave strongly predicted Long COVID, with an adjusted OR of 1.68 (95% CI: 1.22–2.30, $p < 0.001$). Myalgia's presence as an initial symptom was also a significan factor, with an adjusted OR of 1.52 (95% CI: 1.04–2.21, $p = 0.030$). Other factors, for instance, BMI and moderate-to-critical disease severity, showed some association in the unadjusted analysis but did not

Table 2 Point Prevalence of Individual Symptoms of Females for Long COVID Follow-up at 3 and 6 Months after the Delta and Omicron Variant COVID Infection

	At 3 Months (n = 1484)	At 6 Months (n = 1082)
At Least 1 Symptom – No (%)	806 (54.3)	418 (38.6)
Respiratory Symptoms	354 (23.9)	134 (12.4)
Dyspnea	233 (15.7)	76 (7.0)
Cough	196 (13.2)	53 (4.9)
Cardiovascular Symptoms	204 (13.8)	52 (4.8)
Chest Tightness	94 (6.3)	24 (2.2)
Palpitation	108 (7.3)	31 (2.9)
Neurological Symptoms	447 (30.1)	187 (17.3)
Headache	151 (10.2)	44 (4.1)
Attention Defici	171 (11.5)	32 (3.0)
Memory Loss	299 (20.2)	97 (9.0)
Insomnia	209 (14.1)	72 (6.7)
Gastrointestinal Symptoms		
Diarrhea	44 (3.0)	6 (0.6)
Musculoskeletal Symptoms	225 (15.2)	77 (7.1)
Myalgia	164 (11.1)	45 (4.2)
Arthralgia	143 (9.6)	44 (4.1)
Ear, Nose, and Throat Symptoms	228 (15.4)	77 (7.1)
Dizziness	172 (11.6)	42 (3.9)
Loss of Appetite	116 (7.8)	16 (1.5)
Anosmia	58 (3.9)	23 (2.1)
Ageusia	47 (3.2)	8 (0.7)
Dermatological Symptoms	366 (24.7)	172 (15.9)
Rash	79 (5.3)	16 (1.5)
Alopecia	319 (21.5)	150 (13.9)
Psychological/ Psychiatric Symptoms	131 (8.8)	28 (2.6)
Depression	43 (2.9)	7 (0.7)
Stress	116 (7.8)	22 (2.0)
Fatigue & Weakness Symptoms	474 (31.9)	224 (21.0)
Fatigue	183 (12.3)	47 (4.3)
Weakness	449 (30.3)	200 (18.5)

Abbreviation: n, number

Table 3 Univariable Analysis of Associations between Individual Symptoms and Long COVID in Females at 3 and 6 Months after Delta and Omicron Variant SARS-CoV-2 Infection

Factor	3 Month		6 Month	
	Unadjusted OR [95%CI]	P-value[a]	Unadjusted OR [95%CI]	P-value[b]
Age between 40 and 55	1.24 [0.97-1.58]	0.083	1.21 [0.91-1.60]	0.191
Obesity				
Normal	Ref		Ref	
Overweight	1.04 [0.81-1.32]	0.772	0.95 [0.71-1.27]	0.742
≥ BMI 30 kg/m^2	1.51 [1.10-2.07]	0.010*	1.23 [0.86-1.76]	0.265
Comorbidities				
Cardiovascular	0.96 [0.72-1.26]	0.748	1.03 [0.73-1.47]	0.849
Diabetes Mellitus	0.96 [0.68-1.35]	0.810	0.79 [0.50-1.26]	0.330
COVID Waves				
Delta Waves	Ref		Ref	
Omicron Waves	1.69 [1.38-2.08]	< 0.001*	0.81 [0.63-1.03]	0.084
Vaccine History				
0-1 Dose	Ref		Ref	
Completed Vaccine	0.94 [0.73-1.21]	0.612	0.82 [0.62-1.09]	0.173
Booster Vaccine	1.71 [1.34-2.20]	< 0.001*	0.76 [0.56-1.03]	0.081
Severity Level				
Asymptomatic	Ref		Ref	
Mild	1.67 [0.99-2.83]	0.056	2.05 [1.03-4.07]	0.042*
Moderate-to-Critical	1.85 [1.05-3.26]	0.035*	2.49 [1.19-5.18]	0.015*
Symptoms during Acute Illness – No (%)				
Cough	1.21 [0.99-1.50]	0.059	1.15 [0.90-1.47]	0.267
Sore Throat	1.18 [0.96-1.45]	0.115	0.82 [0.64-1.05]	0.121
Myalgia	1.46 [1.01-2.11]	0.042*	1.14 [0.75-1.73]	0.551
Rhinorrhea	0.98[0.77-1.25]	0.877	0.92 [0.68-1.25]	0.596
Sputum Production	1.32 [0.94-1.85]	0.105	0.90 [0.61-1.36]	0.642
Dyspnea	1.09 [0.74-1.60]	0.669	1.28 [0.82-2.00]	0.271
Headache	1.14 [0.88-1.48]	0.311	1.26 [0.90-1.67]	0.192
Loss of Smell	0.99 [0.67-1.47]	0.968	1.82 [1.21-2.76]	0.004*

Abbreviations: BMI, body mass index; CI, confidence nterval; kg, kilogram; m^2, square metre; OR, odds ratio

[a] Comparison between Long COVID and no Long COVID at 3 months

[b] Comparison between Long COVID and no Long COVID at 6 months

* Statistical significanc

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Table 4 Multivariable Analysis of Associations between Individual Symptoms and Long COVID in Females at 3 and 6 Months after Delta and Omicron Variant SARS-CoV-2 Infection

Factor	3 Month		6 Month	
	Adjusted OR[c] [95%CI]	P-value[a]	Adjusted OR[d] [95%CI]	P-value[b]
Age between 40 and 55	1.26 [0.98-1.62]	0.075	1.15 [0.87-1.55]	0.315
Obesity				
Normal	Ref		NA	NA
Overweight	1.04 [0.76-1.44]	0.792	NA	NA
≥ BMI 30 kg/m^2	1.24 [0.98-1.56]	0.077	NA	NA
COVID Waves				
Delta	Ref		Ref	
Omicron	1.68 [1.22-2.30]	0.001*	0.98 [0.67-1.43]	0.909
Vaccine History				
0-1 Dose	Ref		Ref	
Completed Vaccine	0.75 [0.55-1.03]	0.073	0.91 [0.64-1.30]	0.597
Booster Vaccine	1.19 [0.81-1.73]	0.378	0.91 [0.57-1.44]	0.678
Severity Level				
Asymptomatic	Ref		Ref	
Mild	1.29 [0.74-2.23]	0.372	2.07 [1.02-4.19]	0.043*
Moderate-to-Critical	1.55 [0.85-2.80]	0.152	2.34 [1.11-4.94]	0.026*
Symptoms during Acute Illness – No (%)				
Cough	1.15 [0.93-1.43]	0.205	NA	NA
Sore Throat	1.00 [0.80-1.25]	0.980	0.82 [0.63-1.07]	0.137
Myalgia	1.52 [1.04-2.21]	0.030*	NA	NA
Sputum Production	1.20 [0.85-1.69]	0.304	NA	NA
Headache	NA	NA	1.24 [0.91-1.70]	0.179
Loss of Smell	NA	NA	1.62 [1.05-2.50]	0.029*

Abbreviations: BMI, body mass index; CI, confidence interval; kg, kilogram; m^2, square metre; NA, not applicable; OR, odds ratio

[a] Comparison between Long COVID and no Long COVID at 3 months

[b] Comparison between Long COVID and no Long COVID at 6 months

[c] Adjusted odds ratio at 3 months by age, obesity, Dominant waves, vaccine doses, severity and symptoms during acute illness

[d] Adjusted odds ratio at 6 months by female sex, Dominant waves, vaccine doses, severity and symptoms during acute illness

* Statistical significanc

reach statistical significance in the adjusted model.

Analysis at the 6-month follow-up revealed shifts in factors associated with persistent Long COVID symptoms. The initial illness's severity became a more prominent predictor: compared with asymptomatic cases, mild disease had an adjusted OR of 2.07 (95% CI: 1.02–4.19; p = 0.043), and moderate-to-critical disease had an adjusted OR of 2.34 (95% CI: 1.11–4.94; p = 0.026). Loss of smell during the initial illness was also a significan predictor, with an adjusted OR of 1.62 (95% CI: 1.05–2.50; p = 0.029). Notably, at the 6-month follow-up, factors significant at 3 months, such as the Omicron-dominant wave and myalgia as an initial symptom, were no longer statistically significant At this later time point, other variables, including the Omicron-dominant wave and myalgia, did not demonstrate significant associations in either unadjusted or adjusted models.

DISCUSSION

This prospective cohort investigation provides a comprehensive analysis of female-specifi determinants and Long COVID's phenotypic evolution among Thai females during recovery from Delta- and Omicron-dominant waves. The documented decline in Long COVID prevalence from 54.3% at 3 months to 38.6% at 6 months demonstrates substantial, although incomplete, natural recovery trajectories. This evidence aligns with several studies reporting a higher burden of Long COVID among females across settings.[7-11] Moreover, these findings indicate a fundamental temporal shift in principal risk factors, suggesting that Long COVID pathophysiology may evolve from an initial systemic inflammatory phase to subsequent organ-specific sequelae

The observed recovery pattern indicates that although symptoms resolve substantially during the initial 6-month period, more than one-third of affected individuals continue experiencing persistent manifestations. This incomplete recovery trajectory has profound implications for global healthcare resource allocation, occupational health policies, and long-term disability planning. The temporal evolution of risk factor profil s suggests distinct pathophysiological phases requiring various therapeutic approaches and clinical management strategies.

At 3 months, infection during the Omicron-dominant wave emerged as an independent predictor of Long COVID (adjusted OR 1.68) despite its generally milder acute clinical presentation than the Delta-dominant wave. This observation contrasts with several international reports but aligns with finding from studies conducted in Thailand. Other investigations have similarly noted Long COVID's higher prevalence following Omicron compared with Delta. These differences may be infl enced by circulating viral sublineages, host immunity profiles, and variations in primary vaccination series and booster-type combinations across populations.[12] This paradox likely reflects Omicron's enhanced immune evasion, distinct tissue tropism, and altered inflammatory responses. Immune escape mutations in spike protein epitopes might influenc viral persistence, immune memory formation, and inflammatory resolution, thereby generating variant-specifi , post-acute morbidity profiles

Myalgia's prominence as a predictor (adjusted OR 1.52) supports systemic inflammator etiologies, representing a cardinal manifestation of virally induced systemic inflammation that reflects widespread inflammatory mediator release that, in turn, affects skeletal muscle tissues and pain perception pathways. The mechanistic basis involves cytokine-mediated muscle fiber inflammation mitochondrial dysfunction, and altered pain processing mechanisms that might persist beyond viral clearance. Persistent myalgia suggests ongoing inflammatory activation or residual tissue damage affecting neuromuscular function and pain modulation systems, providing clinical evidence for sustained inflammatory processes underlying early Long COVID. In studying COVID-19 acute-phase clinical characteristics that predict Long COVID, Guzman-Esquivel et al. and Fernández-de-Las-Peñas et al. found myalgia to be a risk factor with an odds ratio of 1.5 compared to without Long COVID.[13,14] Their results relate to ours for myalgia and severity levels in univariable analysis at 3 months.

At 6 months, the risk factor profile shifted, with infection during the Omicron-dominant wave and myalgia at initial infection losing significance, while initial disease severity and loss of smell emerged as predominant predictors. This transition suggests Long COVID evolves from early inflammation-drive mechanisms to later phases characterized by residual organ damage.[15] This temporal specificity highlights distinct pathophysiological stages and implies that early interventions targeting inflammation may mitigate progression to long-term structural impairment.[15] At 6 months, moderate-to-critical initial disease severity

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was strongly associated with persistent symptoms (adjusted OR 2.34).[16] Severity levels reflect higher viral loads, extensive multi-organ involvement, and cumulative tissue damage, leading to long-term impairments. Evidence consistently indicates that hospitalized patients are at greater risk of developing persistent symptoms, reinforcing acute viral burden and inflammatory injury's contributions as Long COVID's key determinants. These findings emphasize the importance of early, intensive clinical interventions. At 6 months, loss of smell emerged as an independent Long COVID predictor (adjusted OR 1.62).[17-19] Persistent olfactory dysfunction likely reflect unresolved olfactory bulb inflammation and broader neuronal dysregulation, consistent with neuroimaging evidence of structural brain changes in regions linked to olfactory processing.[20]

Persistent loss of smell might be explained via a neurological pathway in Long COVID, suggesting central nervous system involvement through viral persistence, chronic neuroinflammation, or structural brain alterations.[21] Symptom cluster trajectories revealed heterogeneous decline rates by 6 months, indicating distinct biological mechanisms contributing to varied recovery patterns.[22] Fatigue and weakness remained the most persistent symptoms, consistent with mechanisms involving mitochondrial dysfunction, viral reservoirs, and autonomic dysregulation.[23] Emerging evidence implicates microclot formation and endothelial dysfunction in impaired oxygen delivery and energy metabolism, offering plausible explanations for sustained fatigue and highlighting the need for targeted vascular and metabolic interventions.[24,25] Dermatological symptoms —predominantly alopecia—resolved more rapidly, likely reflecting alopecia's emergence due to acute physiological stress, which typically normalizes with hair cycle restoration.[26] Neurological symptoms declined by half, yet they persisted in nearly one-fifth of patients, emphasizing the central nervous system's particular involvement in Long COVID and the need for specialized management.[27] Heterogeneous recovery patterns across symptom domains suggest multiple underlying pathophysiological processes, supporting the need for crucial individualized diagnostic and therapeutic approaches.[28]

This investigation possesses notable methodological strengths that enhance its validity and clinical relevance. The prospective cohort design allows real-time monitoring of symptoms and risk factors, reducing concerns about retrospective reporting. The substantial cohort of 1,476 female participants provides considerable statistical power for examining gender-specific determinants and addressing an important knowledge gap, given recognized gender disparities in Long COVID's prevalence. Conducting the study during both the Delta and Omicron variant dominant waves enabled comparative analysis of variant-specific risk profiles and symptom evolution. Additionally, comprehensive data collection encompassing demographic, clinical, and symptomatic variables across multiple assessment points further strengthens the study's methodological rigor. Systematic follow-up protocols—with trained interviewers—adapted from the Ministry of Public Health ensure consistent data quality and comparability. Furthermore, integrating hospital database information into structured interview data provides comprehensive characterization of clinical profile and Long COVID manifestations.

Despite these strengths, several limitations warrant consideration. The absence of pre-COVID baseline assessments presents challenges to definitivel attributing symptoms to post-viral pathology rather than to pre-existing conditions. Reliance on self-reported symptoms introduces potential interpretation variations and possible over- or underestimation, which are partially mitigated by structured questionnaires and trained interviewer protocols. Additionally, symptoms were not routinely confirmed by objective clinical, laboratory, or functional assessments, which may have led to symptom misclassification, particularly for subjective or fluctuating manifestations such as fatigue, dyspnea, or anosmia. The study population derives from specifi Thai healthcare settings, potentially limiting generalizability to other ethnic populations, healthcare systems, or regions with different baseline health profil s, variant circulation, or vaccination strategies. Thus, future investigations should replicate findings across diverse populations and contexts. These findings offer important insights for evidence-based clinical care and Long COVID management. The temporal evolution of risk factors suggests that early interventions should focus on preventing systemic inflammatory complications, while later phase management should address organ-specific sequelae and functional rehabilitation needs.

Early interventions should target systemic inflammat on, whereas later management should focus on rehabilitating end-organ damage. Evolving risk profile indicate that short-term morbidity at 3 months

is driven by inflammation influenced by obesity, vaccination status, and viral variant, while 6-month sequelae refle t acute organ injury and neurological involvement, including persistent anosmia. These findings suggest the need for time-sensitive, gender-specific anagement strategies, multidisciplinary rehabilitation, and long-term support, along with implications for clinical practice, public health planning, and resource allocation. Future research should validate these mechanisms through longitudinal biomarker studies.

CONCLUSION

This study shows that determinants of Long COVID in Thai females change over time. Acute myalgia and infection during the Omicron wave are early predictors at 3 months, whereas initial disease severity and loss of smell more strongly predict symptom persistence at 6 months. These findings eflec the evolving course of Long COVID and indicate the importance of time-specific isk stratification. ecognizing these shifting predictors may enhance early identification and enable more targeted follow-up of females at higher risk for prolonged symptoms.

Conflict of Interest

All authors declare no conflicts of interest

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Author Contributions

Conceptualization: P.S.

Data curation: T.C.

Formal analysis: C.C.

Funding acquisition: P.S.

Investigation: P.S.

Methodology: P.S.

Project administration: P.S.

Resources: P.S.

Software: C.C.

Supervision: T.C.

Validation: C.C.

Visualization: C.C.

Writing – original draft preparation: C.C.

Writing – review & editing: P.S.

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