

Clinical Characteristics and Factors Associated with Same-encounter Hospital Admission Among Symptomatic Adults Presenting to the Emergency Department After COVID-19

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Abstract

Aim: To evaluate adults with previously documented severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection who presented to the emergency department with new or persistent symptoms at least 4 weeks after acute coronavirus disease 2019 (COVID-19).

Materials and Methods: We examined presenting symptoms; demographic and clinical characteristics, laboratory and imaging findings; and factors concurrently associated with all-cause hospital admission during the index post-acute emergency department encounter. Medical records of 760 patients with documented previous SARS-CoV-2 infection who presented to the emergency department between January 2020 and November 2022 were reviewed. Patients with ongoing polymerase chain reaction positivity (n=54), with complaints clearly unrelated to the post-acute presentation (n=74), with incomplete laboratory data (n=84), or aged <18 years (n=48) were excluded. The final cohort comprised 500 patients who presented at least 4 weeks after the documented acute COVID-19 diagnosis.

Results: Of the 500 patients, 275 (55.0%) were female and 225 (45.0%) were male; the median age was 52 years (range, 18-90). Thirty patients had an all-cause hospital admission during the index post-acute emergency department encounter. Admission was more frequent among patients who had required hospital-based care during acute COVID-19 than among those managed as outpatients (19.3% vs. 2.3%; p<0.001). After Holm adjustment, white blood cell count, neutrophil count, blood urea nitrogen, C-reactive protein, procalcitonin (PCT), N-terminal pro-B-type natriuretic peptide, and D-dimer levels were significantly higher among hospitalized patients. In the post hoc exploratory Firth-penalized multivariable model, older age, higher PCT and D-dimer levels, and acute-period hospitalization were associated with same-encounter admission after adjustment.

Conclusion: Older age, higher concurrent PCT and D-dimer levels, and hospitalization during acute COVID-19 were associated with all-cause admission at the index post-acute emergency department encounter. These exploratory same-encounter associations do not establish prediction, causation, or hospitalization attributable to a post-COVID condition, and they require external validation.

Keywords: COVID-19, hospitalization, fatigue, Long COVID, dyspnea

Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), became a global pandemic with substantial morbidity and mortality (1). Persistent, recurrent, or new symptoms after acute infection remain an important clinical problem and may impair daily functioning (2,3).

The post-acute spectrum is referred to as Long COVID, post-COVID-19 condition, post-acute sequelae of SARS-CoV-2 infection, ongoing symptomatic COVID-19, or post-COVID-19 syndrome. Definitions differ mainly by duration: WHO describes symptoms beginning within 3 months, lasting at least 2 months, and unexplained by another diagnosis (4); CDC describes a chronic condition lasting at least 3 months (2); and NICE uses Long COVID as an umbrella term for symptoms persisting beyond 4 weeks (5).



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Long COVID may follow infection of any severity and fluctuate across organ systems (6). Common complaints include dyspnea, fatigue, and pain (7); proposed mechanisms include immune dysregulation, inflammation, endothelial and microvascular injury, and persistent organ damage (7,8). The diagnosis, treatment, and management of Long COVID are multidisciplinary and symptom-oriented. In addition to routine treatment methods, patient-specific adjunctive therapies are required (8,9).

Long COVID denotes the study's operational threshold of at least 4 weeks after documented infection under the NICE framework (10).

This study examined symptomatic adults who presented to the emergency department at least 4 weeks after documented COVID-19, consistent with the broader NICE framework. We described symptoms, clinical and laboratory findings, and factors that were concurrently associated with all-cause admission during the index post-acute emergency department encounter.

Materials and Methods

This study was approved by the Scientific Research and Publication Ethics Committee of İnönü University, the Republic of Türkiye, under decision number 2022/3020 at the session held on September 20, 2022. The study was a retrospective observational investigation conducted in the emergency department of a tertiary university hospital.

Adults with documented SARS-CoV-2 infection who presented to the emergency department of a tertiary university hospital between January 2020 and November 2022 with new or persistent symptoms at least 4 weeks after diagnosis were eligible. The interval was calculated from diagnosis because recovery dates were inconsistently recorded. Exclusion criteria were ongoing polymerase chain reaction positivity; age <18 years; missing required laboratory measurements, and complaints unrelated to the post-acute presentation (trauma, pregnancy, or forensic cases). Symptom onset and duration were not uniformly recorded; therefore, the cohort was not reclassified using the stricter WHO definition.

Statistical Analysis

SPSS 26.0 was used for descriptive and univariable analyses. Continuous variables were summarized as mean $\pm$ standard deviation or median (interquartile range [IQR]), and categorical variables were summarized as n (%). Two groups were compared using independent-samples t-tests or Mann-Whitney U tests; comparisons involving more than two groups used the Kruskal-

Wallis test when appropriate. Categorical data were analyzed using the chi-square test, the two-sided Fisher exact test, or the Fisher-Freeman-Halton exact test. Laboratory p values were Holm-adjusted; rank-biserial correlations and 95% confidence intervals (CIs) (5,000 stratified bootstrap resamples) were used to quantify effect size.

Adjusted associations with all-cause ward and/or intensive-care admission during the index post-acute emergency department encounter were examined using Firth-penalized logistic regression. For the revised analysis, a fixed, post hoc, exploratory nine-variable model was defined after a review of the available data and prior analyses, without automated stepwise selection: sex, age, acute-period hospitalization, thoracic involvement, malignancy, white blood cell count (WBC), C-reactive protein (CRP), procalcitonin (PCT), and D-dimer. Female sex and acute outpatient care were the reference categories. Odds ratios (ORs) were reported per 10 years of age, $1 \times 10^3/\mu\text{L}$ WBC, 1 mg/dL CRP, 0.1 ng/mL PCT, and 1 mg/L D-dimer. Profile penalized-likelihood 95% CIs and penalized-likelihood-ratio p-values were reported; variance inflation factors were used to assess collinearity.

Firth estimation was implemented using a custom Python function (Python 3.12; SciPy 1.17) that maximized the Jeffreys-prior-penalized log-likelihood, $\ell F = \ell + 0.5 \log |X'WX|$. Adjusted-score Newton–Raphson updates used step-halving when ℓF decreased. Convergence required a maximum absolute adjusted-score component $<1 \times 10^{-6}$ and a change in ℓF of (maximum 1,000 iterations). Penalized likelihood-ratio p-values were obtained using constrained refits in which the tested coefficient was fixed at zero. Each coefficient was fixed by profile limits; nuisance parameters were re-optimized with L-BFGS-B; and $2\Delta\ell F = \chi^2_{0.95}$ was located. Area under the curve (AUC) (scikit-learn 1.8) was estimated using a stratified bootstrap 95% CI (5,000 resamples); calibration was assessed using intercept, slope, and Brier score. The optimism-adjusted AUC was estimated using 1,000 bootstrap resamples (seed 20260908), refitting the fixed model in each sample. CRP values <0.33 mg/dL were set to 0.33 mg/dL for analysis. PCT was standardized to ng/mL; eight misplaced decimal separators were corrected after review of the source data.

All tests were two-sided, with $p < 0.05$. Complete laboratory and model data were available for all 500 included patients; 84 screened patients lacked at least one required measurement. It was not possible to determine whether missingness was related to severity or disposition because outcomes were incomplete for excluded records. Patient selection is shown in Figure 1.

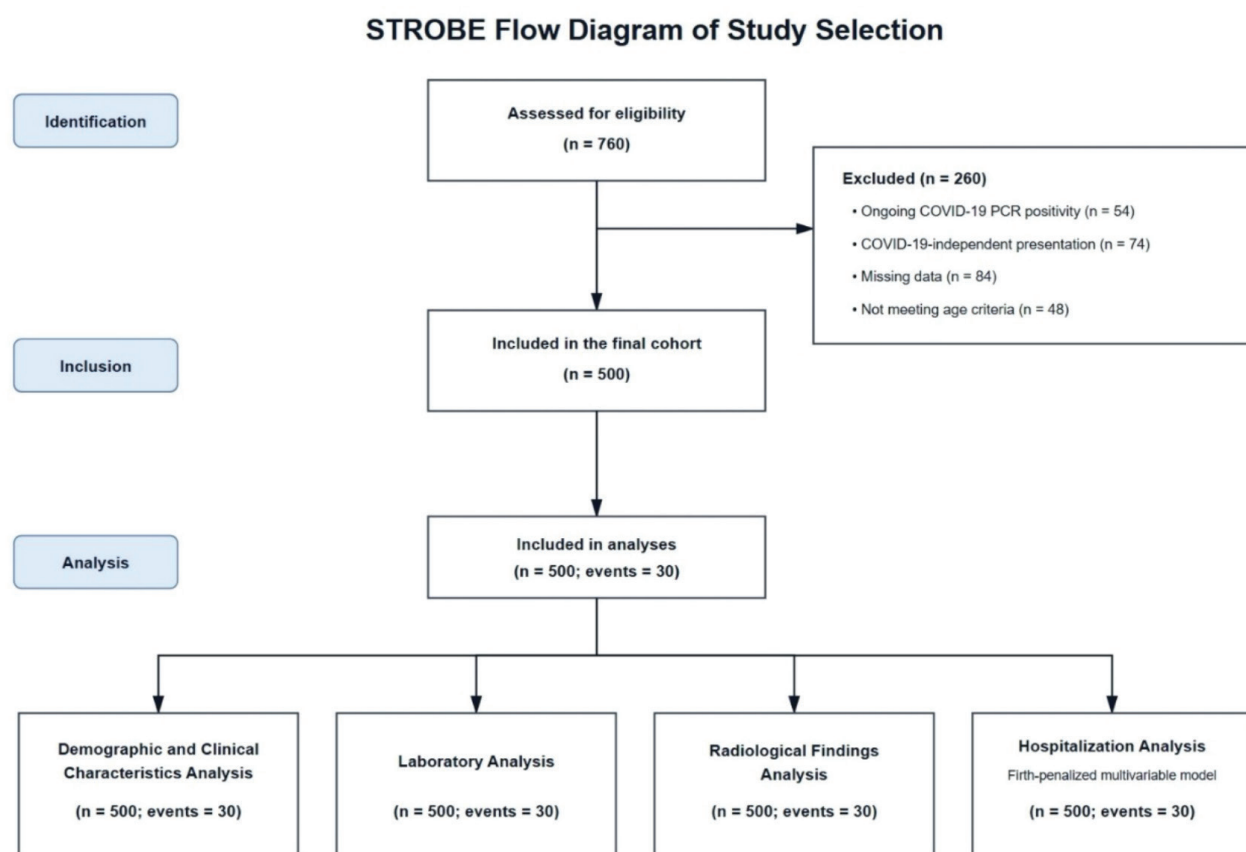


Figure 1. STROBE flow diagram of patient selection and study analysis
COVID-19: Coronavirus disease 2019, PCR: Polymerase chain reaction

Results

Among 500 patients, 275 (55.0%) were women and 225 (45.0%) were men; the median age was 52 years (range, 18-90). The median time from acute diagnosis to presentation was 54 days (IQR, 40-69; range, 30-139). Of these, 445 (89.0%) presented at 4-12 weeks and 55 (11.0%) thereafter. Acute care was outpatient for 391 patients (78.2%), ward-based for 76 (15.2%), and intensive care for 33 (6.6%). At least one comorbidity was present in 71.6% of patients, and thoracic involvement was present in 377 (75.4%) (Table 1).

Common symptoms were dyspnea (73.8%), weakness or fatigue (68.0%), exertional dyspnea (53.4%), loss of appetite (47.0%), cough (33.4%), chest pain (32.2%), myalgia (23.8%), sputum (20.4%), and brain fog (8.0%). Symptoms were not mutually exclusive.

Thirty patients were admitted at the index encounter: 19 to wards and 11 to intensive care. Recorded diagnoses that were not mutually exclusive included pulmonary embolism and pneumonia (n=11 each), residual fibrotic changes (n=6), heart failure and gastrointestinal bleeding (n=2 each), and myocardial infarction, total atelectasis, elevated liver enzymes,

Table 1. Descriptive statistics of patients' sociodemographic characteristics, comorbidities, and acute COVID-19 care

	Number (n)	Percent (%)
Sex		
Female	275	55.0
Male	225	45.0
Acute COVID-19 care		
Outpatient	391	78.2
Inpatient ward	76	15.2
Intensive care unit	33	6.6
Thoracic involvement		
Present	377	75.4
Absent	123	24.6
Comorbidities		
CAD	95	19.0
HT	152	30.4
DM	68	13.6
Malignancy	34	6.8
Asthma/COPD	78	15.6

CAD: Coronary artery disease, HT: Hypertension, DM: Diabetes mellitus, COPD: Chronic obstructive pulmonary disease, COVID-19: Coronavirus disease 2019

adrenal insufficiency, alveolar hemorrhage, and diabetes-related decompensation (n=1 each). Diagnoses and routine-care admission decisions were not independently adjudicated.

Acute and post-acute care levels were associated (Fisher-Freeman-Halton $p<0.001$). Specifically, 5/11 post-acute intensive-care admissions required acute intensive care, and 12/19 post-acute ward admissions received acute ward care (Table 2).

After Holm correction, admitted patients had higher WBC (9.87 vs $7.60 \times 10^3/\mu\text{L}$; adjusted $p=0.012$), neutrophils (5.97 vs 4.38

$\times 10^3/\mu\text{L}$; $p=0.019$), blood urea nitrogen (18.45 vs 14.49 mg/dL; $p=0.009$), CRP (2.96 vs <0.33 mg/dL), PCT (0.099 vs 0.034 ng/mL), N-terminal pro-B-type natriuretic peptide (260.5 vs 52 pg/mL), and D-dimer (1.05 vs 0.33 mg/L FEU; the latter four $p<0.001$) (Table 3). Glucose and alanine aminotransferase were no longer significant after correction; other laboratory measures did not differ.

The fixed post hoc nine-variable Firth model included all 500 patients and 30 events (Table 4). Admission was associated with age (adjusted OR per 10 years= 1.45 ; 95% profile penalized-

Table 2. Comparison of acute COVID-19 care and disposition at the index post-acute emergency department encounter

		Index post-acute ED disposition				
Acute COVID-19 care		Outpatient	Ward	ICU	Total	P
	Outpatient	382 (97.7%)	5 (1.3%)	4 (1.0%)	391	
	Ward	62 (81.6%)	12 (15.8%)	2 (2.6%)	76	<0.001
	ICU	26 (78.8%)	2 (6.1%)	5 (15.2%)	33	
Total		470 (94.0%)	19 (3.8%)	11 (2.2%)	500	

Data are presented as n (row percentage). The p value was calculated using the Fisher-Freeman-Halton exact test. Percentages reported in the text for index admissions to post-acute wards and to intensive care were calculated using the corresponding disposition category as the denominator. ICU: Intensive care unit, ED: Emergency department, COVID-19: Coronavirus disease 2019

Table 3. Comparison of laboratory parameters by disposition at the index post-acute emergency department encounter

Parameter	Reference range	Outpatient, median (IQR)	Hospitalized, median (IQR)	Effect size, r_{rb} (95% CI)	p	Holm-adjusted p
WBC ($\times 10^3/\mu\text{L}$)	4.0-10.0	7.60 (6.20-9.36)	9.87 (7.32-11.81)	0.353 (0.132-0.556)	0.001	0.012
Hemoglobin (g/dL)	Male: 13.5-17.5; female: 12.0-16.0	13.9 (12.4-15.2)	13.2 (10.7-14.9)	-0.176 (-0.408-0.065)	0.107	0.639
Hematocrit (%)	Male: 40-52; female: 36-47	42.7 (38.9-46.2)	40.5 (34.0-45.9)	-0.172 (-0.409-0.075)	0.114	0.639
Platelet ($\times 10^3/\mu\text{L}$)	150-400	266 (222-310)	292 (223-351)	0.144 (-0.103-0.391)	0.187	0.639
Lymphocyte ($\times 10^3/\mu\text{L}$)	1.0-4.0	2.23 (1.73-2.79)	2.08 (1.37-2.67)	-0.157 (-0.381-0.073)	0.149	0.639
Neutrophil ($\times 10^3/\mu\text{L}$)	1.5-7.5	4.38 (3.34-5.88)	5.97 (3.73-8.37)	0.335 (0.104-0.537)	0.002	0.019
Glucose (mg/dL)	70-99 (fasting)	99 (90-115)	111 (98-142)	0.246 (0.039-0.447)	0.024	0.165
AST (U/L)	10-40	21.0 (17.0-25.0)	24.5 (17.0-33.0)	0.159 (-0.096-0.412)	0.144	0.639
ALT (U/L)	7-56	19.0 (14.0-28.0)	25.5 (18.8-37.8)	0.262 (0.050-0.464)	0.016	0.128
BUN (mg/dL)	7-20	14.49 (11.21-18.22)	18.45 (14.14-25.58)	0.366 (0.165-0.549)	<0.001	0.009
Creatinine (mg/dL)	Male: 0.74-1.35; female: 0.59-1.04	0.81 (0.70-1.00)	0.95 (0.72-1.12)	0.166 (-0.085-0.407)	0.123	0.639
CRP (mg/dL)	0-0.33	<0.33 (<0.33-0.69)	2.96 (1.39-5.69)	0.644 (0.463-0.796)	<0.001	<0.001
PCT (ng/mL)	<0.05	0.034 (0.023-0.061)	0.099 (0.049-0.307)	0.557 (0.356-0.730)	<0.001	<0.001
NT-proBNP (pg/mL)	<125 (<75 y); <450 (≥ 75 y)	52 (<20-173)	260.5 (137.0-1072.5)	0.499 (0.302-0.681)	<0.001	<0.001
D-dimer (mg/L FEU)	≤ 0.50	0.33 (0.21-0.54)	1.05 (0.48-7.04)	0.591 (0.409-0.755)	<0.001	<0.001

Continuous variables are presented as median (interquartile range) and compared using two-sided Mann-Whitney U tests. All parameters were available for 470 outpatients and 30 hospitalized patients (total n=500). Effect sizes are unadjusted rank-biserial correlations (r_{rb}); positive values indicate higher measurements among hospitalized patients. The 95% CIs were estimated using 5,000 stratified bootstrap resamples. Holm-adjusted p-values account for multiple testing across laboratory parameters, with statistical significance defined as adjusted $p<0.05$. C-reactive protein values reported below the analytical limit (<0.33 mg/dL) were summarized using the reported-limit notation and were assigned a value of 0.33 mg/dL for statistical analysis. Hospitalization includes ward and intensive care admissions during the index encounter.

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, BUN: Blood urea nitrogen, CI: Confidence interval, CRP: C-reactive protein, FEU: Fibrinogen-equivalent units, IQR: Interquartile range, NT-proBNP: N-terminal pro-B-type natriuretic peptide, PCT: Procalcitonin, WBC: White blood cell count

likelihood CI, 1.07-2.01; $p=0.017$), PCT (per 0.1 ng/mL=1.12; 1.02-1.24; $p=0.013$), D-dimer (per 1 mg/L=1.26; 1.10-1.49; $p<0.001$), and acute-period hospitalization (OR=3.45; 1.31-9.39; $p=0.012$). Concurrent biomarkers should not be interpreted as prospective predictors.

Sex, thoracic involvement, malignancy, and CRP were not significant after adjustment. WBC was borderline (adjusted OR per $1 \times 10^3/\mu\text{L}=1.117$; 95% profile penalized-likelihood CI= 0.9999-1.2386; $p=0.0502$). Apparent AUC was 0.914 (bootstrap 95% CI, 0.870–0.951); optimism-adjusted AUC was 0.885. Calibration

intercept, slope, and Brier score were -0.098 , 1.078 , and 0.039 , respectively; VIFs ranged from 1.06 to 1.42.

Unadjusted analyses associated admission with male sex (OR=3.04; 95% CI, 1.36-6.78; $p=0.007$) and the presence of malignancy (OR=3.04; 1.08-8.53; $p=0.044$), but not with coronary artery disease, asthma/chronic obstructive pulmonary disease, diabetes, or hypertension (Table 5).

After excluding isolated myocardial infarction and gastrointestinal bleeding, 498 patients and 28 events remained. Estimates

Table 4. Post hoc exploratory firth-penalized multivariable analysis of all-cause admission at the index post-acute emergency department encounter

Variable	β	Adjusted OR	95% CI	p
Age, per 10-year increase	0.37	1.45	1.07-2.01	0.017
Thoracic involvement	-0.05	0.96	0.31-3.35	0.939
Malignancy	0.39	1.48	0.36-4.95	0.558
WBC, per $1 \times 10^3/\mu\text{L}$ increase	0.110	1.117	0.9999-1.2386	0.0502
CRP, per 1 mg/dL increase	0.04	1.04	0.94-1.18	0.414
PCT, per 0.1 ng/mL increase	0.11	1.12	1.02-1.24	0.013
D-dimer, per 1 mg/L increase	0.23	1.26	1.10-1.49	<0.001
Acute-period hospitalization (yes vs outpatient)	1.24	3.45	1.31-9.39	0.012
Male sex (vs female)	0.73	2.08	0.83-5.57	0.117

OR: Odds ratio, CI: Confidence interval, WBC: White blood cell count, CRP: C-reactive protein, PCT: Procalcitonin. Hospitalization was defined as all-cause admission to a ward and/or an intensive care unit during the index post-acute emergency department encounter. The fixed post hoc exploratory model included nine variables, 30 events, and all 500 patients. Female sex and outpatient acute care were the reference categories. ORs are reported per 10-year increase in age, per $1 \times 10^3/\mu\text{L}$ increase in WBC, per 1 mg/dL increase in CRP, per 0.1 ng/mL increase in PCT, and per 1 mg/L increase in D-dimer. Profile penalized-likelihood 95% CIs and penalized likelihood-ratio p values were obtained from constrained refits, and therefore used the same inferential framework. The apparent AUC was 0.914 (bootstrap 95% CI, 0.870-0.951); the optimism-adjusted AUC after 1,000 bootstrap resamples was 0.885. The calibration intercept was -0.098 , the slope was 1.078 , and the Brier score was 0.039 . Statistical significance was defined as $p<0.05$.

Table 5. Unadjusted association of sex and comorbidities with all-cause admission at the index post-acute emergency department encounter

Variable	Status	Outpatient (n)	Hospitalized (n)	Total (n)	Crude OR (95% CI)	p
Sex	Female	266	9	275	Reference	0.007
	Male	204	21	225	3.04 (1.36-6.78)	
CAD	Absent	385	20	405	Reference	0.052
	Present	85	10	95	2.26 (1.02-5.01)	
Asthma/COPD	Absent	396	26	422	Reference	1.000
	Present	74	4	78	0.82 (0.28-2.41)	
Malignancy	Absent	441	25	466	Reference	0.044
	Present	29	5	34	3.04 (1.08-8.53)	
DM	Absent	406	26	432	Reference	1.000
	Present	64	4	68	0.98 (0.33-2.89)	
HT	Absent	330	18	348	Reference	0.305
	Present	140	12	152	1.57 (0.74-3.34)	

Data are presented as numbers. Crude ORs and Wald-type 95% CIs indicate unadjusted odds of hospitalization; the OR for sex compares male patients with female patients. Female sex and the absence of the relevant comorbidity were the reference categories. P values were calculated using two-sided Fisher's exact tests. CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease, DM: Diabetes mellitus, HT: Hypertension. Crude odds ratios and Wald-type 95% confidence intervals are reported as measures of association. Because of sparse cell counts, two-sided Fisher's exact tests were used to calculate p values. Consequently, confidence intervals and p-values may not correspond exactly because they were obtained using different inferential methods.

were similar: adjusted ORs were 1.38 per 10 years (95% profile CI, 1.0001-1.95; $p=0.0499$), 1.11 per 0.1 ng/mL PCT (1.02-1.23; $p=0.015$), 1.27 per 1 mg/L D-dimer (1.10-1.50; $p<0.001$), and 3.85 for acute hospitalization (1.41-11.00; $p=0.009$). The apparent AUC was 0.918 (bootstrap 95% CI, 0.873-0.955).

Discussion

Long COVID is thought to be associated with female sex, advanced age, obesity, diabetes, cardiovascular diseases, and other comorbidities. In our study population, however, male sex and the presence of malignancy were associated with hospitalization only in unadjusted analyses and were not significant after adjustment, highlighting the need for cautious interpretation (11,12).

Literature reviews include studies showing that hospitalization during the acute phase is associated with hospitalization during the long COVID period (13,14). Consistent with reports of a greater post-acute burden following severe acute illness, acute-phase hospitalization remained associated with hospitalization during the initial post-acute emergency department encounter (adjusted OR=3.45). This may reflect persistent frailty or healthcare needs; however, the observational design and the all-cause nature of the outcome preclude attributing the findings to causal relationships or specific post-COVID conditions.

Inflammation and endothelial dysfunction are factors potentially contributing to post-acute thromboembolic and multisystem symptoms; higher levels of inflammatory, cardiac stress, and coagulation markers have been observed in patients hospitalized following post-acute presentations (15,16). In the exploratory model, advanced age, concurrent PCT and D-dimer levels, and acute-phase hospitalization showed a significant association with hospitalization during the prolonged period, while WBC count was of borderline significance. Laboratory parameters may reflect acute conditions or influence clinical decisions. Therefore, these biomarkers should be interpreted not as predictors of future deterioration, diagnostic biomarkers, or causal determinants of Long COVID severity, but rather as indicators associated concurrently with hospitalization.

Study Limitations

The retrospective, single-center design relied on routine records and included only symptomatic emergency patients, limiting generalizability and permitting selection, referral, measurement, and classification bias. Symptom onset, duration, and recovery dates were inconsistently documented; therefore, the cohort follows a broad NICE-based threshold. Excluding 84 records with incomplete laboratory data may have favored patients who were

more extensively tested. Vaccination, variant, smoking, body mass index, acute treatments and respiratory support, length of stay, readmission, mortality, and socioeconomic status were unavailable or incomplete, thereby leaving residual confounding.

Only 30 events supported nine model variables. Firth penalization and bootstrap validation reduce but do not eliminate overfitting. Some CIs were wide, and external validation was unavailable. The model was specified post hoc during revision after review of the available data and prior analyses, although no automated stepwise selection was used. Refitting the fixed, selected model in each bootstrap sample estimates optimism conditional on that model, but does not fully account for optimism introduced by analyst-guided model specification. The all-cause outcome was based on routine clinician decisions without standardized criteria or independent adjudication of diagnoses. Alternative acute diagnoses and uncertainty regarding causation remain. Reports of pulmonary fibrosis reflected residual or preliminary imaging interpretations rather than standardized longitudinal diagnoses. Findings are exploratory, not prognostic.

Conclusion

Among symptomatic adults presenting at least 4 weeks after COVID-19, older age, concurrent PCT and D-dimer levels, and hospitalization during acute infection were associated after adjustment with all-cause admission at the index post-acute emergency department encounter. These exploratory same-encounter associations are neither causal nor specific to a post-COVID condition. Prospective multicenter studies with standardized definitions, adjudicated diagnoses, and longitudinal outcomes are needed.

Ethics

Ethics Committee Approval: This study was approved by the Scientific Research and Publication Ethics Committee of İnönü University, the Republic of Türkiye, under decision number 2022/3020 at the session held on September 20, 2022.

Informed Consent: The study was a retrospective observational investigation conducted in the emergency department of a tertiary university hospital.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Y.Ö., Concept: M.E.S., T.K., Design: M.E.S., Data Collection or Processing: Y.Ö., Analysis or Interpretation: M.E.S., T.K., Literature Search: Y.Ö., Writing: Y.Ö.

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