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Original Article

Characteristics and Secondary Infections among Elderly Patients with COVID-19

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SUMMARY

Background: Secondary infection with other pathogens is associated with poor prognosis in patients with viral infections. However, the characteristics of elderly patients and secondary infections are not well known; therefore, we conducted this study.
Methods: We retrospectively reviewed confirmed cases of COVID-19 admitted between February 1 and December 31, 2020. Univariate and multivariate logistic regression analyses were performed to identify the predictors of in-hospital mortality.
Results: A total of 298 patients with confirmed COVID-19 were identified during the study period. Among these, 171 patients (57.4%) were non-elderly (50–64 years) and 127 patients (42.6%) were elderly (over 65 years of age). Patients in the elderly group had a higher frailty scale, and the most common underlying diseases were hypertension, diabetes, heart failure, chronic kidney disease and cerebral vascular accident. The mortality rate was also higher in the elderly group (12.6% vs. 1.2%, $p < 0.001$). Secondary infection was confirmed in 12.8% of patients (38/298). *Streptococcus pneumonia* (22/38, 57.9%) was the most common pathogen in the COVID-19 patients. Secondary infection and elderly were associated with in-hospital mortality.
Conclusions: In this study, 42.6% of patients were elderly COVID-19 patients and 12.8% of patients had secondary infections. Elderly patients and secondary infections were associated with in-hospital mortality.

1. Introduction

Old age is associated with COVID-19 severity and mortality.[1–5] Elderly patients usually have chronic diseases and are more likely to progress to severe illness or death. Elderly patients sometimes have atypical symptoms without fever or cough and several organ dysfunctions. The elderly patient group also experiences various complications compared to those in younger patient groups during hospitalization.[6,7]

Several studies have assessed the bacterial and fungal infections in patients hospitalized for COVID-19, including those in the Republic of Korea. Clinically, distinguishing between isolated COVID-19 infection and possible infection with other pathogens is challenging. Concomitant bacterial infection were reported in 15% of hospitalized COVID-19 patients in Wuhan, China, with a higher incidence in non-survivor groups.[3] However, the incidence of bacterial infections associated with COVID-19 patients is lower than that observed in previous influenza pandemics.[8] The most frequently detected bacterial pathogens were *Mycoplasma pneumoniae*, *Pseudomonas aeruginosa*, *Streptococcus pneumoniae*, and *Haemophilus influenzae*.[8–11]

We previously reported on secondary infections of patients with COVID-19 admitted to the hospital, in which the mortality and severity were high in patients with secondary infections.[12] In this study, we investigated the association of secondary infection with disease severity in hospitalized elderly patients with COVID-19 and identified the most common pathogens to inform the selection of antibiotics for treatment.

2. Patients and methods

All study data were retrieved from electronic medical records (C&U Care, Daejeon, Republic of Korea). We identified elderly patients in this study, including those enrolled in a previous correspondence.[12] Between February 1 and December 31, 2020, a total of 331 patients with confirmed COVID-19 were hospitalized, including those described in a previous correspondence. Of these, 298 patients were enrolled in this study, excluding 23 patients aged < 50 years and 10 patients with incomplete data. Data on the patients' underlying diseases, vital signs at hospitalization, laboratory values, radiologic findings, and bacterial strain identification were collected. This study was approved by the Institutional Review Board of Chunam National University Hospital (2020-07-042), which waived the requirement for informed consent due to the retrospective nature of the study.

2.1. Definitions

Approval of requests was reserved for hospitalized patients with SARS-CoV-2 infection confirmed by reverse-transcriptase polymerase chain reaction (RT-PCR) assay; severe COVID-19 was defined as an oxygen saturation level of 94% or less while breathing ambient air or

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a need for oxygen support.[13] Secondary infection was defined as the presence of clinical signs and/or symptoms of infection and the detection of a pathogen in diagnostic tests,[8,10,14] including respiratory bacterial PCR (endotracheal aspirates and expectorated sputum), nasopharyngeal PCR, and blood cultures emerging during illness or hospital stay. Very elderly patients were defined as those over 80 years of age. For each patient, clinical weakness was assessed using the Clinical Frailty Scale (CFS), which classifies older people into nine categories, ranging from category 1 (very fit) to category 9 (terminal disease, life expectancy < 6 months). The CFS was used to indicate the patient's previous functional independence before hospitalization for SARS-CoV2 infection. In-hospital mortality was defined as death occurring during the hospital stay.

2.2. Statistical analysis

All values are expressed as median (interquartile range) for continuous variables and as percentages for categorical variables. Student's t- or Mann-Whitney U tests were used for continuous data, while Pearson's chi-squared or Fisher's exact tests were used for categorical data. Univariate logistic regression analysis was performed to identify the predictors of disease severity. Multivariate logistic regression analyses with backward elimination, including all predictors with $p < 0.05$ in the univariate analysis were performed to obtain the adjusted odds ratios (OR) and 95% confidence intervals (CI) and to define the variables that were independently associated with in-hospital mortality. All p values were two-tailed, and $p < 0.05$ was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Patient characteristics

A total of 298 patients with confirmed COVID-19 were identified during the study period. Of these, 171 (57.4%) and 127 (42.6%) patients were non-elderly (50–64 years) and elderly (over 65 years), respectively.

The baseline characteristics of the patients are presented in Table 1. Elderly patients were older than non-elderly patients (72 [67–78 years] vs. 58 [54–61 years], $p < 0.001$). The CFS was higher in the elderly group (3.0 [2.0–3.0] vs. 1.0 [1.0–2.0], $p < 0.001$). No statistically significant differences were observed between these groups in sex, body mass index (BMI), and symptoms before hospitalization. Hypertension (49.6% vs. 36.8%, $p = 0.027$), diabetes (32.3% vs. 19.3%, $p = 0.010$), heart failure (8.7% vs. 1.8%, $p = 0.005$), chronic kidney disease (CKD) (6.3% vs. 1.8%, $p = 0.040$) and cerebrovascular accident (CVA) (8.7% vs. 2.3%, $p = 0.014$) were more common in the elderly group. There were no statistically significant differences in other underlying diseases. Illness onset to hospital admission was shorter in the elderly group [2.0 (1.0–5.0) days vs. 3.0 (1.0–6.0) days, $p = 0.006$].

Baseline laboratory and radiologic findings are shown in Table 2. Platelet (182 [152–221] vs. 201 [164–249], $\times 10^3$/uL, $p = 0.013$) was lower in the elderly group. Neutrophil lymphocyte ratio (NLR) (3.02 [1.82–5.04] vs. 2.39 [1.73– 3.64], $p = 0.034$), troponin-I (6.40 [4.50–11.25] vs. 3.70 [2.53–5.88], pg/mL, $p = 0.022$), N-terminal pro-brain natriuretic peptide (NT-proBNP) (130 [57–299] vs. 47 [25–86], pg/mL, $p < 0.001$) and D-dimer (216 [131–375] vs. 145 [94–223], ng/mL, $p = 0.003$) were higher in the elderly group. There were no statistically significant differences between the other laboratory and radiologic findings.

3.2. Treatment and prognosis of patients

Shock was more occurred and norepinephrine, vasopressin and dobutamine were more used in the elderly group. Severe infection was more common and nasal prong was more used in the elderly group. Mortality was higher in the elderly group (12.6% vs. 1.2%, $p < 0.001$). Steroids (37.0% vs. 24.0%, $p = 0.015$) were used more in the elderly group. There were no statistically significant dif-

Table 1
Demographics and baseline characteristics of study population.

Characteristic	Total patients (n = 298)	Non-elderly (n = 171)	Elderly (n = 127)	p-value
Age, years	63 (57–70)	58 (54–61)	72 (67–78)	< 0.001
Frailty scale	2.0 (1.0–3.0)	1.0 (1.0–2.0)	3.0 (2.0–3.0)	< 0.001
Sex				
Male	129 (43.3)	79 (46.2)	50 (39.4)	0.239
Female	169 (56.7)	92 (53.8)	77 (60.6)	0.239
BMI, kg/m²	24.7 (22.6–27.0)	24.7 (22.7–26.7)	24.4 (22.3–27.3)	0.350
Symptom before hospitalization				
No symptom	44 (14.8)	22 (12.9)	22 (17.3)	0.283
Fever	119 (39.9)	68 (39.8)	51 (40.2)	0.946
Cough	74 (24.8)	41 (24.0)	33 (26.0)	0.692
Myalgia	92 (30.9)	60 (35.1)	32 (25.2)	0.068
Sorethroat	49 (16.4)	27 (15.8)	22 (17.3)	0.724
Dyspnea	12 (4.0)	4 (2.3)	8 (6.3)	0.086
Headache	34 (11.4)	24 (14.0)	10 (7.9)	0.098
Diarrhea	5 (1.7)	3 (1.8)	2 (1.6)	0.905
Underlying diseases				
Hypertension	126 (42.3)	63 (36.8)	63 (49.6)	0.027
COPD	13 (4.4)0	7 (4.1)	6 (4.7)	0.792
Diabetes	74 (24.8)	33 (19.3)	41 (32.3)	0.010
Solid cancer	26 (8.7)	13 (7.6)	13 (10.2)	0.426
Hematologic malignancy	1 (0.3)	1 (0.6)	0 (0)	> 0.999
Heart failure	14 (4.7)	3 (1.8)	11 (8.7)	0.005
CKD	11 (3.7)	3 (1.8)	8 (6.3)	0.040
CVA	15 (5.0)	4 (2.3)	11 (8.7)	0.014
Liver cirrhosis	1 (0.3)	0 (0)	1 (0.8)	0.426
Illness onset to hospital admission, days	2.0 (1.0–5.0)	3.0 (1.0–6.0)	2.0 (1.0–5.0)	0.006

Data are presented as median (interquartile range) or number (%), unless otherwise indicated.
BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstruction pulmonary disease; CVA, cerebrovascular accident.

Table 2
Baseline laboratory and radiologic findings of study population.

Characteristic	Total patients (n = 298)	Non-elderly (n = 171)	Elderly (n = 127)	p-value
Laboratory findings				
WBC, /uL	4915 (3715–6160)	5000 (3500–6100)	4890 (3800–6290)	0.581
NLR	2.56 (1.75–4.33)	2.39 (1.73–3.64)	3.02 (1.82–5.04)	0.034
Platelet, $\times 10^3$/uL	193 (155–243)	201 (164–249)	182 (152–221)	0.013
PLR	164 (129–229)	164 (131–222)	165 (127–240)	0.553
Total bilirubin, mg/dL	0.47 (0.35–0.61)	0.46 (0.36–0.61)	0.48 (0.34–0.61)	0.403
Albumin, g/dL	3.9 (3.5–4.2)	4.0 (3.6–4.2)	3.7 (3.4–4.0)	0.685
AST, U/L	28 (21–40)	27 (20–39)	29 (22–43)	0.682
ALT, U/L	24 (17–37)	26 (18–38)	21 (15–32)	0.197
Creatinine, mg/dL	0.67 (0.52–0.83)	0.65 (0.50–0.82)	0.69 (0.54–0.85)	0.106
Troponin-I, pg/mL	4.80 (3.05–8.05)	3.70 (2.53–5.88)	6.40 (4.50–11.25)	0.022
NT-proBNP, pg/mL	65 (34–160)	47 (25–86)	130 (57–299)	< 0.001
D-dimer, ng/mL	160 (106–273)	145 (94–223)	216 (131–375)	0.003
CRP, mg/dL	1.0 (0.4–4.0)	0.8 (0.3–3.1)	1.3 (0.5–6.3)	0.098
Procalcitonin, ng/mL	0.05 (0.05–0.05)	0.05 (0.05–0.05)	0.05 (0.05–0.05)	0.193
Interleukin-6, pg/mL	11.6 (3.9–33.3)	7.9 (3.0–24.0)	16.0 (5.4–40.0)	0.267
Lactic acid, mmol/L	2.1 (1.7–2.6)	2.1 (1.7–2.6)	2.1 (1.8–2.6)	0.651
Radiologic findings				
GGO or GGA	203 (68.1)	109 (63.7)	94 (74.0)	0.060
Consolidation	69 (23.2)	40 (23.4)	29 (22.8)	0.910
Fibrosis	2 (0.7)	1 (0.6)	1 (0.8)	0.832

Data are presented as median (interquartile range) or number (%), unless otherwise indicated.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; GGA, ground-glass attenuation; GGO, ground-glass opacity; NLR, neutrophil lymphocyte ratio; NT-proBNP, N-terminal pro-brain natriuretic peptide; PLR, platelet lymphocyte ratio; WBC, white blood cell.

ferences in other prognoses, O_2 supply, and treatment methods (Table 3).

3.3. Secondary infection with other pathogens in patients with COVID-19

Blood cultures and pneumonia PCR were performed in 89.3% (266⁄298) and 12.1% (36⁄298) of patients, respectively. Of the 298 COVID-19 patients, 38 patients (12.8%) had secondary bacterial (35 patients, 11.7%) and bacterial-fungal infections (3 patients, 1.0%). As shown in Figure 1, nine bacteria and one fungus were detected. The secondary infection pathogens were as follows: *Streptococcus pneumonia* (22⁄38, 57.9%), *Haemophilus influenzae* (14⁄38, 36.8%), *Klebsiella pneumonia* (3⁄38, 7.9%), *Pseudomonas aeruginosa* (2⁄38, 5.3%), *Acinetobacter baumannii* (4⁄38, 10.5%), *Staphylococcus species* (5⁄38, 13.2%), *Corynebacterium* (1⁄38, 2.6%), *Mycoplasma Pneumoniae* (1⁄38, 2.6%), *Enterococcus* (1⁄38, 2.6%), *Candida species* (3⁄38, 7.9%).

After hospitalization, the examination was carried out over 11.8 ± 12.9 days on average. Patients exhibited fever (22⁄38, 57.9%) and aggravation of abnormalities on chest radiography (22⁄38, 57.9%). Laboratory data showed elevated white blood cell counts (WBC, 19⁄38, 50.0%), elevated C-reactive protein (CRP) levels (17⁄38, 44.7%), and elevated procalcitonin levels (2⁄38, 5.3%).

Table 3
Treatment and prognosis of study group.

	Total patients (n = 298)	Non-elderly (n = 171)	Elderly (n = 127)	p-value
Prognosis				
Shock	18 (6.0)	5 (2.9)	13 (10.2)	0.009
Norepinephrine	15 (5.0)	4 (2.3)	11 (8.7)	0.014
Vasopressin	4 (1.3)	0 (0)	4 (3.1)	0.032
Dobutamine	4 (1.3)	0 (0)	4 (3.1)	0.032
O2 supply				
Nasal prong	90 (30.2)	40 (23.4)	50 (39.4)	0.003
Ventilator	37 (12.4)	18 (10.5)	19 (15.0)	0.251
ECMO	10 (3.4)	4 (2.3)	6 (4.7)	0.258
Severe infection*	90 (30.2)	40 (23.4)	50 (39.4)	0.003
Secondary infection	39 (13.1)	22 (12.9)	17 (13.4)	0.895
Mortality	18 (6.0)	2 (1.2)	16 (12.6)	< 0.001
Hospital stay, days	13 (10–17)	12 (9–16)	14 (11–18)	0.148
Treatment				
Steroid	88 (29.5)	41 (24.0)	47 (37.0)	0.015
Antibiotics	110 (36.9)	56 (32.7)	54 (42.5)	0.084
Remdesivir	29 (9.7)	13 (7.6)	16 (12.6)	0.150

Data are presented as median (interquartile range) or number (%), unless otherwise indicated.
* Severe infection: An oxygen saturation level of 94% or less while the patient was breathing ambient air or a need for oxygen support.
ECMO, extracorporeal membrane oxygenation.

3.4. Factors associated with in-hospital mortality of COVID-19

The results of a multivariate analysis of the factors associated with in-hospital mortality of COVID-19 are shown in Table 4. After adjusting for confounders, the independent predictors of in-hospital mortality included age (≥ 65 years) (OR, 20.835; 95% CI 2.139–202.946; p = 0.009), CKD (OR 14.796; 95% CI 1.154–189.657; p =

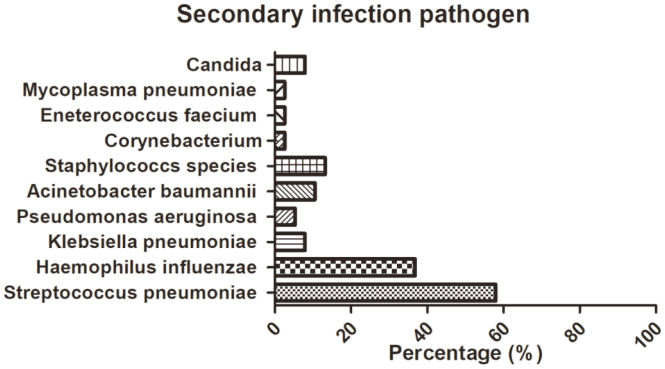

Figure 1. Secondary infection rate by pathogen type in patients with COVID-19.

Table 4
Univariate and multivariate logistic regression analysis addressing the risk factors for in-hospital mortality.

	Univariate analysis			Multivariate analysis		
	OR	95% CI	p-value	OR	95% CI	p-value
Age ≥ 65 years	12.180	2.747–54.009	0.001	20.835	2.139–202.946	0.009
Frailty scale [a]	2.072	1.491–2.880	< 0.001			
BMI	1.044	0.949–1.149	0.376			
Male	0.638	0.233–1.749	0.383			
Underlying disease						
Hypertension	3.842	1.333–11.076	0.013	4.235	0.820–21.883	0.085
Diabetes	3.308	1.261–8.679	0.015	0.719	0.140–3.702	0.694
Heart failure	4.891	1.232–19.411	0.024	6.637	0.572–76.992	0.130
CKD	11.143	2.916–42.587	< 0.001	14.796	1.154–189.657	0.038
CVA	1.118	0.139–9.011	0.917			
Initial lab						
White blood cell, /uL	1.000	1.000–1.001	< 0.001	1.000	1.000–1.000	0.917
Platelet, $\times 10^3$/uL	0.997	0.989–1.005	0.442			
Albumin, g/dL	0.111	0.045–0.276	< 0.001	0.866	0.139–5.390	0.877
Creatinine, mg/dL	1.256	0.571–2.760	0.571			
NT-proBNP, pg/mL	1.002	1.001–1.002	< 0.001	1.001	1.000–1.002	0.011
CRP, mg/dL	1.138	1.067–1.213	< 0.001	1.060	0.945–1.189	0.319
Procalcitonin, ng/mL	1.059	0.926–1.210	0.404			
IL-6, pg/mL	1.001	0.999–1.003	0.543			
Lactic acid, mmol/L	1.239	0.627–2.446	0.538			
Chest imaging						
GGO or GGA	3.979	0.896–17.669	0.069			
Consolidation	6.015	2.233–16.199	< 0.001	16.514	2.850–95.703	0.002
Secondary infection	6.667	2.443–18.192	< 0.001	51.636	6.845–389.517	< 0.001

[a] Frailty scale was not included in the multivariate analysis due to co-linearity with age ≥ 65 years (r = 0.732, p < 0.001).
BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; CRP, C-reactive protein; CVA, cerebrovascular accident; GGA, ground-glass attenuation; GGO, ground-glass opacity; IL-6, interleukin-6; NT-proBNP, N-terminal pro-brain natriuretic peptide; OR, odds ratio.

0.038), NT-proBNP (OR 1.001; 95% CI 1.000–1.002; p = 0.011), consolidation on chest imaging (OR 16.514; 95% CI 2.850–95.703; p = 0.002), and secondary infection (OR 51.636; 95% CI 6.845–389.517; p < 0.001).

4. Discussion

In this study, 42.6% of COVID-19 patients were elderly (over 65 years). The underlying disease was more common in the elderly group than in the non-elderly group. Mortality was higher in the elderly group. Secondary infection occurred in 12.8% of COVID-19 patients, and secondary infection and elderly were associated with in-hospital mortality.

While several studies have reported older age as a risk factor for severe infection and mortality in patients with COVID-19,[1–5] studies in the elderly group have been limited. Elderly patients account for a significant percentage of COVID-19 patients. In this study, approximately 42.6% of patients with COVID 19 were elderly. In other studies, the proportion of elderly patients varied from 11.25% to 37%.[7,15,16]

In this study, hypertension, diabetes, heart failure, CKD and CVA were more common comorbid diseases in elderly patients. This is similar to the results of other studies. In the elderly group, there were many patients with at least one underlying disease. The accompanying diseases were as follows; hypertension, diabetes, hypertension, cardiovascular disease, etc.[6,15,17–19] The accompanying symptoms in this study did not show any significant difference in elderly patients. However, another study reported fever, cough, shortness of breath, and fatigue to be the most common symptoms in elderly patients.[7,15,18]

In this study, age ≥ 65 years, CKD, NT-proBNP, consolidation on chest imaging, and secondary infection were associated with in-hospital mortality of COVID-19. Gilis et al. showed that CFS, age, and dyspnea were associated with all-cause 30-day mortality.[20] Li et al. showed that dyspnea, age, neutrophilia, elevated ultra-troponin I, and elevated d-dimer levels were risk factors for mortality in elderly patients.[21] Guo et al. showed that 40% of old-old patients experienced complications (acute respiratory distress syndrome, acute cardiac injury, acute kidney injury, sepsis, and pneumothorax) compared to 14.1% of young patients.[16] Moreover, invasive mechanical ventilation was applied more frequently in old-old patients.[16] These findings suggest that the elderly patients are more likely to develop severe infection and have higher in-hospital mortality.

The current literature suggests that the rate of co-infection and secondary infection ranges from 3% to 47.2% of patients.[4,8–11,14,22–26] In the meta-analysis, bacterial secondary infection was identified in 14.3% of COVID-19 patients (95% CI 9.6–18.9%).[27] In a study investigating infections with bacterial pathogens in patients with COVID-19 were *S. pneumoniae*, *K. pneumoniae*, *H. influenzae*, *Acinetobacter baumannii*, and M. *pneumoniae*.[8–10,14,22,24] The findings vary depending on the hospital setting and country. Some co-infections were cases of co-colonization, while others involved conditional pathogens. Infections with fungal pathogens such as *Candida albicans* and *Aspergillus* species have also been confirmed.[8–10,14,22] Although no respiratory virus pathogens were found in this study, other studies have reported rhinovirus/enterovirus, respiratory syncytial virus, influenza, etc.[23,26]

Bacterial infections were more commonly identified in critically ill COVID-19 patients.[27] Higher infection rates have been reported in intensive care unit (ICU) patients (14–31%) and non-survivors (50%).[1,2,28] Li et al. reported that COVID-19 patients with co-infection were more likely to experience complications such as acute respiratory distress syndrome and shock (p < 0.05), as well as severe breathing difficulties (p < 0.05).[25] Zhu et al. showed that the proportions of viral, fungal, and bacterial-fungal co-infections were highest in cases with severe COVID-19.[11] Langford et al. observed

that bacterial infections were more common in critically ill patients.[27] Therefore, co-infection and secondary infections affect the disease severity and prognosis in patients with COVID-19.

This study had several limitations. First, the study group included only patients in a tertiary healthcare setting in South Korea. Second, data were collected from the electronic health records database which excluded the level of detail possible by a manual review of the medical records. Third, the subgroup descriptive statistics were not adjusted for potential confounders. Fourth, clinical outcome data were provided only for inpatients. Fifth, we have a COVID-19 quarantine bed operating at ward, where intensive care is possible. Thus, it was not possible to analyze the strain difference according to ward and ICU.

In conclusion, 42.6% of COVID-19 patients were elderly (≥ 65 years) and in-hospital mortality was higher in the elderly. Secondary infections were identified in 12.8% of COVID-19 patients, and the most common pathogen was *Streptococcus pneumonia*. Older age (≥ 65 years) and secondary infections were associated with COVID-19 patient's in-hospital mortality.

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Competing interests

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Data sharing statement

All data underlying the findings are within the paper.

Declaration of any potential financial and non-financial conflicts of interest

No potential conflict of interest relevant to this article was reported.

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