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COVID-19 Morbidity and Severity in Patients With Age-Related Macular Degeneration: A Korean Nationwide Cohort Study



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- **PURPOSE:** To determine the potential association between age-related macular degeneration (AMD), a representative chronic age-related degenerative disease of the retina associated with inflammation and aging, and susceptibility to SARS-CoV-2 infection and severe COVID-19 outcomes.
- **DESIGN:** Nationwide cohort study with propensity-score matching.
- **METHODS:** A population-based nationwide cohort in Korea was examined. Data were obtained from the Health Insurance Review & Assessment Service of Korea, including all patients aged ≥ 40 years who underwent SARS-CoV-2 testing in South Korea between January 1, 2020 and May 15, 2020 (excluding self-referral). The primary outcome was SARS-CoV-2 test positivity and the secondary outcome was severe clinical outcome of COVID-19.
- **RESULTS:** The unmatched cohort consisted of 135,435 patients who were tested for SARS-CoV-2: 4531 patients (3.3%) tested positive for SARS-CoV-2 and 5493 (4.1%) had AMD. After propensity score matching, exudative AMD was associated with an increased likelihood of susceptibility to SARS-CoV-2 infection (adjusted odds ratio [aOR], 1.50; 95% confidence interval [CI], 1.03-2.25), and a considerably greater risk of severe clinical outcomes of COVID-19 (aOR, 2.26; 95% CI, 1.02-5.26), but not any AMD and non-exudative AMD.

- **CONCLUSIONS:** In a Korean nationwide cohort, data suggest that clinicians should be aware of the greater risk of susceptibility to severe clinical outcomes of COVID-19 in patients with exudative AMD. These findings provide an improved understanding of the relationship between the pathogenesis of COVID-19 and chronic neurological disorders. (Am J Ophthalmol 2022;239: 159-169. © 2021 Elsevier Inc. All rights reserved.)

INTRODUCTION

CORONAVIRUS DISEASE 2019 (COVID-19) RESULTING from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is a global emergency.¹ Recent studies on factors that increase susceptibility to COVID-19 or worsen clinical outcomes of this disease have focused on common diseases and conditions such as cardiopulmonary disorders, cancer, and diabetes mellitus.^{2,3} Although little attention has been paid to extrapulmonary comorbidities, associations between chronic central nervous system comorbidity and COVID-19 outcomes have been reported.^{4,5}

Age-related macular degeneration (AMD), a major vision-threatening disease of the retina, is a representative chronic age-related degenerative disease of the retina associated with inflammation and aging (termed “inflammaging”).⁶⁻⁸ Because AMD is one of the common comorbidities of chronic lung diseases, and advanced stage of AMD is associated with all-cause mortality, a possible association between AMD and the clinical outcomes of COVID-19 has been suspected.^{9,10} Importantly, inflammatory mechanisms that facilitate the development of AMD, such as aberrant innate immunity (eg, macrophages and the complement pathway), also contribute to the development of severe COVID-19.¹¹

Ramlall and associates¹² recently found that patients with macular degeneration have a 25% greater risk of severe COVID-19 outcomes; they analyzed 11,116 patients who presented to a single medical center. The study comprehensively demonstrated that an impaired complement system,

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one of the major pathogenic mechanisms of AMD development, may predispose patients to adverse clinical outcomes following SARS-CoV-2 infection. However, this study was limited as it involved a relatively small number of total patients and patients with macular degeneration at a single center. Moreover, the study lacked data on the association between AMD and susceptibility to SARS-CoV-2 infection and did not adjust for confounders, including known systemic risk factors for AMD. Importantly, failure to classify AMD as non-exudative versus exudative may have biased the results, since AMD subtypes may have different pathophysiology. Therefore, additional research is warranted to offer validated information regarding the association between AMD and COVID-19.

This study hypothesized that inflammation represented as AMD might be associated with increased susceptibility to SARS-CoV-2 infection and/or severe COVID-19 outcomes (ie, admission to the intensive care unit, mechanical ventilation, oxygen supplementation, or death). Using a large-scale Korean nationwide cohort, this study aimed to evaluate whether the presence of AMD is associated with increased susceptibility to SARS-CoV-2 infection and/or severe clinical outcomes in COVID-19, overall or stratified by AMD disease status (non-exudative versus exudative).

METHODS

The study protocol was approved by the Institutional Review Board of Sejong University (no. SJU-HR-E-2020-012).¹³ The requirement for written consent was waived by the ethics committee due to urgent medical needs during the COVID-19 pandemic. This study adhered to the tenets of the Declaration of Helsinki.

• **DATA SOURCE:** Data were based on a Korean national health insurance claims-based database and national COVID-19 registers. This large nationwide cohort included all patients who had undergone SARS-CoV-2 testing in South Korea from January 1, 2020 to May 15, 2020 through services facilitated by the Health Insurance Review & Assessment Service of Korea, the Korea Centers for Disease Control and Prevention (KCDC), and the Ministry of Health and Welfare (<https://hira-covid19.net>).^{2,14,15} Amidst the ongoing COVID-19 pandemic, the Korean government supported obligatory and complementary health services and insurance for every COVID-19 patient. Medical information provided from the national health insurance claims-based database consisted of personal data, information abstracted from inpatient and outpatient healthcare visits during the past 3.5 years (January 1, 2017 to May 15, 2020), including data on healthcare and pharmaceutical visits, prescriptions, diagnoses, and procedures. COVID-19 information obtained from national

registers included COVID-19-associated clinical outcomes and records of deaths. All patient data were anonymized by the Korean government to ensure patient confidentiality.¹⁶

• **STUDY POPULATION:** This study included patients aged ≥ 40 years who received SARS-CoV-2 testing in South Korea from January 1, 2020 to May 15, 2020. Testing was conducted by referral through the KCDC of South Korea Government and/or licensed doctors, based on relevant signs and symptoms (excluding asymptomatic self-referrals), with a total enrollment of 135,435 participants. SARS-CoV-2 testing results were based on RT-PCR assays of nasal or pharyngeal swabs, authorized by the KCDC and established by the World Health Organization guidelines.^{2,14}

• **EXPOSURE:** Age-related macular degeneration was defined based on International Classification of Diseases (10th revision; ICD-10) codes recorded at inpatient or outpatient visits during the study period (January 1, 2017 to May 15, 2020). It can be classified as non-exudative (early stage) or exudative (advanced stage) according to the progression of the disease; however, for the purposes of this study, AMD was classified into any AMD (H35.3), non-exudative AMD (H35.30), and exudative AMD (H35.31). If the ICD-10 codes for non-exudative AMD and exudative AMD were both present during the observational period, AMD was classified as exudative within statistical analyses.¹⁷

• **OUTCOMES:** The primary outcome was defined as a positive RT-PCR test result for SARS-CoV-2 infection among participants who received SARS-CoV-2 testing. The secondary outcome was considered as severe clinical outcomes (requirement for oxygen therapy, intensive care unit admission, invasive mechanical ventilation, or death) among COVID-19 patients.^{2,14}

• **COVARIATES:** Information on age, sex, and region of residence was obtained from insurance eligibility data. The region of residence was defined as rural or urban, as previously reported.^{2,14,18} The appropriate ICD-10 code was used to define disease history, as previously described.^{2,14} The Charlson comorbidity index score was calculated as previously reported.¹⁹ Pharmaceutical visits and prescriptions at inpatient or outpatient visits were used to define previous medication use (within 180 days of the prescription) before the SARS-CoV-2 test, as previously reported.^{2,14}

• **STATISTICS:** A logistic regression model with adjustment for potential confounders and propensity-score matching was used to reduce the potential bias of confounders and balance the baseline covariate of the two groups. Potential confounders within propensity-score matching and covariate adjustment for the logistic regression model included:

age (continuous); sex; region of residence (urban versus rural);²⁰ history of diabetes mellitus, cardiovascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, asthma, hypertension, and/or chronic kidney disease; Charlson comorbidity index; and previous use of medication, including aspirin, metformin, statins, and systemic steroids. Although the most common implementation of propensity-score matching is 1:1 matching, 1:1 matching caused a significant loss of sample size of AMD subjects, which increased the maximum propensity score difference as well as the width of the CIs in the cohort. 1:M matching that minimized the loss of the sample size and demonstrated adequate *P*-value with precise CI was optimized, and 3 for M was chosen for this study.^{21,22} From the predicted probability of: 1) patients with AMD versus those without AMD (among patients who received SARS-CoV-2 testing; n = 135,435); 2) patients with non-exudative AMD versus those without AMD among patients who received SARS-CoV-2 testing; 3) patients with exudative AMD versus those without AMD among patients who received SARS-CoV-2 testing; 4) patients with AMD versus those without AMD among COVID-19 patients (n = 4531); 5) patients with non-exudative AMD versus those without AMD among COVID-19 patients; and 6) patients with exudative AMD versus those without AMD among COVID-19 patients. Comparison of propensity score densities (Figures S1-S6) and standardized mean differences (SMDs) were used to validate the acceptability of matching.

Categorical data were described as numbers and percentages (%) and continuous data were described as means and standard deviations (SD). Data were analyzed using a logistic regression model and presented by adjusted odds ratios (aORs) with 95% CIs after adjusting for the aforementioned covariates.

In this cohort study, the exposure category consisted of diagnosis of any AMD, non-exudative AMD, and/or exudative AMD. The primary outcome was SARS-CoV-2 test positivity among patients who received SARS-CoV-2 testing and the secondary outcome was severe COVID-19 outcomes among COVID-19 patients. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc.). Two-sided *P*-values with a threshold of .05 were defined as statistically significant.

RESULTS

• **DEMOGRAPHIC AND CLINICAL CHARACTERISTICS:** The characteristics of 135,435 patients (aged ≥ 40 years) who received SARS-CoV-2 testing are described in Table 1. In this study population, 129,942 patients (95.9%) did not have AMD (mean age [SD], 61.6 [14.3] years; male, 63,004 [48.5%]), while 5493 patients (4.1%) presented with AMD (mean age [SD], 72.5 [11.5] years; male, 2687 [48.9%]) in the full unmatched cohort. Compared with patients with

non-exudative AMD, those with exudative AMD were older (71.6 versus 76.0 years; $P < .001$), more frequently male (45.3% versus 62.2%; $P < .001$), and more likely to present with a history of comorbidities ($P < .001$) (Table 1, Table S1). There were no between-group differences in medication use. A positive SARS-CoV-2 test result was observed in 4381 patients (3.4%) without AMD and 150 patients (2.7%) with AMD (Figure 1).

• **COVID-19 MORBIDITY AND AMD:** Propensity score matching was performed in patients who received SARS-CoV-2 testing (n = 135,435; Table 2 and Figures S1-S3) and no significant differences were observed in baseline characteristics between each matching group (all SMDs < 0.08). In matching 1 (patients without AMD versus those with AMD), the positivity rate of SARS-CoV-2 test result was 458 of 16,435 patients (2.8%) without AMD and 150 of 5488 patients (2.7%) with AMD (Table 2 and Figure 2; fully aOR, 1.00; 95% CI, 0.83-1.21). In matching 2 (patients without AMD versus those with non-exudative AMD), the positivity rate of SARS-CoV-2 test result was 373 of 12,902 patients (2.9%) without AMD and 114 of 4303 patients (2.6%) with non-exudative AMD (fully aOR, 0.94; 95% CI, 0.76-1.16). In matching 3 (patients without AMD versus those with exudative AMD), the positivity rate of SARS-CoV-2 test result was 74 of 3542 patients (2.1%) without AMD and 36 of 1185 patients (3.0%) with exudative AMD (fully aOR, 1.50; 95% CI, 1.03-2.25). For patients aged ≥ 55 years, the SARS-CoV-2 positivity rate was 69 of 3291 patients (2.1%) without AMD and 35 of 1105 patients (3.2%) with exudative AMD (fully aOR, 1.54; 95% CI, 1.03-2.33).

• **COVID-19 ASSOCIATED CLINICAL OUTCOMES AND AMD:** Propensity-score matching was performed in COVID-19 patients (n = 4531), and the association with severe COVID-19 outcomes (Figures S4-S6) revealed no significant between-group differences (Table 3; all SMDs < 0.1 , except Charlson comorbidity index among patients without AMD versus those with AMD [SMD = 0.104] and history of hypertension among patients without AMD versus those with non-exudative AMD [SMD = 0.105]). In matching 4, a severe clinical outcome was observed in 122 of 408 patients (29.9%) without AMD and in 43 of 144 patients (29.9%) with AMD (fully aOR, 0.88; 95% CI, 0.55-1.40). In matching 5, a severe clinical outcome was observed in 99 of 312 patients (31.7%) without AMD and in 29 of 109 patients (26.6%) with non-exudative AMD (full aOR, 0.75; 95% CI, 0.44-1.27). In matching 6, a severe clinical outcome was observed in 26 of 94 patients (27.7%) without AMD and 15 of 33 patients (45.5%) with exudative AMD (fully aOR, 2.26; 95% CI, 1.02-5.26). For the subset of patients aged ≥ 55 years, a severe clinical outcome was observed in 25 of 89 patients (28.1%) without AMD and in 15 of 31 patients (48.4%) with exudative AMD (fully aOR, 2.38; 95% CI, 1.02-5.55).

TABLE 1. Demographic and Clinical Characteristics of Patients Without AMD and With AMD in the Korean Nationwide Cohort

Characteristic	Korean Nationwide Cohort (n = 135,435)			
	Without AMD	With AMD	With AMD	
			With Non-Exudative AMD	With Exudative AMD
Total, n (%)	129,942 (95.9)	5493 (4.1)	4304 (3.2)	1189 (0.9)
Age, years (SD)	61.6 (14.3)	72.5 (11.5)	71.6 (11.7)	76.0 (9.9)
Sex, n (%)				
Male	63,004 (48.5)	2687 (48.9)	1948 (45.3)	739 (62.2)
Female	66,938 (51.5)	2806 (51.1)	2356 (54.7)	450 (37.9)
Region of residence, n (%)				
Rural	54,500 (41.9)	2113 (38.5)	1689 (39.2)	424 (35.7)
Urban	75,442 (58.1)	3380 (61.5)	2615 (60.8)	765 (64.3)
History of diabetes mellitus, n (%)	34,146 (26.3)	2388 (43.5)	1829 (42.5)	559 (47.0)
History of cardiovascular disease, n (%)	29,296 (22.6)	2180 (39.7)	1631 (37.9)	549 (46.2)
History of cerebrovascular disease, n (%)	20,183 (15.5)	1494 (27.2)	1120 (26.0)	374 (31.5)
History of COPD, n (%)	15,806 (12.2)	1182 (21.5)	873 (20.3)	309 (26.0)
History of asthma, n (%)	24,037 (18.5)	1629 (29.7)	1245 (28.9)	384 (32.3)
History of hypertension, n (%)	59,673 (45.9)	3843 (70.0)	2955 (68.7)	888 (74.7)
History of chronic kidney disease, n (%)	13,170 (10.1)	1061 (19.3)	761 (17.7)	300 (25.2)
Charlson comorbidity index, n (%)				
0	47,720 (36.7)	821 (15.0)	671 (15.6)	150 (12.6)
1	17,512 (13.5)	630 (11.5)	519 (12.1)	111 (9.3)
≥ 2	64,710 (49.8)	4042 (73.6)	3114 (72.4)	928 (78.0)
Use of medication, n (%)				
Aspirin	14,307 (11.0)	1050 (19.1)	806 (18.7)	244 (20.5)
Metformin	17,279 (13.3)	1164 (21.2)	920 (21.4)	244 (20.5)
Statin	37,010 (28.5)	2404 (43.8)	1895 (44.0)	509 (42.8)
Systemic steroid	48,193 (37.1)	2384 (43.4)	1873 (43.5)	511 (43.0)
COVID-19, n (%)	4381 (3.4)	150 (2.7)	114 (2.7)	36 (3.0)

Abbreviations: AMD = age-related macular degeneration; COPD = chronic obstructive pulmonary disease; COVID-19 = coronavirus disease; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SD = standard deviation.

DISCUSSION

This study investigated potential associations between SARS-CoV-2 infection incidence and AMD among patients who received SARS-CoV-2 testing, and between severe COVID-19 outcomes and AMD among COVID-19 patients. The study was conducted in a Korean nationwide cohort (total n = 135,435). It found that AMD and non-exudative AMD were not associated with the risk of a positive SARS-CoV-2 test or with COVID-19 severity, although patients with exudative AMD had a higher likelihood of having a positive SARS-CoV-2 test as well as worse COVID-19 clinical outcomes.

Given the global severity of the COVID-19 pandemic, the risk factors and comorbidities associated with severe COVID-19 outcomes need to be elucidated and are currently an urgent issue. Identified risk factors include old age, diabetes, obesity, cardiovascular disease, chronic kidney diseases, and allergic conditions, and it is noteworthy

that most of these conditions involve inflammaging as the underlying pathophysiology.^{2,7,8} Inflammaging is a term that describes human aging characterized by chronic, low-grade systemic inflammation.¹⁰ This chronic low-grade inflammatory condition is known to contribute to age-related degenerative diseases in the central nervous system (CNS) such as the brain (eg, Alzheimer's disease) and the retina (eg, AMD).⁸ In addition, inflammaging is a known risk factor for both morbidity and mortality in older individuals.²³ Importantly, the increase in baseline inflammation has implications for age-associated immune fragility, especially to those with overwhelming inflammation such as in COVID-19.²³ Along with the immune fragility that may increase susceptibility to infection, baseline inflammation and defective resolution of immune response due to senescent cells may act synergistically to exacerbate COVID-19. Therefore, the patient's inflammatory status may serve as a potential prognostic factor for morbidity and severity of COVID-19.

Despite this, no CNS disorder as a manifestation of inflammaging has been evidenced as a significant risk fac-

TABLE 2. 1:3 Propensity Score-Matched Characteristics and Adjusted ORs (95% CIs) for the Risk of Patients With AMD Testing Positive for SARS-Cov-2 Among All Patients Who Were Tested for SARS-Cov-2 (N = 21,923)

Characteristic	Matching 1			Matching 2			Matching 3		
	Without AMD	With AMD	SMD [‡]	Without AMD	With Non-Exudative AMD	SMD [‡]	Without AMD	With Exudative AMD	SMD [‡]
Total, n (%)	16,435	5488		12,902	4303		3542	1185	
Age, years (SD)	72.8 (11.9)	72.5 (11.5)	0.024	71.8 (12.1)	71.6 (11.7)	0.018	76.3 (10.7)	75.9 (9.9)	0.034
Sex, n (%)			0.003			0.010			0.014
Male	8063 (49.1)	2683(48.9)		5904 (45.8)	1947 (45.3)		2172 (61.3)	735 (62.0)	
Female	8372 (50.9)	2805(51.1)		6998 (54.2)	2356 (54.8)		1370 (38.7)	450 (38.0)	
Region of residence, n (%)			0.013			0.009			0.018
Rural	6223 (37.9)	2112 (38.5)		5002 (38.8)	1689 (39.3)		1299 (36.7)	424 (35.8)	
Urban	10,212 (62.1)	3376 (61.5)		7900 (61.2)	2614 (60.8)		2243 (63.3)	761 (64.2)	
History of diabetes mellitus, n (%)	6914 (42.1)	2384 (43.4)	0.029	5299 (41.1)	1828 (42.5)	0.030	1582 (44.7)	558 (47.1)	0.051
History of cardiovascular disease, n (%)	6233 (37.9)	2175 (39.6)	0.038	4644 (36.0)	1630 (37.9)	0.041	1542 (43.5)	546 (46.1)	0.055
History of cerebrovascular disease, n (%)	4330 (26.4)	1492 (27.2)	0.021	3273 (25.4)	1119 (26.0)	0.016	1053 (29.7)	374 (31.6)	0.044
History of COPD, n (%)	3410 (20.8)	1180 (21.5)	0.020	2479 (19.2)	873 (20.3)	0.029	813 (23.0)	307 (25.9)	0.076
History of asthma, n (%)	4604 (28.0)	1626 (29.6)	0.038	3531 (27.4)	1245 (28.9)	0.037	1075 (30.4)	381 (32.2)	0.042
History of hypertension, n (%)	11,502 (70.0)	3838 (69.9)	0.001	8851 (68.6)	2954 (68.7)	<0.001	2638 (74.5)	884 (74.6)	0.003
History of chronic kidney disease, n (%)	2837 (17.3)	1056 (19.2)	0.056	1961 (15.2)	760 (17.7)	0.071	823 (23.2)	296 (25.0)	0.046
Charlson comorbidity index, n (%)			0.040			0.034			0.061
0	2631 (16.0)	821 (15.0)		2216 (17.2)	671 (15.6)		486 (13.7)	150 (12.7)	
1	2042 (12.4)	630 (11.5)		1675 (13.0)	519 (12.1)		375 (10.6)	111 (9.4)	
≥ 2	11762 (71.6)	4037 (73.6)		9011 (69.8)	3113 (72.4)		2681 (75.7)	924 (78.0)	
Use of medication, n (%)									
Aspirin	2957 (18.0)	1046 (19.1)	0.030	2233 (17.3)	805 (18.7)	0.040	677 (19.1)	243 (20.5)	0.038
Metformin	3420 (20.8)	1163 (21.2)	0.010	2723 (21.1)	920 (21.4)	0.007	687 (19.4)	244 (20.6)	0.032
Statin	6978 (42.5)	2400 (43.7)	0.027	5691 (44.1)	1894 (44.0)	0.002	1455 (41.1)	506 (42.7)	0.034
Systemic steroid	6993 (42.6)	2379 (43.4)	0.016	5633 (43.7)	1872 (43.5)	0.003	1477 (41.7)	508 (42.9)	0.024
COVID-19, n (%)	458 (2.8)	150 (2.7)		373 (2.9)	114 (2.6)		74 (2.1)	36 (3.0)	
Minimally adjusted OR* (95% CI)	0.97 (0.81 to 1.17)			0.91 (0.74 to 1.13)			1.48 (1.01 to 2.22)		
Fully adjusted OR [§] (95% CI)	1.00 (0.83 to 1.21)			0.94 (0.76 to 1.16)			1.50 (1.03 to 2.25)		

Abbreviations: AMD = age-related macular degeneration; CI = confidence interval; COPD = chronic obstructive pulmonary disease; COVID-19 = coronavirus disease; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SMD = standardized mean difference; OR = odds ratio.

Propensity score-matched covariates: age; sex; region of residence; history of diabetes mellitus, cardiovascular disease, cerebrovascular disease, COPD, asthma, hypertension, or chronic kidney disease; Charlson comorbidity index; and previous use of medication (aspirin, metformin, statin, or systemic steroid)

*Minimally adjusted for age and sex

[§]Fully adjusted for age; sex; region of residence; history of diabetes mellitus, cardiovascular disease, cerebrovascular disease, COPD, asthma, hypertension, or chronic kidney disease; Charlson comorbidity index; and previous use of medication (aspirin, metformin, statin, or systemic steroid).

[‡]An SMD < 0.1 indicates no major imbalance. All SMD values were < 0.08 in the propensity score-matched cohort. Numbers in bold indicate significant differences ($P < .05$).

TABLE 3. 1:3 Propensity Score-Matched Characteristics and Adjusted ORs (95% CIs) for the Association of the Composite Endpoint of COVID-19 With AMD Among All Patients Who Tested Positive for SARS-Cov-2 (N = 552)

Characteristic	Matching 4			Matching 5			Matching 6		
	Without AMD	With AMD	SMD**	Without AMD	With Non-Exudative AMD	SMD**	Without AMD	With Exudative AMD	SMD**
Total, n (%)	408	144		312	109		94	33	
Age, years (SD)	67.6 (11.3)	68.2 (11.1)	0.051	67.5 (12.0)	67.8 (11.5)	0.022	68.2 (11.3)	69.3 (10.0)	0.095
Sex, n (%)			0.016			0.002			0.059
Male	164 (40.2)	59 (41.0)		112 (35.9)	39 (35.8)		54 (57.5)	18 (54.6)	
Female	244 (59.8)	85 (59.0)		200 (64.1)	70 (64.2)		40 (42.6)	15 (45.5)	
Region of residence, n (%)			0.038			0.006			0.024
Rural	189 (46.3)	64 (44.4)		144 (46.2)	50 (45.9)		41 (43.6)	14 (42.4)	
Urban	219 (53.7)	80 (55.6)		168 (53.9)	59 (54.1)		53 (56.4)	19 (57.6)	
History of diabetes mellitus, n (%)	143 (35.1)	52 (36.1)	0.024	100 (32.1)	39 (35.8)	0.084	34 (36.2)	11 (33.3)	0.065
History of cardiovascular disease, n (%)	70 (17.2)	29 (20.1)	0.083	53 (17.0)	19 (17.4)	0.011	21 (22.3)	8 (24.2)	0.045
History of cerebrovascular disease, n (%)	66 (16.2)	26 (18.1)	0.054	54 (17.3)	20 (18.3)	0.026	13 (13.8)	5 (15.2)	0.040
History of COPD, n (%)	44 (10.8)	16 (11.1)	0.011	34 (10.9)	13 (11.9)	0.035	10 (10.6)	3 (9.1)	0.050
History of asthma, n (%)	75 (18.4)	28 (19.4)	0.029	47 (15.1)	20 (18.3)	0.086	14 (14.9)	6 (18.2)	0.089
History of hypertension, n (%)	197 (48.3)	75 (52.1)	0.078	153 (49.0)	59 (54.1)	0.105	40 (42.6)	15 (45.5)	0.059
History of chronic kidney disease, n (%)	35 (8.6)	13 (9.0)	0.017	25 (8.0)	9 (8.3)	0.009	8 (8.5)	3 (9.1)	0.023
Charlson comorbidity index, n (%)			0.104			0.076			0.069
0	142 (34.8)	39 (27.1)		94 (30.1)	29 (26.6)		26 (27.7)	10 (30.3)	
1	57 (14.0)	23 (16.0)		50 (16.0)	16 (14.7)		13 (13.8)	7 (21.2)	
≥ 2	209 (51.2)	82 (57.0)		168 (53.8)	64 (58.7)		55 (58.5)	16 (48.5)	
Use of medication, n (%)									
Aspirin	46 (11.3)	17 (11.8)	0.018	40 (12.8)	14 (12.8)	< 0.001	6 (6.4)	2 (6.1)	0.012
Metformin	87 (21.3)	32 (22.2)	0.024	77 (24.7)	26 (23.9)	0.022	20 (21.3)	6 (18.2)	0.089
Statin	123 (30.2)	45 (31.3)	0.025	95 (30.5)	35 (32.1)	0.037	24 (25.5)	8 (24.2)	0.030
Systemic steroid	121 (29.7)	44 (30.6)	0.020	91 (29.2)	34 (31.2)	0.044	25 (26.6)	9 (27.3)	0.015
Severe clinical outcomes of COVID-19 *, n (%)	122 (29.9)	43 (29.9)		99 (31.7)	29 (26.6)		26 (27.7)	15 (45.5)	
Minimally adjusted OR* (95% CI)	0.94 (0.60 to 1.47)			0.75 (0.45 to 1.26)			2.28 (1.05 to 5.30)		
Fully adjusted OR [§] (95% CI)	0.88 (0.55 to 1.40)			0.75 (0.44 to 1.27)			2.26 (1.02 to 5.26)		

Abbreviations: AMD = age-related macular degeneration; CI = confidence interval; COPD = chronic obstructive pulmonary disease; COVID-19 = coronavirus disease; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SMD = standardized mean difference; OR = odds ratio.

Propensity score-matched covariates: age; sex; region of residence; history of diabetes mellitus, cardiovascular disease, cerebrovascular disease, COPD, asthma, hypertension, or chronic kidney disease; Charlson comorbidity index; and previous use of medication (aspirin, metformin, statin, or systemic steroid)

*Severe clinical outcomes of COVID-19 comprised requirement for oxygen therapy, admission to the intensive care unit, invasive ventilation, or death.

[§]Minimally adjusted for age and sex[†]Fully adjusted for age; sex; region of residence; history of diabetes mellitus, cardiovascular disease, cerebrovascular disease, COPD, asthma, hypertension, or chronic kidney disease; Charlson comorbidity index; and previous use of medication (aspirin, metformin, statin, or systemic steroid).

**An SMD < 0.1 indicates no major imbalance. All SMD values were < 0.1 in the propensity score-matched cohort, except Charlson comorbidity index among patients without AMD versus those with AMD, and history of hypertension among patients without AMD versus those with non-exudative AMD. Numbers in bold indicate significant differences ($P < .05$).

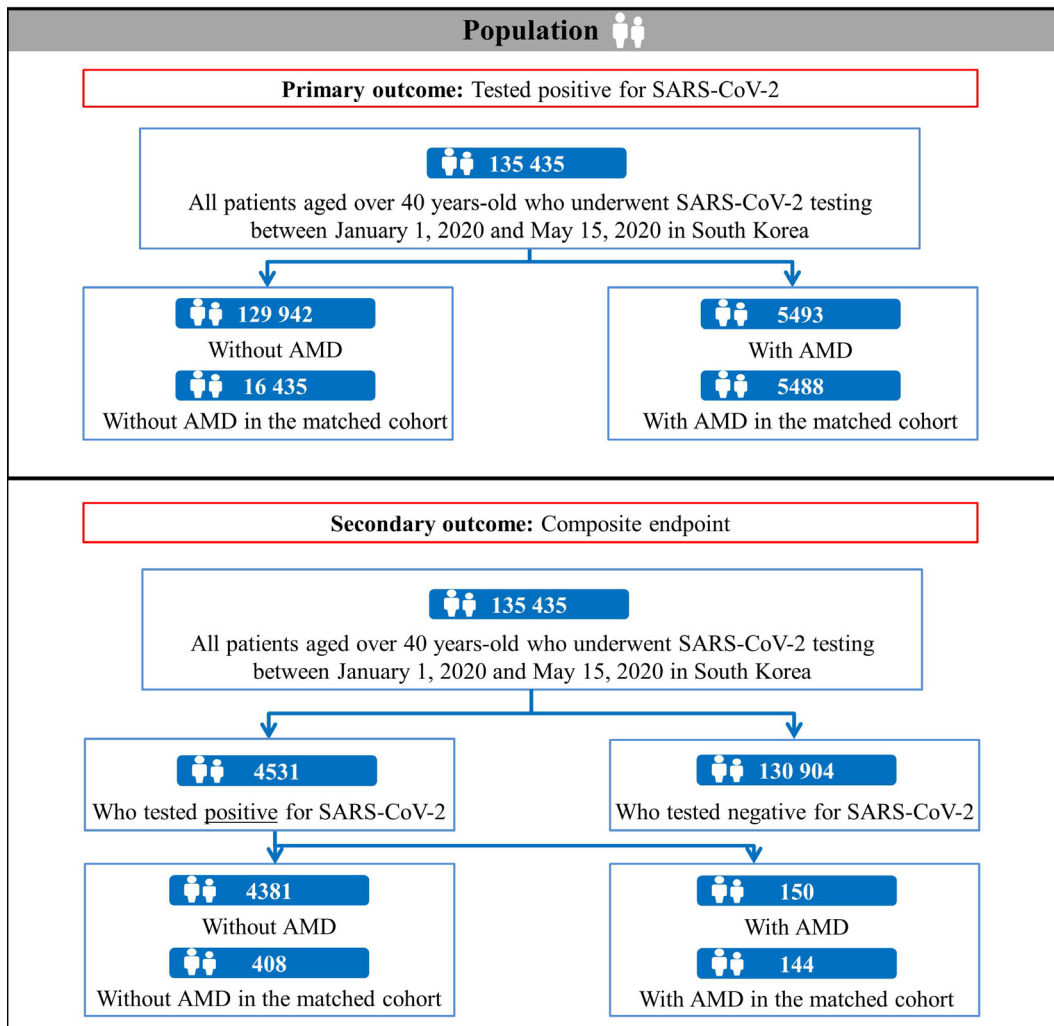


FIGURE 1. A graphical depiction of the study profile in the Korean nationwide cohort.

tor of COVID-19.²⁴ Pathogenesis of AMD involves baseline chronic inflammation and dysregulation of immune-mediated processes such as complement activation in the retina and the choroid at an advanced stage of the disease.²⁵ A previous study reported that late AMD was associated with all-cause mortality as well as mortality, independent of cardiovascular diseases or cancer.⁹ Furthermore, pulmonary disorders such as emphysema and the presence of respiratory symptoms were associated with exudative AMD in the cohorts of the Beaver Dam Eye Study, suggesting mutual interaction between chronic lung disease and exudative AMD.¹⁰ Since AMD serves as a biomarker of biological aging and chronic CNS inflammation,⁷ the increased risk of mortality in patients with exudative AMD in the current cohort strongly supports that inflammaging might be one of the risk factors for severe clinical outcomes of COVID-19.²³ However, future studies involving other inflammaging-related neurodegenerative diseases (eg,

Alzheimer's disease, Parkinson's disease) are necessary for strengthening the validity of this association.

Notably, patients with exudative AMD had a greater incidence of SARS-CoV-2 positivity in this study. Understanding susceptibility to SARS-CoV-2 infection is critical for determining the degree of social distancing for a particular subset of patients, although this topic remains highly understudied.¹ Previous studies have reported that AMD is associated with community-acquired pneumonia²⁶ and *Chlamydia pneumoniae* has been detected by PCR or immunohistochemistry in the choroidal neovascular membrane of patients with exudative AMD,²⁷ suggesting a strong possibility of lung infection as a comorbid condition in patients with exudative AMD. Given these associations, increased infectivity could result from impaired immune protection with regard to other microorganisms. Interestingly, dysregulation of complement cascades is a common feature of both AMD and COVID-19.²⁸ The comple-

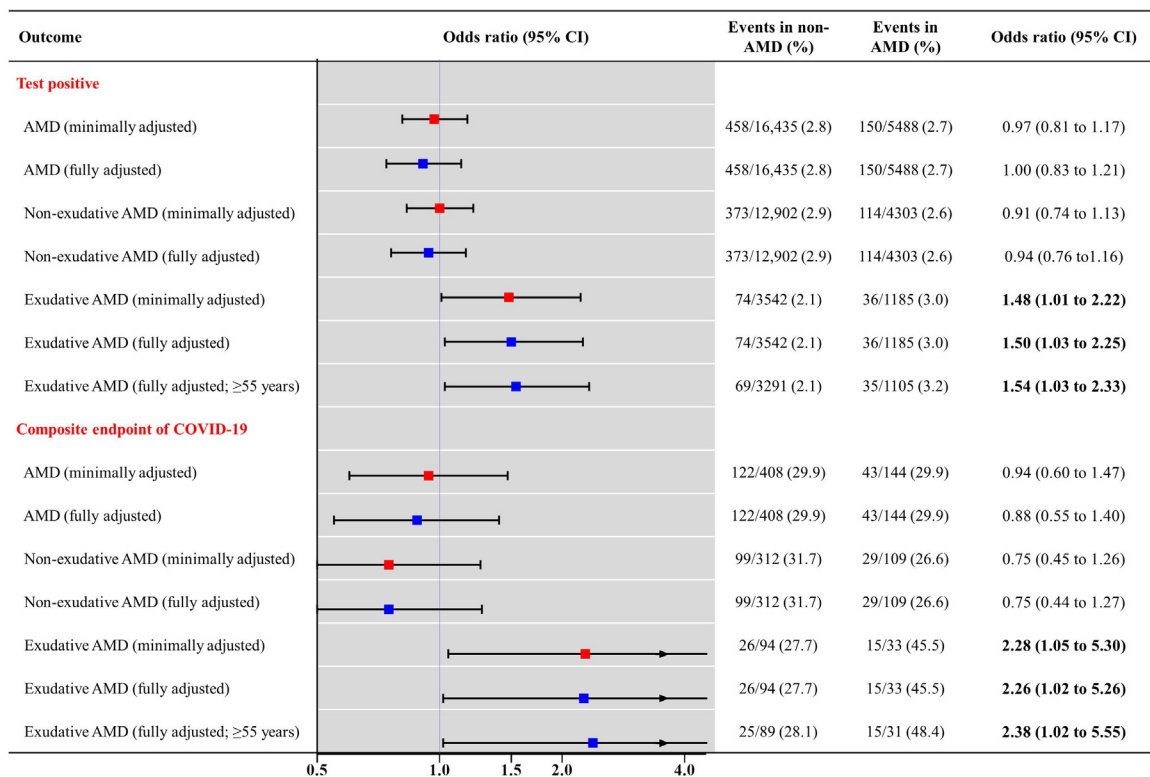


FIGURE 2. Association of AMD with positive SARS-CoV-2 test results in 135,435 patients tested for SARS-CoV-2 infection (primary outcome), and the association of AMD with severe COVID-19 outcomes in 4531 patients with confirmed COVID-19 (secondary outcomes). *x*-axis = a log-scale; red dots = minimal adjustment; blue dots = full adjustment; error bars = 95% CI.

ment system is a mediator of protection in various viral infections, including SARS-CoV-2.^{28,29} Moreover, Ramlall and associates¹² explained that dysregulation of the complement system (as evidenced by significant enrichment of complement-related gene sets in RNA seq data of SARS-CoV-2-positive patients), as well as single nucleotide polymorphisms in complement pathway components, may predispose patients to SARS-CoV-2 infection.³⁰ These findings substantiate the potential role of complement pathway dysregulation in increasing susceptibility to SARS-CoV-2 infection.

Although Ramlall and associates¹² have demonstrated, using a multimodal analytical approach, that patients with macular degeneration have a greater risk of severe COVID-19 clinical outcomes, this study had several limitations in terms of the clinical analysis. However, the current study compensates for the weaknesses of the study by Ramlall and associates.¹² First, it provides more confident statistics that involve a larger number of participants (total *n* = 135,435; AMD *n* = 5493) compared to the study by Ramlall and associates (total *n* = 11,161; AMD *n* = 88). Second, it performed meticulous matching and adjustments to minimize the effect of confounding by known COVID-19 risk factors (eg, age, sex, history of diabetes, cardiovas-

cular diseases),^{2,3,14} while the study by Ramlall and associates did not adjust for key covariates. Third, it classified AMD as non-exudative and exudative – this classification is critical for both prognostic information and the treatment plan – while the study by Ramlall and associates¹² evaluated AMD as a whole without subcategorizing it into subtypes. Although non-exudative and exudative forms of AMD share basic pathomechanisms, exudative AMD is more advanced and more active, and additionally involves retinochoroidal vascular pathology compared with the non-exudative forms.^{12,23,29} Thus, classifying AMD into subtypes is necessary for elucidating the pathophysiology of COVID-19 associated with AMD.

SARS-CoV2 employs the angiotensin-converting enzyme 2 (ACE2) receptor, a negative regulator of the renin-angiotensin system (RAS).^{31,32} This ACE2 expression is not only limited to the respiratory systems; extrapulmonary expression is likewise evident in vascular endothelial cells.^{33,34} Interestingly, RAS (including ACE2/Ang1-7) is actively present in the retina. Specifically, RAS is present in retinal vascular endothelial cells, RPEs, the choroid, and photoreceptor cells, suggesting that impairment of RAS represents the majority of retinal pathology.³⁵ In this regard, AMD is one of the known systemic

manifestation of RAS impairment as well as ACE2 deficiency, and is correlated with disease progression.^{35,36} Moreover, this imbalance in RAS potentiates progression of AMD and choroidal neovascularization, and drugs that block RAS (such as ARBs and ACEIs) suppress choroidal neovascularization.^{35,36} Systemically, activated RAS is known to increase vascular endothelial permeability in the lung as well as in the CNS via down-regulation of Dll4-Notch signaling; this may exacerbate pulmonary dysfunction, thereby increasing mortality and worsening phenotype in COVID-19 patients.³⁷ Therefore, associations between impaired RAS, downregulation of ACE2, and advanced-stage AMD may partly explain the vulnerability to COVID-19 observed in patients with exudative AMD.

• **LIMITATIONS AND STRENGTHS:** This study had several limitations. First, AMD was defined based on ICD codes; the accuracy of AMD diagnoses could not be verified by a review of medical charts. However, the observed prevalence of AMD (4.1%) was comparable with past studies,³⁸ and claims-based definitions of AMDs are widely used in epidemiologic investigations.^{39,40} In addition, the Korean National Health Insurance program has strict criteria and review processes in place for the diagnosis of rare, intractable diseases such as exudative AMD. Although the review of diagnosis by the government, as well as similar prevalence rates observed across studies, may ensure the reliability of the operational definition of AMD, subsequent studies involving medical chart review would be valuable in clarifying and validating this literature. Second, given the urgency of data processing during a global pandemic, the COVID-19-related information provided by the Korean government includes 3 years of patient history; therefore, patients who were diagnosed with AMD 3 years prior to the pandemic or who had not visited an ophthalmologist within 3 years could have been excluded from the AMD cohort. However, most patients with AMD visit clinics regularly and access to hospital-based healthcare is easy in South Korea. In addition, patients with exudative AMD receive financial support from the government, with reduced coinsurance rates for medical expenses. Given these conditions, the possibility of missing diagnoses is likely to have been minimal. Third, the analysis did not adjust for potential confounders such as alcohol consumption and cigarette smoking, although these covariates may affect the status and progression of AMD. The study included patients with a history of known systemic diseases that have a close association with these factors, such as cardiovascular disease, diabetes, and respiratory disease, and it adjusted for these conditions as confounding variables; however, first-hand information on alcohol usage and smoking history was not accessible from official governmental data. Further studies adjusting for alcohol usage and smoking history could validate the relationship between COVID-19 clinical outcomes and AMD observed in the current investigation. Fourth, the

main results showed relatively wide, imprecise CIs; since covariates were matched and controlled for through sophisticated statistical methodology (ie, 6 iterations of independent matching with a high balance of covariates [very low SMD < 0.08]) and multivariate-adjusted logistic regression analyses were performed with another full adjustment of the confounders, less precise (though more accurate) CIs were inevitable. Despite strict control for confounders among a large number of patients, the statistically significant results ($P < .05$) observed in the study indicate the direct effect of AMD (especially exudative AMD) on the severity of COVID-19 with great reliability. Further national and international cohorts with a larger number of patients and multi-ethnic patients would be valuable and important for validating the findings. Fifth, although the study population was based on COVID-19 testing through referral by the KCDC or other medical professionals, information regarding specific symptoms was unavailable. Symptomatic patients and those with systemic factors tend to frequently utilize health services and may thus have biased the study results. However, as mentioned before, previous studies based on the nationally representative Korea National Health and Nutrition Examination Survey cohort reported that the prevalence of any AMD ranged between 6.1% and 6.6%;^{38,41} these rates were slightly higher, although comparable, to the prevalence of AMD in this cohort. Moreover, since an entire Korean nationwide cohort (135,435 patients aged ≥ 40 years) was included to minimize selection bias, and 6 independent meticulous propensity score matching iterations were used to minimize statistical bias, it is believed that the prevalence of systemic factor-induced bias was minimal. Sixth, accurate data on individual viral loads and contact tracing results were available; therefore, positive SARS-CoV-2 testing results should be cautiously interpreted.

Despite these limitations, this large-scale study uniquely highlights the potential association between AMD with susceptibility to COVID-19 and COVID-19 severity within a Korean nationwide cohort using propensity score matching. In addition to a large sample size ($n = 135,435$), this study is supported by a well-designed statistical analysis utilizing robust propensity score-matching that increased the generalizability and reliability of the results.

This large-scale nationwide cohort study supports the hypothesis that exudative AMD is associated with an increased risk of susceptibility to SARS-CoV-2 infection and the devastating outcomes of COVID-19. Therefore, the findings provide insight into the association between the pathophysiology of COVID-19 and chronic neurological disorders. Although the prevalence of AMD is relatively low, the scale and expandability of the current SARS-CoV2 crisis means that even a low prevalence of AMD could lead to a large number of cases and may affect disease severity. Special attention must be paid to people with exudative AMD who may be vulnerable to COVID-19.

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Author Contributions: Dr DKY had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. All authors approved the final version before submission. Study concept and design: JMY, SWL, and DKY; acquisition, analysis, or interpretation of data: SWL and DKY; drafting of the manuscript: JMY, DA, and DKY; critical revision of the manuscript for important intellectual content: JMY, JYL, DA, and DKY; Statistical analysis: JMY, SYM, SWL, and DKY; Study supervision: SWL and DKY. DKY is guarantor. The corresponding authors attest that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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