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Association Between Chronic Use of Immunosuppresive Drugs and Clinical Outcomes From Coronavirus Disease 2019 (COVID-19) Hospitalization: A Retrospective Cohort Study in a Large US Health System

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Background. It is unclear whether chronic use of immunosuppressive drugs worsens or improves the severity of coronavirus disease 2019 (COVID-19), with plausible mechanisms for both.

Methods. Retrospective cohort study in 2121 consecutive adults with acute inpatient hospital admission between 4 March and 29 August 2020 with confirmed or suspected COVID-19 in a large academic health system, with adjustment for confounding with propensity score–derived stabilized inverse probability of treatment weights. Chronic immunosuppression was defined as prescriptions for immunosuppressive drugs current at the time of admission. Outcomes included mechanical ventilation, in-hospital mortality, and length of stay.

Results. There were 2121 patients admitted with laboratory-confirmed (1967, 93%) or suspected (154, 7%) COVID-19 during the study period, with a median age of 55 years (interquartile range, 40–67). Of these, 108 (5%) were classified as immunosuppressed before COVID-19, primarily with prednisone (>7.5 mg/day), tacrolimus, or mycophenolate mofetil. Among the entire cohort, 311 (15%) received mechanical ventilation; the median (interquartile range) length of stay was 5.2 (2.5–10.6) days, and 1927 (91%) survived to discharge. After adjustment, there were no significant differences in the risk of mechanical ventilation (hazard ratio [HR], .79; 95% confidence interval [CI], .46–1.35), in-hospital mortality (HR, .66; 95% CI, .28–1.55), or length of stay (HR, 1.16; 95% CI, .92–1.47) among individuals with immunosuppression and counterparts.

Conclusions. Chronic use of immunosuppressive drugs was neither associated with worse nor better clinical outcomes among adults hospitalized with COVID-19 in one US health system.

Keywords. COVID-19; immunosuppression; prescription medicines; clinical outcomes.

As of 11 September 2020, the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused more than 6.4 million infections and 193 000 deaths in the United States [1]. The gravity of the pandemic has unleashed unprecedented scientific activity focused on better understanding the pathogenesis and epidemiology of coronavirus disease 2019 (COVID-19) as well as identifying treatments that may change its course [2].

It is unclear how immunosuppression impacts outcomes among those with COVID-19. While some information suggests chronic immunosuppression may be a risk factor for more severe disease [3], early evidence from individuals with COVID-19 in China did not suggest such an association [4], nor did evidence from prior coronavirus outbreaks, including the Middle East respiratory syndrome (MERS) [5] and severe acute respiratory syndrome (SARS) [6]. In addition, there is early evidence of the benefits of acute immunosuppression with dexamethasone among individuals with COVID-19 receiving oxygen or mechanical ventilation [7]. European studies have examined the association between chronic immunosuppression and COVID-19 outcomes. In a cross-sectional analysis of Northern Italian patients treated with calcineurin inhibitors, the clinical course of COVID-19 was mild [8]. Another study assessed COVID-19 outcomes within a multicenter, prospective, observational registry of patients with rheumatologic

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disease treated with biologic agents; disease course and mortality were similar to that in the general population [9]. Most analyses of the relationship between chronic immunosuppression and COVID-19 have focused on disease-based definitions of specific clinical subpopulations, such as individuals with rheumatoid arthritis or organ transplantation, and have found nonsignificant effects (adjusted mortality odds ratio, 1.1; 95% confidence interval [CI], .8–1.6) [10] or small hazardous effects (adjusted mortality hazard ratio [HR], 1.19; 95% CI, 1.11–1.27) [11].

To better understand whether chronic immunosuppression worsens outcomes for hospitalized patients with COVID, we conducted a retrospective cohort study using electronic medical record data.

METHODS

Data and Subjects

We used the Johns Hopkins CROWN Registry, a cohort of patients with COVID-19 derived using a computable phenotype based on International Classification of Diseases, 10th revision (ICD-10), diagnostic codes and laboratory results [12]. The Johns Hopkins CROWN registry collects data from a large academic health system, including 5 hospitals and approximately 2500 beds, serving a large area in Maryland, Virginia, and Washington, DC. We included adults aged 18 years or older who were hospitalized with suspected or confirmed COVID-19 between 4 March 2020 and 29 August 2020. We excluded patients who were ventilated upon admission (transferred patients or ventilated in the emergency department) and persons who had "do not resuscitate" or "do not intubate" advance directives placed within 24 hours of admission. We followed persons from the date of their COVID-19 admission through discharge, death, or 29 August 2020, whichever came first.

Exposures

Based on prescription medicines used at the time of hospital admission, we defined 2 mutually exclusive exposure groups. We categorized patients as immunosuppressed if they had medications for immunosuppressive drugs current on the date of COVID-19 hospitalization. These were defined as World Health Organization Anatomical Therapeutic Chemical (ATC) class L04 "selective immunosuppressants," class L01 "antineoplastic agents," or prednisone greater than 7.5 mg or equivalent. Everyone else was defined as immunocompetent for the primary analysis.

Outcomes

Our primary outcome was the use of mechanical ventilation, defined as the time from hospital admission to the first use of mechanical ventilation. Secondary outcomes included in-hospital mortality and hospital length of stay.

Covariates

We identified potential confounders through a review of the peer-reviewed literature [11, 13, 14] and expert consultation. We considered calendar week, hospital, sociodemographics (age, sex, zip code, self-reported race and ethnicity), clinical features (substance-use disorder, alcohol use, smoking history, body mass index, admission from a nursing home), days between positive SARS-CoV-2 polymerase chain reaction test and hospital admission, vital signs within 24 hours of admission (body temperature, pulse, respiratory rate, SpO_2:FiO_2 ratio [ratio of oxygen saturation by pulse oximetry to the fractional percentage of inspired oxygen]), and laboratory measures within 2 days of admission (elevated C-reactive protein, creatinine, troponin, albumin, high or low white blood cell count). We generated the Rx-Risk score [15] and calculated the summary Elixhauser Comorbidity Index for each person, using all look-back data available in the electronic medical record [16]. We also controlled for specific autoimmune or inflammatory conditions, namely chronic obstructive pulmonary disease, rheumatic diseases, renal disease, cancer, and human immunodeficiency virus (HIV). We created indicator variables for missing binary covariates and dropped patients who were missing a continuous covariate.

Statistical Analyses

We used means and standard deviations for continuous variables or frequencies and percentages for categorical variables to characterize the study cohort. The primary analysis used an inverse probability of treatment weighting (IPTW) approach to control for confounding [17]. To derive propensity scores, we constructed a logistic regression model to predict immunosuppression status by including all patient demographic and clinical characteristics listed in the "Covariates" section above. We calculated stabilized inverse probability treatment weights [18] and trimmed at the 1st and 99th percentile to avoid exertion of outliers. We calculated standardized mean differences (SMDs) in the original weighted samples to assess covariate balance. We used Fine and Gray's competing risk model for mechanical ventilation and length of stay, where death was considered as a competing risk [19]. Multivariable Cox proportional hazards regression models were used for in-hospital mortality. Any variables unbalanced after weighting (SMD >10%) were additionally controlled for in regression analyses [20].

In secondary analyses, we used propensity score matching or propensity score–adjusted regression. For propensity score matching, we used a 1:1 greedy matching algorithm and a caliper of 0.5 pooled standard deviations of the estimated propensity score.

Sensitivity Analyses

First, to examine whether the absence of data predating hospitalization created misclassification bias, we restricted our analysis to persons with at least 1 health system encounter prior to COVID-19 admission. Second, to examine whether our results would vary when considering broader groups of immunosuppression diagnoses, we repeated our analyses including the Agency for Healthcare Research and Quality's Immunocompromised State Diagnosis Codes [21]. To do so, we used all available look-back time up to and including the date of COVID-19 admission. Third, we made our definition more strict by considering prednisone greater than 10 mg as immunosuppressed. Finally, to examine whether our results would vary based on a less conservative definition of respiratory failure, we included high-flow nasal cannulae or noninvasive positive-pressure ventilation. In each sensitivity analysis, we recalculated propensity scores and updated the set of unbalanced covariates for doubly robust adjustment.

Analyses were conducted using SAS software, version 9.4, of the SAS System for Windows. The Johns Hopkins Medicine Institutional Review Board reviewed this study (#IRB00248349), waived the requirement for informed consent, and deemed the work to be exempt research.

RESULTS

There were 2492 adults admitted between 4 March 2020 and 29 August 2020 with confirmed or suspected COVID-19. We excluded 71 due to ventilation at hospital admission and 300 had advance directives at admission. The median age was 55 years (interquartile range, 40–67 years). Of the remaining 2121 individuals, 108 (5%) used immunosuppressing medications and 2013 (95%) did not (Supplementary Table 1). The medications most often used were prednisone greater than 7.5 mg, tacrolimus, and mycophenolate mofetil.

Characteristics at Admission

Among immunocompromised patients, the mean age was 55.0 ± 14.8 years, 49% were male, 45% Black, and 18% Hispanic (Table 1). Prior to IPTW, immunocompromised persons were more likely to be non-Hispanic, have past tobacco use, and used significantly more medicines. Individuals with chronic immunosuppression also had higher mean Elixhauser Comorbidity Index scores (10.2 ± 12.7) compared with their counterparts (4.0 ± 8.6). Weighting reduced the differences between groups, although differences remained, most notably for comorbidity burden and Rx-Risk score.

Association Between Chronic Immunosuppression and Clinical Outcomes

There was no significant difference in the proportion of persons discharged alive (88% among immunocompromised vs 91% among immunocompetent individuals; $P = .28$). (Table 2) The distribution of COVID-19 admissions by calendar week did not differ between the 2 groups (Supplementary Figure 1). The median length of hospital stay was not different (6.9 vs 5.1 days; $P = .09$) and the proportion undergoing mechanical ventilation was similar (16% vs 15%; $P = .75$) between the 2 groups, and the median time to ventilation was slightly longer for immunocompromised individuals (3.0 vs 2.6 days; $P = .02$). For in-hospital death, neither the proportion (7% vs 7%; $P = .73$) nor the median time to death (27.2 vs 13.3 days; $P = .25$) differed by immune system status.

In the unadjusted regression analyses, there was no difference in the hazard of each of the outcomes (Table 3). Similarly, after IPTW, there were no statistically significant differences in the likelihood of mechanical ventilation (HR, .79; 95% CI, .46–1.35), in-hospital mortality (HR, .66; 95% CI, .28–1.55), or length of stay (HR, 1.16; 95% CI, .92–1.47) among individuals with chronic immunosuppression and their counterparts. Results were generally similar using propensity score matching and propensity score adjustment.

Sensitivity Analyses

Restriction to the subset of persons with at least 1 encounter prior to the date of their COVID-19 admission yielded findings substantively similar to the main analysis (Supplementary Table 2). Analyses that considered immunosuppression diagnoses, with or without medications, identified 232 individuals (11%) with immunosuppression; most had end-stage renal disease (n = 56) or HIV (n = 32). With the inclusion of these patients, we found a significantly shorter length of stay with immunosuppression, but no difference in use of mechanical ventilation or death (Supplementary Table 3). In analyses to restrict the exposure definition to individuals on prednisone greater than 10 mg per day, we again found no significant difference in the risk of mechanical ventilation or death, although immunosuppressed persons were discharged sooner (HR, .72; 95% CI, .60–.85). Finally, with expansion of the outcome definition to include noninvasive ventilation, there remained no significant differences between groups (HR, 1.15; 95% CI, .76–1.74) (Supplementary Table 4).

DISCUSSION

The COVID-19 pandemic continues to cause widespread morbidity and mortality. We examined 1 important subpopulation, individuals with chronic use of immunosuppressive medications. After adjustment for potentially confounding covariates, there were no statistically significant differences in the risk of mechanical ventilation, in-hospital mortality, or length of stay among those with immunosuppression and their counterparts. Our results were consistent in sensitivity analyses varying both exposure and outcome definitions. These findings are important because of the magnitude of continuing morbidity and

Table 1. Characteristics of Individuals on Date of Hospitalization With Confirmed or Suspected COVID-19, by Immune System Status Prior to COVID-19

	Original Sample (N = 2121)			After IPTW		
	Immunocompromised (n = 108)	Immunocompetent (n = 2013)	Absolute Standardized Mean Difference	Immunocompromised	Immunocompetent	Absolute Standardized Mean Difference
Age, years	55.0 (14.8)	54.3 (17.6)	.0420	55.0 (13.7)	54.9 (17.3)	.0056
Male sex, n (%)	53 (49)	1062 (53)	.0737	39 (47)	1049 (54)	.1342
Race, n (%)						
White	34 (32)	479 (24)	.1725	24 (29)	479 (24)	.0885
Black	49 (45)	751 (37)	.1643	33 (40)	741 (38)	.0469
Neither White nor Black	25 (23)	783 (39)	.3455	26 (31)	733 (38)	.1306
Ethnicity, n (%)						
Hispanic	19 (18)	646 (32)	.3404	22 (27)	606 (31)	.0889
Non-Hispanic	87 (80)	1359 (68)	.3009	60 (72)	1339 (69)	.0863
Refused or unknown	2 (2)	8 (<1)	.1383	1 (1)	8 (<1)	.0145
Drug abuse	7 (6)	53 (3)	.1853	4 (5)	56 (3)	.1058
Current alcohol use, n (%)						
Yes	34 (32)	524 (26)	.1206	20 (24)	522 (27)	.0727
No	53 (49)	929 (46)	.0586	39 (47)	892 (46)	.0333
Missing or not asked	21 (19)	560 (28)	.1981	24 (29)	539 (27)	.0330
Smoking history, n (%)						
Current smoker	15 (14)	194 (9)	.1323	7 (9)	195 (10)	.0465
Former smoker	25 (23)	296 (15)	.2168	18 (21)	300 (15)	.1650
Nonsmoker	51 (47)	1101 (55)	.1499	42 (50)	1052 (54)	.0773
Missing or not asked	17 (16)	422 (21)	.1352	16 (20)	406 (21)	.0295
Body mass index, n (%)						
Not overweight or obese	21 (20)	337 (17)	.0703	12 (14)	333 (17)	.0714
Overweight	26 (24)	435 (22)	.0587	19 (23)	420 (21)	.0213
Obese	25 (23)	645 (32)	.2000	22 (26)	619 (32)	.1178
Missing	36 (33)	596 (29)	.0803	31 (37)	581 (30)	.1502
Admission from skilled nursing facility, n (%)	3 (3)	114 (6)	.1439	4 (5)	111 (6)	.0256
Days between positive COVID-19 test and hospital admission	0.4 (2.2)	0.3 (1.7)	.0561	0.7 (1.7)	0.3 (1.8)	.2121
Vital signs within 24 hours of admission						
Temperature, °C	36.9 (0.5)	37.1 (0.6)	.3946	37.0 (0.5)	37.1 (0.6)	.2087
Pulse, beats per minute	85 (12)	85 (14)	.0556	85 (12)	85 (14)	.0038
Respiratory rate >22 breaths/minute, n (%)	41 (38)	913 (45)	.1504	38 (46)	901 (46)	.0029
SpO_2:FiO_2 ratio	409 (113)	391 (113)	.1540	380 (110)	391 (113)	.1009
Laboratory measures ±2 days of admission, n (%)						
↑ C-reactive protein	75 (87)	1485 (92)	.0961	59 (87)	1446 (92)	.0676
↑ Creatinine	36 (34)	458 (23)	.2372	17 (21)	463 (24)	.0724
↑ Troponin	17 (20)	296 (18)	.0289	13 (19)	293 (18)	.0270
↑ White blood cells	20 (19)	393 (20)	.0256	17 (21)	372 (28)	.0494
↓ Albumin	53 (52)	1027 (52)	.0389	43 (54)	988 (52)	.0134
↓ White blood cells	40 (38)	606 (30)	.1472	27 (33)	606 (31)	.0323
Rx-Risk score	13 (11)	6 (8)	.7835	9 (7)	6 (9)	.4221
Elixhauser comorbidity score	10.2 (12.7)	4.0 (8.6)	.5737	5.6 (8.6)	4.4 (9.0)	.1348
Chronic obstructive pulmonary disease, n (%)	11 (10)	92 (4)	.2392	6 (7)	89 (5)	.1125
Rheumatic disease, n (%)	7 (7)	33 (2)	.2472	2 (2)	37 (2)	.0398
Renal disease, n (%)	27 (25)	200 (10)	.4048	10 (13)	211 (11)	.0567
Cancer, n (%)	19 (18)	133 (7)	.3417	9 (10)	141 (7)	.1096
HIV, n (%)	4 (4)	29 (2)	.1472	1 (1)	29 (1)	.0364

Continuous variables are represented as mean (standard deviation) and categorical variables as n (%). Fifty-seven individuals had unavailable vital signs and were excluded from the IPTW sample (46, body temperature; 32, pulse; 44, SpO_2:FiO_2 ratio). Laboratory results were missing for persons who did not have test ordered ±2 days of admission: 415, C-reactive protein; 26, creatinine; 411, troponin; 11 white blood cell count; 6, albumin. In the IPTW sample, indicator variables were used for missing laboratory values as data were assumed to be missing at random given clinical utility. Laboratory values in the table represent individuals with abnormal values above or below the referent standard, and the denominator for the proportions excludes persons missing the test.

Abbreviations: COVID-19, coronavirus disease 2019; HIV, human immunodeficiency virus; IPTW, inverse probability of treatment weighting; SpO_2:FiO_2, ratio of oxygen saturation by pulse oximetry to the fractional percentage of inspired oxygen; ↑, increased; ↓, decreased.

Table 2. Unadjusted Clinical Outcomes by Immune System Status Prior to COVID-19

	Immune System Status Prior to COVID-19		
	Immunosuppressed (n = 108)	Immunocompetent (n = 2013)	*P*
Discharged alive, n (%)	95 (88)	1832 (91)	.2848
Remains hospitalized as of 29 August 2020, n (%)	6 (6)	33 (2)	.0032
Mechanical ventilation, n (%)	17 (16)	294 (15)	.7452
<2 days after admission	6 (35)	161 (55)	
2–7 days	7 (41)	113 (38)	
>7 days	4 (24)	20 (7)	
Median (IQR) time to mechanical ventilation, days	3.0 (1.3–6.8)	2.6 (0.4–3.7)	.0159
In-hospital death, n (%)	7 (7)	148 (7)	.7348
<2 days after admission	0	10 (7)	
2–7 days	1 (14)	23 (16)	
>7 days	6 (86)	115 (78)	
Median (IQR) time to death, days	27.2 (7.9–56.7)	13.3 (8.1–22.7)	.2453
Length of stay, median (IQR), days	6.9 (2.8–13.2)	5.1 (2.5–10.5)	.0853
Among those discharged	6.1 (2.2–10.1)	4.8 (2.3–9.1)	.2136
Among those still admitted as of 29 August 2020	13.2 (10.3–18.8)	18.3 (9.2–24.2)	.7407
Among those who died	27.2 (7.9–56.7)	13.3 (8.1–22.6)	.2453

For counts, the *P* value was calculated using a chi-square test. For median times, the *P* value was calculated using the Wilcoxon rank-sum test for difference in medians.
Abbreviations: COVID-19, coronavirus disease 2019; IQR, interquartile range.

mortality attributable to the pandemic, as well as the frequent use of immunosuppressive medications for the management of a range of chronic conditions.

While our study adds to case series and investigations of specific subpopulations of individuals with immunosuppression [10, 11, 22–24] suggesting similar clinical COVID-19 outcomes among individuals with immunosuppression and their counterparts, our study was not designed to characterize the pharmacodynamics of these medications and how they may interact with COVID-19. The immunosuppressive agents we considered have varied mechanisms of action targeting cellular and humoral immune responses. It is possible that chronic immunosuppression might decrease the severity of the hyperinflammatory response that can complicate SARS-CoV-2 infection, and thus protect against the severity of any cytokine storm. In addition, individuals on chronic immunosuppressive medications, once hospitalized with COVID-19 may be managed in ways that mitigate potential harms that would otherwise accrue, such as through the use of stress-dose steroids among those on chronic prednisone. On the other hand, chronic immunosuppression might also plausibly increase morbidity and mortality caused by earlier disease stages that are predominated by harms from viral replication, as well as predispose individuals to greater risks from secondary infection.

Table 3. Association Between Chronic Immunosuppression and Clinical Outcomes in COVID-19

	Hazard Ratio (95% Confidence Interval)		
	Mechanical Ventilation[a]	In-hospital Death	Length of Stay[a]
Unadjusted regression analysis	.97 (.61–1.55)	.61 (.30–1.25)	.87 (.71–1.05)
Primary analysis			
Inverse probability treatment weights	.79 (.46–1.35)	.66 (.28–1.55)	1.16 (.92–1.47)
Secondary analyses			
Propensity score matching[b]	.91 (.50–1.67)	1.50 (.41–5.45)	.89 (.67–1.17)
Propensity score adjustment	1.10 (.66–1.84)	.59 (.28–1.22)	.990 (.80–1.22)

Abbreviation: COVID-19, coronavirus disease 2019.

[a]The models for risk of ventilation and length of stay incorporated the competing risk of death using Fine & Gray's methodology.

[b]Matches were made using 1:1 greedy matching, and 108 pairs were identified.

Our analyses have limitations. First, our relatively small sample sizes of individuals with these conditions precluded analyses among distinct clinical subpopulations, such as those with solid-organ transplant or HIV/AIDS. Second, exposure misclassification, which was based on medications used at the time of hospital admission, is possible. Third, we characterized a limited set of short-term outcomes; further work is needed to examine the association between chronic immunosuppression and longer-term morbidity and mortality. Fourth, our analysis took place during a period with dynamic clinical treatment protocols (eg, proning, criteria for intensive care unit transfer), although we are not aware that these were differentially applied to individuals based on their use of chronic immunosuppressive medications. Finally, our approach has limitations inherent to observational research, including the potential for unmeasured confounding.

These limitations notwithstanding, our analysis also has many strengths. We examined the real-world experience of a large and diverse cohort of individuals hospitalized with COVID-19 within a health system that included 5 hospitals serving a large geographic region. Our data came from a comprehensive patient registry that included sequentially identified persons with confirmed or suspected COVID-19. Data elements of the electronic medical record included medical history, laboratory data, vital signs, medication administration record, ventilatory support, and respiratory mechanics. In addition, we used a variety of methods to maximize causal inference, such as excluding persons who had advance directives such that they were not at risk of the primary outcome, stabilized IPTW with doubly robust adjustment, and accounting for the competing risk of death where death was not the primary outcome. We also included several sensitivity analyses to examine how varying assumptions would modify our substantive findings and interpretation and updated the propensity score calculations for each sensitivity analyses.

Our findings raise several important questions for future research. More work is needed to understand how the use of chronic immunosuppressive drugs may affect the safety and efficacy of dexamethasone, given its ability to reduce short-term mortality among hospitalized individuals receiving respiratory support [7]. Also, it is unclear whether pre-existing duration of chronic immunosuppressive use may affect the associations of interest. In addition, it is unknown whether specific patient characteristics, such as age or other independent risk factors for more severe disease [25, 26], may modify the relationship between chronic immunosuppression and COVID-19 outcomes. Finally, as we note above, more research is needed to understand whether and how provider behavior and in-hospital treatment may contribute to the lack of independent harm that we observe from the use of chronic immunosuppressive therapies.

Conclusions

In this analysis of a large, diverse cohort of adults hospitalized with COVID-19 in the United States, we did not find differences in risk of mechanical ventilation, in-hospital mortality, or length of stay among individuals with and without chronic use of immunosuppressive medications. Our results contribute to a growing body of evidence that should provide reassurance to clinicians and patients using chronic immunosuppressive medicines [27, 28].

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Potential conflicts of interest. P. G. A. is a shareholder of Johnson & Johnson. G. C. A. previously served as Chair of the Food and Drug Administration's Peripheral and Central Nervous System Advisory Committee; has served as a paid advisor to IQVIA; and is a consultant and holds equity in Monument Analytics, a healthcare consultancy whose clients include the life sciences industry as well as plaintiffs in opioid litigation; and is a member of OptumRx's National P&T Committee. This arrangement has been reviewed and approved by Johns Hopkins University in accordance with its conflict of interest policies. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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