Predictors of hospitalization for COVID-19 in patients with autoimmune rheumatic diseases: results from a community cohort follow-up

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Abstract

Objective The identification of risk factors for COVID-19 adverse course in autoimmune rheumatic diseases (ARDs) is of the utmost importance when approaching patient management; however, data are scarce in relation to the Latin American population. The objective of this study was to determine predictors of hospitalization for COVID-19 patients from an ARD community cohort.

Methods A real setting longitudinal study (March to November 2020) in an ARD community cohort was carried out. Potential predictors of hospitalization for COVID-19 examined included (1) sociodemographic variables (age, gender, education, tobacco use, socioeconomic status, and co-inhabitants), (2) comorbidities, (3) time to COVID-19 diagnosis, and (4) ARD’s features: clinical (disease type, disease duration, activity), treatment [corticosteroids use/doses, use of synthetic DMARDs (cDMARDs, tsDMARDs, and bDMARDs)], treatment schedule and non-adherence, and the Multidimensional Health Assessment Questionnaire (MDHAQ). Univariable and multivariable regression analysis were conducted; OR and 95% CI (p < 0.05) were determined.

Results One thousand and one hundred forty-eight patients with ARDs were included; 154 had COVID-19; of these 139 (90.3%) were women, aged 52.5 (13.7) years; 33.1% had hypertension and 61.0% an affected organ by ARD. Infection was detected 8.4 (10.1) days after symptoms started; there were 33 hospitalized patients (rate 21.4%). Predictors of hospitalization by multivariable analysis were age (OR: 1.06; CI: 1.01–1.10; p: 0.01), comorbidities: hypertension (OR: 3.95; 95% CI: 1.40–10.95; p: 0.01) and neoplasm (OR: 9.0; 95% CI: 1.6–52.3; p: 0.01), number of organs involved by ARD (OR: 2.26; 95% CI: 1.16–4.41; p: 0.02), and infection diagnosis delay (OR: 1.36; 95% CI: 1.03–1.80; p: 0.01).

Conclusions In our ARD patients with COVID-19, older age, comorbidities (neoplasm and hypertension), and a delay in COVID-19 diagnosis were predictors of hospitalization. The only ARD-associated predictor feature was the number of organs involved.

Key Points

- Patients with ARD and COVID-19 have an adverse course in comparison to the general population.
- Previous predictors of COVID-19 hospitalization, including known risk factors (such as older age and comorbidities) and systemic manifestations, should be taken into account in the management of these patients.
- Delayed diagnosis of COVID-19 impacts negatively on prognosis.
- Availability of diagnostic tests is of utmost importance.

Keywords Autoimmune rheumatic disease · COVID-19 · COVID-19 adverse predictors · SARS-CoV-2
Introduction

The new coronavirus disease (COVID-19) may cause severe acute respiratory syndrome and was declared a pandemic by the World Health Organization (WHO) in March 2020; case zero was reported in our country around the same time. Currently, Perú is one of the most affected countries in the world with over 1,460,779 COVID-19 cases confirmed by March 20, 2021 [1], a health problem which has had a severe impact on the general population and especially in patients with autoimmune rheumatic disease (ARD). Risk factors for the development of an adverse COVID-19 course include older age, male gender, the presence of chronic comorbidities such as diabetes mellitus (DM), lung disease (LD), obesity, chronic renal failure (CRF), neoplasms, cardiovascular diseases (CVD), chronic liver disease (CLD), among others [2–6]; several of them have been already described in ARD patients; however, there is inconsistent data about the impact of ARD clinical features such as the type of disease, activity status, or immunosuppressive treatment on the course and outcome of this infection. Published data about ARD and COVID-19 at the time this study began were limited to case reviews and case series, most of them coming from either China or Europe; conclusions from these initial reports assumed little risk of an adverse course in ARD patients in whom this infection had occurred; however, these studies included a relatively small number of patients [7–13]. Analysis carried out later by the Global Rheumatology Alliance Registry (GRA), the largest database of patients with rheumatological diseases affected by COVID-19, described the clinical characteristics of patients with this infection [14]; higher rates of hospitalization and lethality and risk factors for hospitalization such as comorbidities (hypertension, LD, DM, and CRF), and corticosteroid use were found [15].

The COVID-19 pandemic has been and continues to be critical in Latin America and that includes patients with ARDs; analysis from GRA USA data showed a higher risk of hospitalization in patients with a Latin American background (OR: 1.71, 95% CI: 1.18–2.49) in comparison to whites, with a three-fold increased risk of ventilatory support (OR: 3.25, 95% CI 1.75, 6.05) [16]; such adverse disease course could be explained by several factors including geographic location, socioeconomic disparities [17], and the near collapse of the health system in some of the countries of the region with the consequent reduction of opportunities for receiving care in their corresponding centers; determining early adverse predictors of COVID-19 in the context of community care is of utmost importance. The objective of our study was to determine the predictors of hospitalization in a cohort of ARD patients from a single rheumatological center followed up over several months in the community; the starting point for this study was March 11, 2020 which is the date the Peruvian government declared our country’s health to be in a state of emergency.

Methods

A longitudinal study of an ARD cohort followed up at a single medical center (Hospital Nacional Guillermo Almenara Irigoyen-EsSalud), a component of the Peruvian Social Security System, was conducted between March and November 2020 during the COVID-19 health emergency in our country. The study had the approval of the Hospital Ethics Committee and informed consent was obtained from the patients before they were enrolled and followed up. All ARD patients 18 years of age and older with a confirmed diagnosis and a minimum of 3 months of follow-up at our institution prior to enrollment were included. ARD included the following diagnosis: rheumatoid arthritis (RA), seronegative spondyloarthritis including psoriatic arthropathy (PsA), systemic lupus erythematosus (SLE), systemic autoimmune vasculitis (SAV) including small, medium, and large vessels vasculitis, idiopathic inflammatory myopathies (polymyositis, dermatomyositis, and inclusion body myopathies, IIM), systemic sclerosis, Sjogren’s syndrome (SS), and other ARDs; in this category uncommon/infrequent rheumatologic diagnosis such as undifferentiated connective tissue diseases, overlapping syndromes, relapsing polychondritis, antiphospholipid syndrome, Bechet’s disease, IgG4 disease, polymyalgia rheumatica, and others were included. Patients without clinical or laboratory evidence of autoimmunity, even if an ARD diagnosis was noted on the medical records, were excluded. At the baseline visit the medical records were reviewed and sociodemographic and clinical data were obtained; the subjects were then followed up (Law 30,036, Supreme Decree No. 009–2015-TR) by a trained rheumatologist, by means of virtual or face-to-face visits; presential visits were performed depending on clinical status according to pre-defined investigators’ established criteria; in each visit, in addition to the assessment of clinical and treatment features, an electronic survey that included the study variables was administered, which also included symptoms of COVID-19 infection. The potential predictors of hospitalization considered were (1) sociodemographic: age, gender, education level, tobacco use, socioeconomic status (measured by the GRAFAR scale) [18], and the number of home co-inhabitants (shared common space); (2) pre-existing comorbidities: LD, hypertension, DM, cerebrovascular disease (CD), CVD such as valvular heart disease and cardiac arrhythmias [additionally, congestive heart failure (CHF) was collected as an
independent variable], neoplasm, hypothyroidism, dyslipidemia, CRF including end stage renal disease, CLD, body mass index (BMI), and obesity (BMI of 30 or more kg/m²); (3) COVID-19 diagnostic delay defined as the number of days between the onset of symptoms and the diagnosis made by a physician; and (4) ARD’s clinical and treatment features including (a) disease features: disease type, disease duration, and disease activity status defined by the Clinical Disease Activity Index (CDAI) and the Routine Assessment of Patient Index Data 3 (RAPID-3) for RA, the SLE Disease Activity Index (SLEDAI), the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) for axial spondyloarthritis, and the Birmingham Vasculitis Activity Score version 3 (BVAS-v3) for SAV; for the rest of ARD disease activity status was defined by the investigator based on the number of organs involved, (b) treatment features such as (b.1) treatment non-adherence, (b.2) use and dose of corticosteroids (as a prednisone dose equivalence), (b.3) disease-modifying antirheumatic drugs (DMARDs): synthetic DMARDs [conventional (cDMARDs) and targeted synthetic (tsDMARDs)], biological (bDMARDs), and antimalarials, and (b.4) treatment schedule (mono or combined therapy), and (c) functional capacity assessed with the Multidimensional Health Assessment Questionnaire (MDHAQ). The cDMARDs considered were methotrexate, leflunomide, azathioprine, sulfasalazine, cyclosporine, mycophenolate mofetil, tacrolimus, cyclophosphamide, D penicillamine, and antimalarials. The bDMARDs included were antitumor necrosis factor (anti-TNF), rituximab, abatacept and within the tsDMARDs, tofacitinib and baricitinib. Use of these drugs was considered if the patients had received the drug for at least 3 months before the baseline visit; in addition, adherence to treatment was assessed at each follow-up visit using an open-ended question.

Clinical COVID-19 was defined if the subject had known associated symptoms (fever, headache, cough, sore throat, chest pain, odynophagia, respiratory distress, anosmia, dysgeusia, myalgia, or other reported), had compatible images on computerized tomography (CT) of the chest, and/or a positive epidemiological history (contact with a known subject infected by COVID-19); a confirmatory test (molecular and/or serological) was required. Incident cases were recorded at each visit; new COVID-19 cases were reported during the virtual visits using a platform developed during the emergency/contingency period.

The total incidence of COVID-19 infections was calculated dividing the number of new cases by the total number of patients in the cohort during the study period. In the same manner specific incidence by pathology was calculated dividing the number of new cases by the total number of patients for each ARD. COVID-19 cases were followed up to determine their clinical outcome (recovery, hospitalization, or death). In addition, lethality (number of deaths between total number of infected patients per 100) and mortality (number of deaths for the total number of patients in the cohort per 1000) rates were calculated.

Statistical analysis

Data for the continuous variables are described as means and standard deviations (SD), and for categorical variables as numbers and percentages. In order to evaluate the predictors of hospitalization, univariable and then multivariable binary logistic regression models were performed; variables with a p-value < 0.1 were entered into this model using a backward selection method; the alpha to stay in the model was set at 0.05. Results are reported as OR and their 95% confidence interval (CI). All statistical analyses were performed using SPSS v. 28.0 (IBM, Chicago, IL).

Results

A total of 1148 patients with ARD were followed up from March to November 2020; 154 of them developed COVID-19 with an incidence of 13.4%. The ARDs with the highest number of incident cases were SAV (17.8%), followed by RA (14.7%) and SLE (13.1%).

The mean age of the 154 patients afflicted by COVID-19 was 52.5 (13.7) years; the great majority of whom were women (139, 90.3%). There were no differences between patients who developed COVID-19 and the rest of the cohort in terms of age [54.8 (13.39) vs 52.5 (13.7) years; p = 0.23). The major-
was confirmed in the majority of the cases by a serological test (86.3%). The mean (SD) delay in the diagnosis of the infection was 8.4 (10.1) days. Table 3 shows the clinical characteristics of COVID-19 infection in our ARD patients. There were thirty-three hospitalized (21.4%) of 154 COVID-19 infected patients being the mean (SD) number of days of hospitalization 5.5 (8.1). Laboratory tests at admission demonstrated a high level of ferritin [1762.02 (2332.9) ng/L; cutoff: 5–148 in women and 28–365 in men], C-reactive protein [108.48 (90.27) IU/mL; cutoff: 5–10 IU/ml],
aspartate aminotransferase [223.18 (28.77) IU/L; cutoff: 10–49 IU/L], and alanine aminotransferase [225.82 (31.83) IU/L; cutoff: 10–34 IU/L]. The white cell count was 11.2 (46.3) \times 10^3/\mu L, lymphocyte 0.2 (0.3) \times 10^3/\mu L, and platelet level 201.28 (81.072) \times 10^3/\mu L; cutoff: 150–500 \times 10^3/\mu L. The mean D-dimer was 1.73 (1.29) \mu g/mL; cutoff < 0.40 \mu g/mL and fibrinogen 4.45 (0.68) g/L; cutoff 2–4.2 g/L. Twelve patients died, being the lethality rate 7.8% and the mortality rate 10.45 per 1000.

Predictors of hospitalization in univariable analysis were age (OR: 1.04; 95% CI: 1.00–1.08; p: 0.03), the number of cohabitants in the household (OR: 0.76; 95% CI: 0.61–0.95; p: 0.02), the presence and number of comorbidities (OR: 3.37; 95% CI: 1.26–9.01; p: 0.02 and OR: 7.28 95% CI: 1.16–4.41; p: 0.02), neoplasms (OR: 7.96; 95% CI: 3.21–20.6; p: 0.01), hypertension (OR: 3.77; 95% CI: 1.56–9.09; p: 0.01), and LD (OR: 2.94; 95% CI: 1.16–7.46; p: 0.02); clinical and treatment features of ARD associated with hospitalization were the presence of systemic involvement (OR: 3.03; 95% CI: 1.28–7.22; p: 0.01), the number of organs involved (OR: 2.17; 95% CI = 1.28–3.63; p: 0.00), the diagnosis of systemic autoimmune vasculitis (OR: 7.33; 95% CI: 1.42–37.87; p: 0.02), the use of corticosteroids (as prednisone) (OR: 1.13; 95% CI: 1.03–1.25; p: 0.02), and medium/high dose of this drug (OR: 4.08; 95% CI: 1.04–16.03; p: 0.04). Delay in the diagnosis of the infection was also a predictor (OR: 1.31; 95% CI: 1.05–1.63; p: 0.02). Variables significant in the multivariable analyses were age (OR: 1.06; 95% CI: 1.01–1.10; p: 0.01), comorbidities including neoplasms (OR: 9.06; 95% CI: 1.57–52.25; p: 0.01) and hypertension (OR: 3.95; 95% CI: 1.40–10.95, p: 0.01), the number of organs involved by the ARD (OR: 2.26; 95% CI: 1.16–4.41; p: 0.02), and the diagnostic delay of the infection (OR: 1.36; 95% CI: 1.03–1.80; p: 0.01). These data are depicted in Table 4.

Due to the non-homogeneous clinical manifestations of ARD disease, further analyses were performed considering three ARD’s subsets: (1) inflammatory joint diseases (RA and spondyloarthritis including PsA), (2) systemic connective tissue disease (SLE, inflammatory myopathies, and systemic sclerosis), and (3) a group including systemic vasculitis and other autoimmune conditions. In these analyses, we did not find differences in the rates of hospitalization or lethality (data not shown).

**Discussion**

In this longitudinal real-setting study of an ARD cohort followed up during several months, we have identified previously reported predictors of hospitalization in COVID-19, but, most importantly, we have identified factors associated with ARDs per se and a critical variable in terms of health community care: the delay in the diagnosis of this infection. To our knowledge, these data have not yet emanated from our region and up until now there is contradictory and scarce information from other parts of the world.

We found a higher incidence rate of COVID-19 infection with respect to our general population (the incidence of COVID-19 in Perú was about 4.1% for the period of this study) [19]; divergent data about this issue has been reported. Similarly to ours, a study from Spain found a cumulative incidence rate of 1.21%; 95% CI: 0.42–1.99% in ARD vs 0.58; 95% CI: 0.56–0.60 in the general population; although confirmatory tests were performed on both, symptomatic and asymptomatic ARD subjects that was not the case for the general population which could have led to an increase in the rate of infection in the first group [20]. In a study from the USA, a higher incidence of COVID-19 infections in ARD patients of Latin origin (17.97%) was found with respect to those of non-Latin origin (4.69 to 5.89%); the non-ARD Latin patients also had a higher infection rate than the non-Latin ones (1.54 to 3.43%) patients [21]. By contrast, in a study from China, a higher incidence of COVID-19 in the general population as compared to ARD patients (0.0142 vs 0.0126%) [22] was found. Finally, a systematic review and meta-analysis...
Table 4 Predictors of hospitalization in 154 patients with ARD and COVID-19 infection, univariable and multivariable analysis*

|                                      | Univariable analysis |          | Multivariable analysis |          |
|--------------------------------------|----------------------|----------|------------------------|----------|
|                                      | OR                   | p value  | OR                     | p value  |
| **Sociodemographic variables**       |                      |          |                        |          |
| Male gender                          | 0.78 (0.16–3.80)     | 0.76     |                        |          |
| Age                                  | 1.04 (1–1.08)        | 0.03     | 1.06 (1.01–1.10)       | 0.009    |
| >65 years                            | 2.61 (0.97–7.02)     | 0.06     |                        |          |
| Education level                      | 1.00 (0.89–1.31)     | 0.94     |                        |          |
| **Socioeconomic status (GRAFAR)**    |                      |          |                        |          |
| High/medium high                     | Ref.                 |          |                        |          |
| Medium                               | 4.50 (0.47–42.97)    | 0.19     |                        |          |
| Medium low/low                       | 2.01 (0.24–16.84)    | 0.52     |                        |          |
| Cohabitants                          | 0.76 (0.61–0.95)     | 0.02     |                        |          |
| Tobacco use                          |                      |          |                        |          |
| Never                                | Ref.                 |          |                        |          |
| Current                              | 0.76 (0.08–6.80)     | 0.81     |                        |          |
| Past                                 | 0.63 (0.13–3.01)     | 0.57     |                        |          |
| **Preexisting comorbidities**        |                      |          |                        |          |
| Body mass index                      | 0.98 (0.90–1.07)     | 0.71     |                        |          |
| Obesity                              | 0.71 (0.26–1.93)     | 0.50     |                        |          |
| Neoplasm                             | 7.96 (1.77–35.77)    | 0.01     | 9.06 (1.57–52.25)      | 0.01     |
| Dyslipidemia                         | 1.22 (0.41–3.66)     | 0.73     |                        |          |
| Diabetes mellitus                    | 1.23 (0.31–4.79)     | 0.77     |                        |          |
| Hypertension                         | 3.77 (1.56–9.09)     | 0.00     | 3.95 (1.40–10.95)      | 0.01     |
| Chronic lung disease                 | 2.94 (1.16–7.46)     | 0.02     |                        |          |
| Interstitial lung disease            | 1.91 (0.66–5.58)     | 0.23     |                        |          |
| Cerebrovascular disease              | 4.24 (0.57–31.58)    | 0.16     |                        |          |
| Cardiac disease                      | 1.00 (0.11–9.33)     | 1.00     |                        |          |
| Congestive heart failure             | 1.34 (0.13–13.47)    | 0.80     |                        |          |
| Chronic liver disease                | 0.59 (0.12–2.76)     | 0.49     |                        |          |
| Hypothyroidism                       | 1.27 (0.38–4.26)     | 0.69     |                        |          |
| Chronic renal failure                | 1.80 (0.43–7.49)     | 0.42     |                        |          |
| Presence of comorbidities            | 3.37 (1.26–9.01)     | 0.02     |                        |          |
| One comorbidity                      | 1.63 (0.51–5.22)     | 0.41     |                        |          |
| Two or more comorbidities            | 7.28 (2.42–21.89)    | <0.01    |                        |          |
| **Clinical features of ARD**         |                      |          |                        |          |
| Disease type                         |                      |          |                        |          |
| Rheumatoid arthritis                 | Ref.                 |          |                        |          |
| Systemic lupus erythematosus         | 1.52 (0.54–4.26)     | 0.43     |                        |          |
| Systemic autoimmune vasculitis       | 7.33 (1.42–37.87)    | 0.02     |                        |          |
| Inflammatory myopathy                | 5.50 (0.69–43.69)    | 1.11     |                        |          |
| Systemic sclerosis                   | 1.83 (1.17–19.44)    | 0.61     |                        |          |
| Seronegative spondyloarthropathy     | NE                   |          |                        |          |
| Other ARD                            | 1.10 (0.21–2.79)     | 0.91     |                        |          |
| ARD disease duration                 | 1.00 (0.97–1.04)     | 0.81     |                        |          |
| Active status                        | 1.98 (0.74–5.32)     | 0.18     |                        |          |
| Organ involvement                    |                      |          |                        |          |
| Presence                             | 3.03 (1.28–7.22)     | 0.01     |                        |          |
| Number                               | 2.17 (1.28–3.63)     | 0.01     | 2.26 (1.16–4.41)       | 0.02     |
| Disability (MDHAQ)                   | 0.75 (0.36–1.57)     | 0.44     |                        |          |
| **Treatment features of ARD**        |                      |          |                        |          |
| Corticosteroids use**                | 1.13 (1.03–1.25)     | 0.01     |                        |          |
of 26 observational studies showed that patients with ARD had an increased risk of developing COVID-19 compared with the general population [23]. In addition, although the possible role of ethnicity per se cannot be discarded, our higher rates could be explained by the fact that we identified cases over a longer period of time and we also included patients from the community many of whom had a mild COVID-19 disease [24].

Our data provide indirect evidence of an adverse COVID-19 course in ARD patients with respect to the general Peruvian population, in terms of hospitalization and lethality rates reported during the same time period [19]; although these rates are variable in different studies around the world, two well designed studies indicate an adverse COVID-19 course in ARD patients. The first is the GRA registry in which higher rates in comparison with the data we are now reporting were found [15]; the differences between our study and the data from GRA could be related to the data collection methods (from each health service center in GRA and from the community in our study). The second study is a recent meta-analysis of 1138 patients from 38 studies; even higher hospitalization and lethality rates (58% and 7%, respectively) were found [25]; however, no Latin American centers were included in these analyses. The design of our study did not permit us, however, to do the same analysis for lethality due to the relatively small sample size.

Divergent results about the impact of ARD’s treatment features in adverse COVID-19 courses exist in terms of hospitalization [15, 30, 36, 40, 41], lethality [40, 42, 43], and intensive care unit admissions [33, 44]; the majority of these studies have explored the role of bDMARDs and tsDMARDs and have shown evidence that monotherapy (b/DMARDs or tsDMARDs) could be protective against adverse course [15, 45]. We have not been able to demonstrate that any treatment type or schedule confer a deleterious or protective risk for the course of COVID-19; however, our cohort had a small...
number of patients on bDMARDs and tsDMARDs which could have impacted on our results. Regarding antimalari-
als, we did not find any protective effect and no conclusive
data are currently available [28, 30, 31, 45, 46]; we did not
identify corticosteroids use or doses as a risk factor for hos-
pitalization (doses higher than 5 [32, 34] or 10 mg/day [15]
were have been reported previously); however, these differences
could be explained by the low doses of corticosteroid use in
the majority of our patients (and none on a high doses). The
low number of each ARD type did not permit us to examine
the impact of the treatment on each subset of disease.

An important result in our study relates to community health care: a longer time to confirm COVID-19 diagnosis
after initial symptoms (a mean of 8 days, considered late)
was found to be a predictor of hospitalization. The COVID-
19 pandemic has had a serious impact on the health care
system around the world, with middle/low-income countries
experiencing worse impact. No studies about this delay in
COVID-19 diagnosis have been described before in ARDs
and even in the general population there is a scarcity of data.
A systematic review which examined predictors of hospital-
azation for COVID-19 in ARD patients found few studies
exploring this variable [47] and the data currently available
are still controversial [48–50]; however, this variable could
be critical in terms of mortality if the health system col-
lapses or is near collapse; for example, a low level of oxygen
saturation at admission has been found to be associated with
mortality in a recent Peruvian study; once again a delay in
hospitalization of about 8 days since initial symptoms was
observed in that study [51]. We considered our results to be
of the utmost importance in the care of patients with ARDs
in the community.

Our study has some limitations, the most important being
the potential underreporting of cases due to the confirm-
antory serologic method being used instead of molecular tests,
due to their relative inaccessibility and cost in our country;
the same situation relates to the opportunity for hospitali-
azation (patients with moderate/severe forms of infection
could not have been admitted and thus, are not recorded);
and the requirement for intensive care admissions. Given
that COVID-19 disease was defined by a confirmatory test
or images, it is likely that mild forms with negative sero-
logical tests (especially during the initial days of the pan-
demic), no molecular tests and without imaging evidence,
may have not been properly recorded. We have, nevertheless,
the advantage of collecting potential clinical parameters pre-
dictors adequately before the event and over a long follow-up
period. On the other hand, our center forms part of a social
security health care system with a regularity in visits, access
to health services, and baseline features fully corroborated
by an electronic medical record. Also, the remote follow-up
model with electronic questionnaire surveys in each visit
and the virtual platform created guarantees the collection of
most incident cases.

In conclusion, we were able to identify previously
described predictive factors of hospitalization in patients
with ARD and COVID-19, such as age and comorbidities
including a predictor related to the clinical features of the
ARD (the number of organs involved). Of greater interest in
community medical care, we have identified delay in diagno-
asis of COVID-19 infection as a predictor of adverse course.
The profile of this type of ARD patient must be considered
for an opportunite management in the context of the COVID-
19 pandemic.

Declarations
Disclosures None.

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