Immunosuppression is associated with a lower risk of moderate to severe acute respiratory distress syndrome in COVID-19.

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Abstract

BACKGROUND: Coronavirus disease 2019 (COVID-19) is an emerging infectious disease that has spread rapidly worldwide. The role of immunosuppression among COVID-19 patients has not been elucidated and management may be challenging.

OBJECTIVE: To assess differences in severe outcomes of hospitalized patients with COVID-19 according to immune system state.

DESIGN: Retrospective single-center observational study with confirmed COVID-19 patients admitted to Hospital Universitario Ramón y Cajal from March 18, 2020 to April 04, 2020. The final date of follow-up was April 09, 2020.

PARTICIPANTS: Confirmed COVID-19 patients.

MAIN MEASURES: The primary endpoint was development of moderate-severe acute respiratory distress syndrome (ARDS). Time to moderate-severe ARDS, the need for mechanical or non-invasive ventilation (MV/NIV), death, and a composite of death or MV/NIV were secondary endpoints.

KEY RESULTS: Of 138 patients included, 29 (21%) were immunocompromised (IC), with 95 (68.8%) male patients and a median (IQR) age of 68 (54 – 78) years. Among the baseline characteristics, no relevant or significant differences were observed between IC and non-immunocompromised (non-IC) patients. A significantly lower proportion of IC patients (24.1% [95% CI, 11.4 – 44.0%]) compared to non-IC patients (49.5% [95% CI, 40.1 – 59.0%]) developed moderate-severe ARDS, in both unadjusted (OR 0.32 [95% CI, 0.13 – 0.82], p=0.018) and adjusted (aOR 0.16 [95% CI, 0.05 – 0.52], p=0.003) analyses. A positive non-significant trend toward a longer time to moderate or severe ARDS, a lower need for MV/NIV, and a lower risk of death or MV/NIV were detected in IC. A trend toward a shorter- hospitalization in IC was observed.

CONCLUSIONS: In our cohort of COVID-19 patients, immunosuppression was associated with a lower risk of moderate-severe ARDS. This suggests a potential protective effect from a hypothesized host hyper-inflammatory response and warrants reconsideration of drug discontinuation in IC patients.

Background

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), known to cause Coronavirus disease 2019 (COVID-19), was first reported in Wuhan, China[1] and has rapidly spread worldwide.

The most common symptoms at COVID-19 onset are fever, dry cough, and myalgia/fatigue. The first published data from China indicated that nearly one-third of patients may subsequently develop acute respiratory distress syndrome (ARDS), which results in a higher likelihood of needing mechanical ventilation (MV) and of death[2]. Older age and the presence of comorbidities have been associated with a higher risk of ARDS, and with progression from ARDS to death[3].

Patients with an immunosuppression were initially thought to be at an increased risk of severe COVID-19. However, preliminary data suggest a three-stage SARS-CoV-2 infection, with two distinct but overlapping subsets[4]: the first triggered by the virus itself and the second consisting of a deregulated and excessive host immune response, which appears to be the main driver of lung tissue damage[5]. Therefore, we hypothesize that a weaker immune response to the virus might prevent immunosuppressed patients from developing a severe disease.

We aimed was to evaluate differences in the inflammatory response during COVID-19 between immunocompromised (IC) and non-immunocompromised (non-IC) patients by assessing the risk of ARDS, the need for mechanical (MV) or non-invasive ventilation (NIV), death and the length of hospitalization.

Methods

Study design

This single-center, retrospective, observational study was performed at Hospital Universitario Ramón y Cajal, Madrid, a tertiary hospital in the region with the highest incidence of cases of the pandemic of COVID-19 in Spain[6]. Due to the emergency outbreak, the hospital was completely restructured and nearly all the specialists of the Neurology department were assigned to attend COVID-19 patients. A multidisciplinary group of Internal Medicine, Infectious Diseases, and Neumology experts elaborated on clinical guidelines, which were strictly followed by all the physicians treating COVID-19 patients. A specialist in one of the three specialties supervised the clinical activity of each group to ensure excellence and adherence to guidelines in routine care. All adult inpatients with confirmed or highly suspected SARS-CoV-2 infection from March 18, 2020 to April 4, 2020 were consecutively enrolled (Figure 1). For the analysis, only those with a laboratory-confirmed infection and a minimum of baseline and outcome variables available (detailed below) were included. According to the WHO guidance[7], confirmation of SARS-CoV-2 was defined as a positive result of real-time reverse transcriptase–polymerase chain reaction (RT-PCR) assay of nasal and pharyngeal swabs. The RT-PCR assay was performed by expert microbiologists from the same center. The patients were followed- up with until April 9, 2020.

This study was approved by the institutional ethics board of Hospital Universitario Ramón y Cajal. Due to the nature of the retrospective chart review, the need for informed consent from individual patients was waived.

Data collection

The electronic medical records of the participants were reviewed by a trained team of physicians from Hospital Universitario Ramón y Cajal during the epidemic period, after selection based on the eligibility criteria. Baseline characteristics included were: demographics, medical history, comorbidities, laboratory examinations, radiological findings, and clinical and respiratory variables. Additionally, we included such variables as bacterial co-infection and treatments administered. Immunocompromised patients were

defined as those with an inherited or acquired immunodeficiency or taking any drug with an immunomodulatory or immunosuppressive effect (see Supplement Material for a complete description of all IC patients).

The primary endpoint was the development of moderate or severe acute respiratory distress syndrome (ARDS), defined according to the Berlin Definition[8]. Secondary endpoints were percentages of death among those with a final outcome, need for mechanical (MV) or non-invasive ventilation (NIV), a composite of need of MV/NIV or death, length of hospitalization to April 9, 2020, and time to moderate-severe ARDS between the cohorts.

Statistical analysis

Continuous variables were described using means and standard deviations or medians and quartiles depending on whether or not data were normally distributed. The Shapiro-Wilk test was used to test the normality of data distributions. Categorical variables were described using absolute and relative frequencies. The Fisher test was used to analyze categorical variables and the Mann-Whitney U test was used for quantitative variables. Logistic regression models were conducted to study the association between primary and secondary endpoints and immunosuppression; in the case of the length of hospitalization, we used linear regression instead. We performed both unadjusted (crude) and multivariate (adjusted) models, taking into account potential confounding factors (sex, age, and time from onset of symptoms to event or end of follow-up). As a secondary analysis, we performed Kaplan-Meier survival curves of time to moderate or severe ARDS with a log-rank test adjusted by immunosuppression status. A bivariate adjusted Cox proportional-hazards model was used to determine HR and 95% CIs on the development of the primary endpoint between both groups. All data analyses were conducted using R (R Core Team (2017), Version 3.6.3., R Foundation for Statistical Computing, Vienna, Austria). Statistical hypotheses were tested using $p<0.05$ as the level of significance.

Results

From March 18, 2020 to April 4, 2020, 157 patients with highly suspected or confirmed COVID-19 were admitted and attended to by the treating physicians and were therefore selected for this study. After the exclusion of those who did not fulfill the eligibility criteria (17 patients due to a negative test result for SARS-CoV-2 and 2 patients due to insufficient data), 138 patients were included in the analysis. From the final cohort, 21% (n=29) of patients were IC and 79% (n=109) were non-IC. Among the IC patients, 55.2% (n=16) were diagnosed with an autoimmune disease (AD) and 44.8% (n=13) were diagnosed with other diseases (Figure 1). Additional information about the IC patients is provided in the Supplement Material. Table outlines the demographic, clinical and laboratory baseline characteristics of all patients and both groups. Overall, 68.8% (95 of 138 patients) were male and the median (IQR) age was 68 (54 – 78) years, distributed similarly among both cohorts. No statistically significant differences were observed between IC and non-IC in terms of comorbidities, excepting for subsidiary diseases of immunosuppression such as AD (55.2% vs. 2.8%, $p<0.001$), active malignancy (13.8% vs. 7.3%, $p=0.017$), and organ transplant

(17.2% vs. 0%, p<0.001). The median (IQR) time from onset of symptoms to admission was 7 (4 – 11) days and a similar respiratory situation was observed between both groups, with a median (IQR) SatO2 of 93% (88 – 96%) on room air, PaO2 (available in 94 patients, done mainly to those with a low SatO2) of 57 (51 – 66) mmHg, and a PaO2/FiO2 (n=94) of 267 (233 – 310) mmHg. Bilateral pneumonia was the most frequent radiological finding (72.4% vs. 84.4% in IC vs. non-IC, respectively, p=0.25), with a median (IQR) CURB-65 score of 1 (1 – 2) and 2 (1 – 2) (p=0.51), respectively. Laboratory examinations were practically identical, with a mild lymphopenia (median [IQR] 855 [620 – 1210] cells/µL) and a high D-dimer (n=110, median [IQR] 794.5 [535 – 1447] µg/L), except for a trend (p=0.096) toward a higher C-reactive protein among non-IC (median [IQR] of 119.1 [56.7 – 186.1]) compared to IC (74.5 [33.7 – 144.9] mg/L). Bacterial co-infection was infrequent in the overall population (14.5%) and the most frequently used treatments were hydroxychloroquine (98.6%) and lopinavir/ritonavir (72.4% vs. 88.1% [p=0.046] in IC and non-IC, respectively). Corticosteroids (48.3 vs. 65.1%) and the monoclonal antibodies Tocilizumab (3.5 vs. 13.8%) and Anakinra (0 vs. 2.8%) were more widely used during hospitalization in non-IC, although the differences were not statistically significant. Among treatment-induced IC patients, the immunosuppressive drug was discontinued at admission in 6 of 26 patients (23.1%).

Comparison of complications during hospitalization

The primary endpoint (development of moderate or severe ARDS) was significantly lower for IC patients (24.1% [95% CI, 11.4 to 44.0%]) compared to non-IC patients (49.5% [95% CI, 40.1 to 59.0%]), with a crude OR of 0.32 (95% CI, 0.13 to 0.82) (p=0.018). After adjusting by sex, age, and time from onset of symptoms to event or end of follow-up, the adjusted OR (aOR) showed a stronger protective effect for IC (aOR 0.16 [95% CI, 0.05 to 0.52]) (p=0.003). The logistic regression model was therefore replicated, stratifying by AD among IC patients, and similar results were observed for IC-AD (aOR 0.13 [95% CI, 0.03 to 0.61], p=0.011) compared to IC-NAD (aOR 0.17 [95% CI, 0.03 to 0.91], p=0.038). An adjusted Cox regression was subsequently conducted, finding a non-significant trend toward a shorter time to moderate-severe ARDS in non-IC (mean [SD] 9.77 [±4.33] days) compared to IC (mean [SD] 9.5 [±5.39] days) (aHR 0.47 [95% CI, 0.21 to 1.04], p=0.064), despite a significant difference in the log-rank test (p=0.044) (Figure 3).

Although a favorable trend was observed for IC patients, no statistically significant differences were observed in risk of need for MV/NIV (3.4% vs. 11.9%, aOR 0.14 [95% CI, 0.02 to 1.29], p=0.083) or in risk of a composite of need for MV/NIV or death (10.3% vs. 17.4%, aOR 0.24 [95% CI, 0.05 to 1.14], p=0.072) in IC compared to non-IC, respectively. A final outcome (death/discharge) was recorded in 79 patients (57.2%), with an overall mortality of 19% (95% CI, 11.65 to 29.4%). A comparison of both groups detected no significant differences between IC (21.4%) and non-IC (18.5%), with an adjusted OR of 0.88 (95% CI, 0.17 to 4.46) (p=0.87) (Figure 2). The median (IQR) stay was 9 (5 – 12) days for the overall population, with a trend toward a lower stay (β= -2.36 [95% CI, -4.87 to 0.11] days, p=0.065) for IC after adjusting by age and time from onset of symptoms to admission.

Discussion

In this retrospective, single-center, observational study with inpatients with COVID-19 in Madrid, Spain, a better outcome, in terms of lower risk to moderate or severe ARDS, was observed among IC as compared to non-IC. A trend, albeit non-significant, toward a longer time to moderate-severe ARDS, a lower need for MV/NIV, and shorter hospitalization was also detected. A comparison of both groups observed no differences were observed in the death ratio.

Immunosuppression has been widely considered a risk factor for infections, with a higher incidence and a worse outcome, including those caused by a respiratory virus[9]. For example, influenza infection was observed to be associated with a higher risk of more hospitalizations, a longer length of virus shedding, a more severe disease, and complications requiring intensive care and MV[10]. Additionally, several studies consider immunosuppression to be a risk factor of a more severe disease in MERS-CoV infection[11-14]. Previous works have already described risk factors predicting a worse outcome in COVID-19 patients, such as older age[3, 15-17], comorbidities (hypertension, diabetes, or vascular diseases)[3, 15, 17], -and laboratory findings, with special attention paid to those indicating hyperinflammation or cytokine storm syndrome[18, 19], like elevated serum D-dimer, ferritin, C-reactive protein, or interleukin (IL)-6 levels[3, 15-17]. Nevertheless, none of these works has specifically assessed immunosuppression as a risk factor in COVID-19 patients. A recent population-based study in China evaluated cancer patients with recent surgery or chemotherapy, and found a higher risk of severe events[20], while newly released data detected a 3.7x lower risk of intensive care unit (ICU) admission among IC patients compared to viral pneumonia[21]. In our study, a lower proportion of IC patients developing moderate or severe ARDS was observed, with a trend toward a longer time to event. We decided to assess this variable as a primary endpoint due to its higher specificity in detecting more inflammatory patients. To delve into a possible pathology or drug explaining these results, we further differentiated IC patients between those with an AD and those with other diseases (such as cancer or an organ transplant). However, both cohorts showed similar results, suggesting the immunocompromised state itself confers the protective effect. In line with this result, a trend toward a lower risk of MV/NIV, a composite of the need for MV/NIV or death, and a shorter length of hospitalization were also detected, probably due to the lower risk of ARDS.

This data might be explained by pathophysiological findings, such as the three-stage classification model of SARS-CoV-2 infection proposed by Siddiqi et al.[4], with two distinct but overlapping subsets. The first triggered by the virus itself and the second, occurring in a minority of patients, host-mediated and based on an excessive immune response, leading to ARDS, the need for MV, and, potentially death[3, 16-18]. Pathophysiology similar to that of SARS-CoV has been hypothesized for SARS-CoV-2 infection[22], in which a marked elevation of cytokines of the Th1 cell-mediated immunity (such as interferon (IFN)-g, IL-1, IL-6, and IL-12) and hyperinnate (neutrophil chemokine IL-8, monocyte chemoattractant protein-1 (MCP-1), and Th1 chemokine IFNg-inducible protein-10 [IP-10]) inflammatory response[23] have been observed. For this reason, several immunomodulatory drugs, such as corticosteroids, intravenous immune globulin, and cytokine inhibitors, have been proposed depending on whether the hyperinflammation stage is suspected[18, 19, 22]. Preliminary data suggest a potential benefit of methylprednisolone in terms of the risk

of death after the development of ARDS[3], though clinical trials are required before recommending this therapy. All these results support, in line with other authors' opinions[5] and recent data[21], the notion that immunosuppression might confer a protective effect in the most severe stages of the disease.

No differences in death rate were observed in our cohort. The reasons for these results might be explained by the smaller sample size of patients with a final outcome, the short follow-up, or unknown confounding factors. For example, during cytokine storm syndrome, ARDS is not the single inflammatory complication observed, as evidence of multi-organ dysfunction, with acute cardiac injury[24] and liver and renal impairment[3, 16, 17, 25] , has been described. This might be attributable to the widespread distribution of angiotensin converting enzyme 2 —the functional receptor for SARS-CoV-2— in multiple organs[26]. In addition, the results may be biased by the fact that IC patients might never get to mechanical ventilation, being considered too frail or disabled, so they are more likely to die than non-IC patients. Also, several factors related to the development of ARDS that were not associated with death have been described[3], which indicates that different pathophysiological changes –from hospital admission to the development of ARDS and from the development of ARDS to death- may exist.

Thus, our results might have relevance in terms of establishing recommendations for physicians treating IC patients. Discontinuation of immunosuppressive drugs may have implications with respect to diminishing the underlying disease control, with potential fatal outcomes in either cancer or organ transplant patients or the reactivation[27] or even rebound[28] of disease activity among autoimmune disorders. Taking into account this data, careful individual decision-making about maintaining immunosuppressive drugs in COVID-19 patients must be performed. Second, less aggressive anti-inflammatory management among IC patients might be contemplated, lowering the risk of bacterial co-infections. Third, social and preventive care recommendations might be reconsidered for these patients.

This study has several limitations. First, a potential selection bias might have occurred, as only hospitalized (outside of ICU) patients were evaluated and IC might be admitted more easily by its own condition than non-IC. To diminish this bias, all consecutive admitted patients were selected. Second, this study was conducted at a single center with a limited sample size. Third, due to the lack of evidence-based treatment protocols, the treating physicians took different management approaches (especially with anti-viral drugs or corticosteroids), which could have altered the development of the outcomes. Fourth, the retrospective character of the study and the short follow-up time warrant caution in interpreting the data. Further studies with a prospective design and a larger sample size, including outpatients, might gain a better understanding of the role that immunosuppression plays among COVID-19 patients.

In conclusion, in our cohort immunosuppression was associated with a lower risk of moderate or severe ARDS, a trend toward a reduced need for MV/NIV, a shorter hospitalization and a longer time before moderate or severe ARDS occurs. We found the mortality rate was not increased in IC patients. This reinforces that there is a potential protective effect of immunosuppression against a possible hyperinflammation host response observed in SARS-CoV-2 infection and warrants reconsideration of the

decision to discontinue immunosuppressive drugs in patients with severe underlying diseases and the management of these diseases during infection.

Declarations

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Contributors:

Drs Monreal and Sainz de la Maza had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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CONFLICT OF INTERESTS

The authors report no conflict of interests.

DATA AVAILABILITY

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Table

Demographic, clinical and laboratory characteristics at admission				
	Total (n=138)	Immunocompromised (n=29)	Non-immunocompromised (n=109)	p Value
Age (years), median (IQR)	68 (54 – 78)	67 (48 – 80)	68 (56 – 76)	0.87
Men, No. (%)	95 (68.8%)	19 (65.5%)	76 (69.7%)	0.66
Comorbidities, No. (%)				
None	28 (20.3%)	0	28 (25.7%)	**0.001**
Hypertension	70 (50.7%)	18 (62.1%)	52 (47.7%)	0.21
Diabetes type 2	36 (26.1%)	4 (17.8)	31 (28.4%)	0.15
Obesity (BMI ≥30)	39 (28.3%)	6 (20.7%)	33 (30.3%)	0.36
Cardiovascular disease*	33 (23.9%)	8 (27.6%)	25 (22.9%)	0.63
Chronic renal disease	18 (13.0%)	7 (24.1%)	11 (10.1%)	0.06
Chronic liver disease	9 (6.5%)	3 (10.3%)	6 (5.5%)	0.40
Chronic respiratory disease†	32 (23.2%)	5 (17.2%)	27 (24.8%)	0.47
Autoimmune disease	19 (13.8%)	16 (55.2%)	3 (2.8%)	**<0.001**
Active malignancy	15 (10.9%)	7 (24.1%)	8 (7.3%)	**0.017**
Malignancy in remission	12 (8.7%)	4 (13.8%)	8 (7.3%)	0.27
Organ transplant	5 (3.6%)	5 (17.2%)	0	**<0.001**
Time from symptoms onset to admission (days), median (IQR)	7 (4 – 11)	6 (4 – 11)	7 (5 – 11)	0.45
Respiratory parameters				
SatO2 (%), median (IQR)	93 (88 – 96)	95 (92 – 97)	92 (87 – 96)	0.07
PaO2 (mm Hg), No. with data	94	15	78	
Median (IQR)	57 (51 – 66)	59.5 (50 – 73)	57 (51 – 66)	0.76
PaO2/FiO2 (mm Hg), median (IQR)	267 (233 – 310)	264 (232 – 348)	267 (233 – 310)	0.92
Pneumonia				0.25
None	6 (4.3%)	2 (6.9%)	4 (3.7%)	
Unilateral	19 (13.8%)	6 (20.7%)	13 (11.9%)	
Bilateral	113 (81.9%)	21 (72.4%)	92 (84.4%)	
CURB-65 score, median (IQR)	1,5 (1 – 2)	1 (1 – 2)	2 (1 – 2)	0.51
qSOFA, median (IQR)	1 (0 – 1)	1 (0 – 1)	1 (0 – 1)	0.63
Blood analysis, median (IQR)				
White blood cell, /µL	6515 (4850 – 9140)	6810 (4630 – 9730)	6420 (4860 – 9730)	0.95
Neutrophil, /µL	4935 (3420 – 7540)	4550 (3100 – 7950)	4980 (3500 – 7370)	0.47
Lymphocyte, /µL	855 (620 – 1210)	850 (610 – 1200)	860 (630 – 1210)	0.94
C-reactive protein, mg/L	113 (51.3 – 173.4)	74.5 (33.7 – 144.9)	119.1 (56.7 – 186.1)	0.096
D-dimer (µg/L), No. with data	110	22	88	
Median (IQR)	794.5 (535 – 1447)	897.5 (606 – 1733)	784 (484.5 – 1377.5)	0.45
Ferritine (ng/mL), No. with data	57	6	51	
Median (IQR)	961 (544 – 1836)	435.4 (228 – 1084)	983 (585 – 1890)	0.11
Bacterial co-infection, No. (%)	20 (14.5%)	4 (13.8%)	16 (14.7%)	>0.99
Treatments administered, No. (%)				
Lopinavir/Ritonavir	117 (84.8%)	21 (72.4%)	96 (88.1%)	**0.046**

Hydroxychloroquine	136 (98.6%)	28 (96.6%)	108 (99.1%)	0.38
Antibiotics	94 (69.1%)	20 (69.0%)	74 (69.2%)	>0.99
Azithromycin	95 (68.8%)	17 (58.6%)	78 (71.6%)	0.19
Corticosteroids	85 (61.6%)	14 (48.3%)	71 (65.1%)	0.13
Tocilizumab	16 (11.6%)	1 (3.5%)	15 (13.8%)	0.19
Anakinra	3 (2.2%)	0	3 (2.8%)	>0.99

Abbreviations: BMI: body mass index. CURB-65: Confusion, Urea >7 mmol/L, Respiratory Rate ≥30/min, Systolic (≤90 mmHg) or Diastolic (≤60 mmHg) blood pressure and Age ≥65 years. IQR: interquartile range. FiO2: fraction of inspired oxygen. NS: non-significant. PaO2: arterial partial pressure of oxygen. qSOFA: quick Sepsis-related Organ Failure Assessment. SatO2: oxygen saturation. *Heart failure, myocardiopathy, ischemic and moderate-severe valvular heart diseases. †Chronic obstructive pulmonary disease, obstructive sleep apnea-hypopnea syndrome and diffuse interstitial lung disease.

Appendice

The COVID-HRC group [Masjuan, J; Fortún, J; Montero-Errasquín, B; Manzano, L; Máiz-Carro, L; Sánchez-García, EM; Hidalgo, F; Domínguez, AR; Pérez-Molina, JA; Sánchez-Sánchez, O; Comeche, B; Monge-Maillo, B; Barbolla-Díaz, I; Aranzábal Orgaz, L; Cobo, J; Rayo, I; Fernández-Golfín, C; González, E; Rincón-Díaz, LM; Ron, R; Mateos-Muñoz, B; Navas, E; Moreno, J; Norman, J; Serrano, S; Quereda Rodríguez-Navarro, C; Vallés, A; Herrera, S; Mateos del Nozal, J; Moreno-Cobo, MA; Gioia, F; Concejo-Badorrey, MC; Ortiz Barraza, EY; Moreno, A; Chamorro, S; Casado, JL; Almonacid, C; Nieto, R; Diz, S; Moreno, E; Conde, M; Hermida, JM; López, M; Monreal, E; Sainz de la Maza, S; Costa-Frossard, L; Natera-Villalba, E; Chico-García, JL; Beltrán-Corbellini, Á; Martínez-Sanz, J; García-Barragán, N; Buisán, J; Toledano, R; Alonso-Canovas, A; Pérez-Torre, P; Matute-Lozano, MC; López-Sendón, JL; García-Ribas, G; Corral, Í]. The Coronavirus disease 2019 – Hospital Ramón y Cajal (COVID-HRC).

Figures

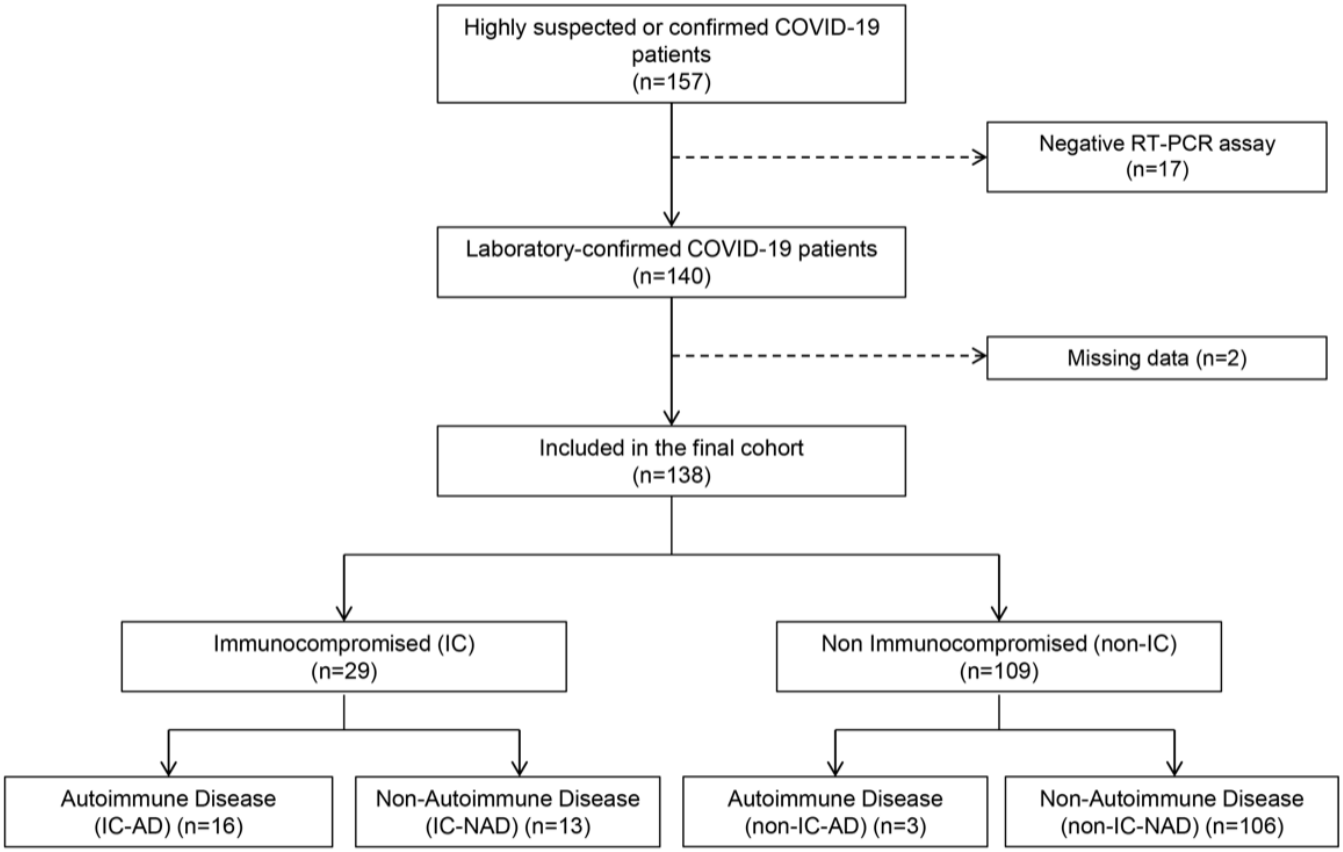

Figure 1

Study selection. RT-PCR: reverse transcriptase–polymerase chain reaction.

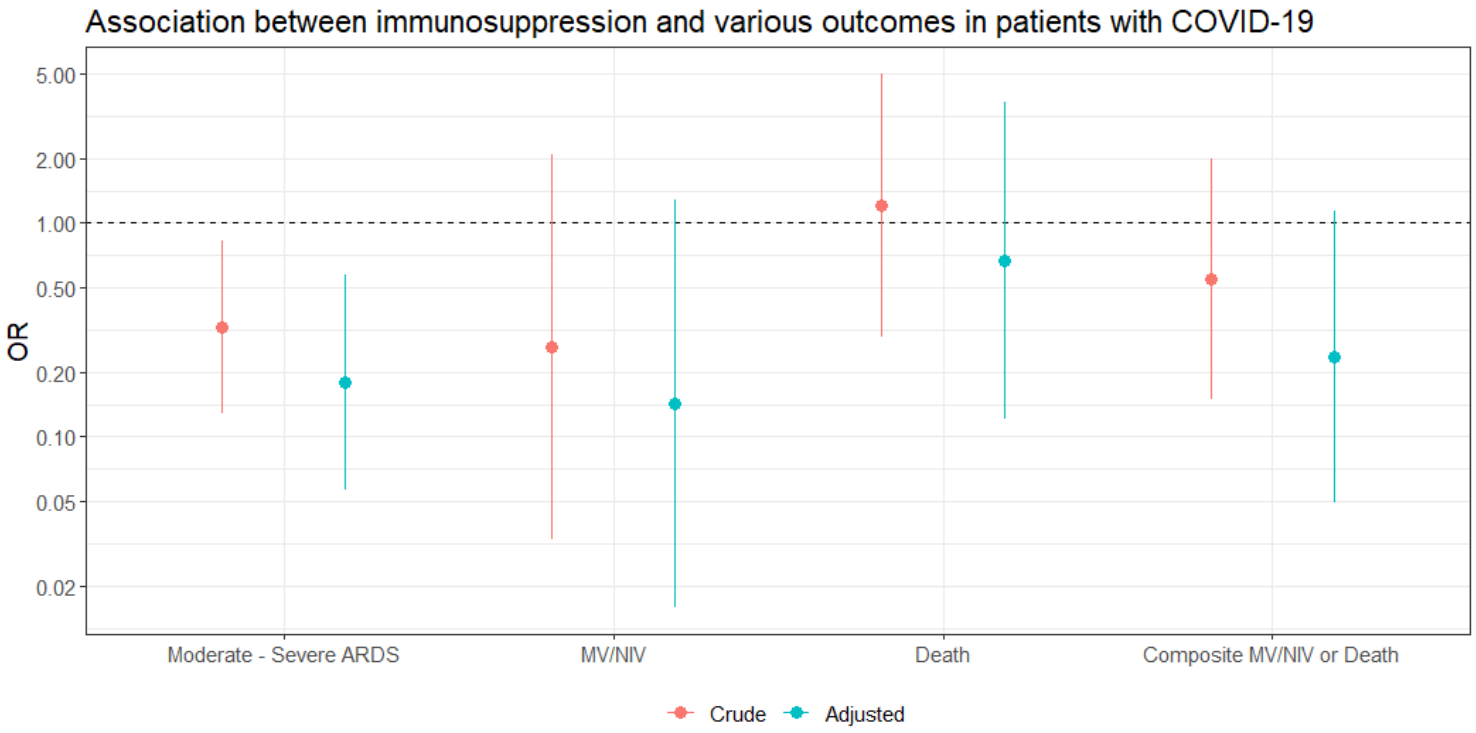

Figure 2

Primary and secondary endpoints. The figure shows the crude (red line) and adjusted (blue line) OR of the primary (moderate or severe ARDS) and secondary (ARDS, MV/NIV, a composite of MV/NIV and death and death) endpoints. ARDS: acute distress respiratory syndrome. MV: mechanical ventilation. NIV: non-invasive ventilation. OR: odds ratio.

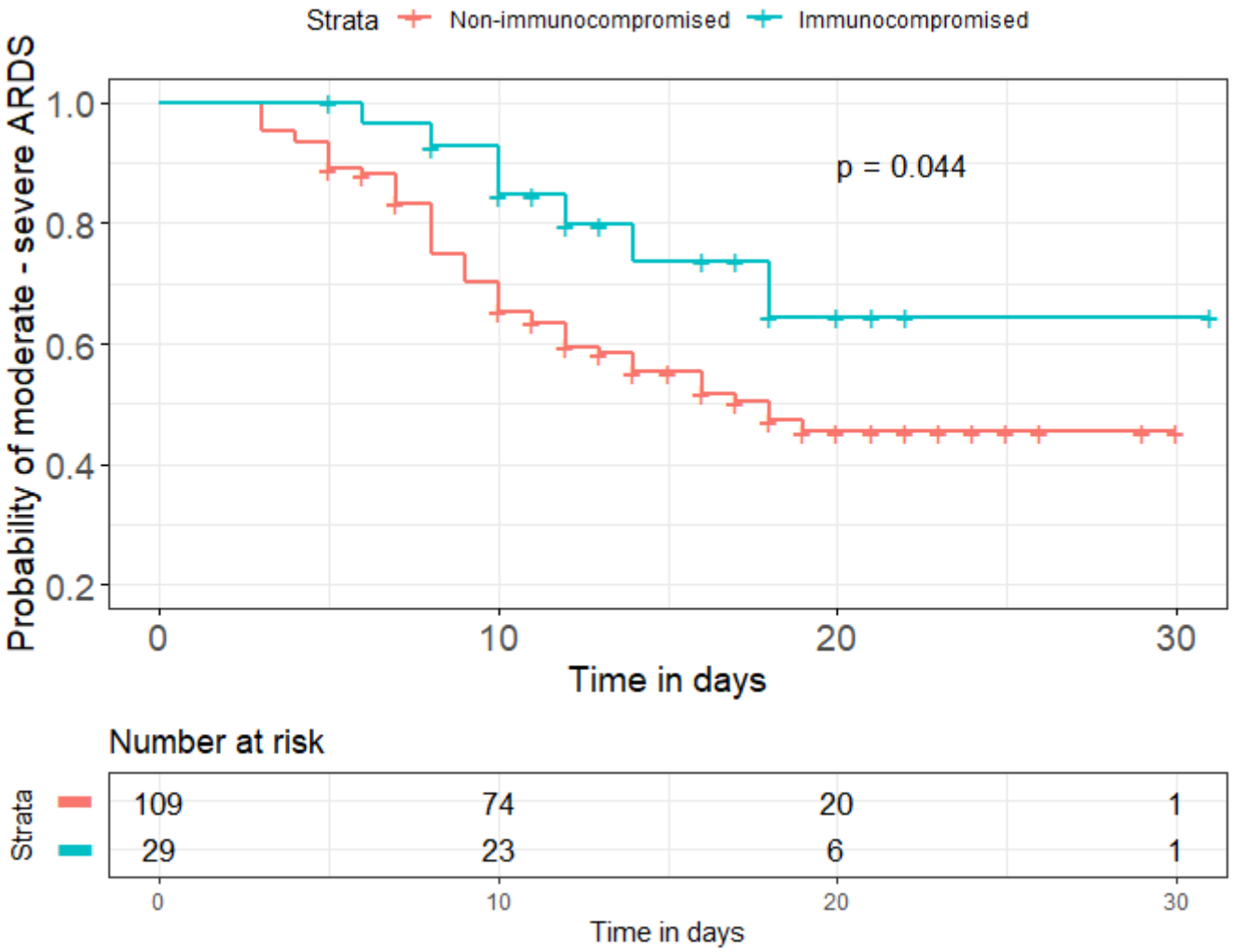

Figure 3

Time to moderate or severe ARDS. ARDS: acute distress respiratory syndrome.

Supplementary Files

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- SupplementalMaterial.docx