TO THE EDITOR:

High frequency of low-count monoclonal B-cell lymphocytosis in hospitalized COVID-19 patients

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Low-count monoclonal B-cell lymphocytosis (MBL^{lo}, <500 clonal B-cells/μL) is a highly prevalent condition in the general population (4% to 16% of otherwise healthy adults), which increases significantly with age.[1-7] In most cases, clonal B-cells share phenotypic and cytogenetic features with chronic lymphocytic leukemia (CLL), but only a small fraction (≈1.8%) progresses to high-count MBL (MBL^{hi}; ≥500 and <5000 clonal B-cells/μL)[3] in the medium-term.[8] However, previous reports showed that MBL^{lo} subjects had an increased risk of severe infections in association with a (predominantly) secondary antibody deficiency,[8-10] suggesting that MBL^{lo} might be a risk marker for developing more severe infections.

In December 2019, COVID-19 emerged as a new disease in humans, with a highly variable clinical course and outcome.[11,12] Since then, myriad studies have shown an association between a more aggressive clinical behavior of the disease and both advanced age[13,14] and the coexistence of particular comorbidities.[12-15] In parallel, several studies have confirmed the relevance of an adequate and virus-specific immune response for the control of the disease.[13,16] Despite these findings, all the above features alone fail to accurately predict the risk of more-severe COVID-19, particularly among older adults.

Here, we investigated the frequency of MBL^{lo} in COVID-19 patients in the first waves of the infection (prior to vaccination), compared to that in the general population of the same geographic region studied before the pandemic, and its potential association with disease severity. For this purpose, we studied 249 COVID-19 patients (133 men and 116 women; median age, 60 years [range: 18-99 years]) who were attended to at the University Hospital of Salamanca between April 2020 and April 2021, together with 728 healthy controls (333 men and 395 women; median age, 61 years [range: 25-97 years])

recruited from the same geographic area before the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic. Identification of clonal B-cells and leukocyte subpopulations in blood was performed using high-sensitivity flow cytometry. (Semi)quantitation of IgM, IgG, and IgA plasma levels against the spike (S) and nucleocapsid (N) proteins of SARS-CoV-2 was performed using enzyme-linked immunosorbent assay. Diagnostic and classification criteria for COVID-19 and disease severity, inclusion and exclusion criteria, and the clinical and biological characteristics of patients (according to the methods used), together with the flow-cytometry and enzyme-linked immunosorbent assay protocols are detailed in the supplemental Methods, available on the *Blood* website; supplemental Tables 1-3. A multivariable regression model (binary logistic regression) was used to assess the independent contribution of MBL^{lo} to the risk of hospitalization for COVID-19 (supplemental Methods; supplemental Table 12).

Overall, the presence of MBL^{lo} was detected in 73 of 249 COVID-19 patients (29%), a frequency twice that observed in the general population (99 of 728, 14%; P < .0001; Figure 1A).[6] Noteworthy, the prevalence of MBL^{lo} was even higher in patients admitted to the hospital (54 of 135, 40%; P < .0001; Figure 1B), including critically ill patients (12 of 31, 39%; P = .0007; Figure 1C). As expected, the frequency of MBL^{lo} among COVID-19 patients progressively increased with age (Figure 1),[4-7] with a significantly higher prevalence of MBL^{lo} among patients aged ≥50 years vs age-matched controls: 29 of 89 (33%) vs 39 of 312 (13%) in subjects aged 50 to 70 years (P < .0001); and 40 of 82 (49%) vs 51 of 227 (22%) among adults aged >70 years (P < .0001). Most MBL^{lo} patients displayed B-cell clones with a CLL-like phenotype (67 of 73, 92%), whereas non-CLL-like clonal B-cells were detected in 6 of 73 COVID-19 patients (8%). This incidence led to an overall
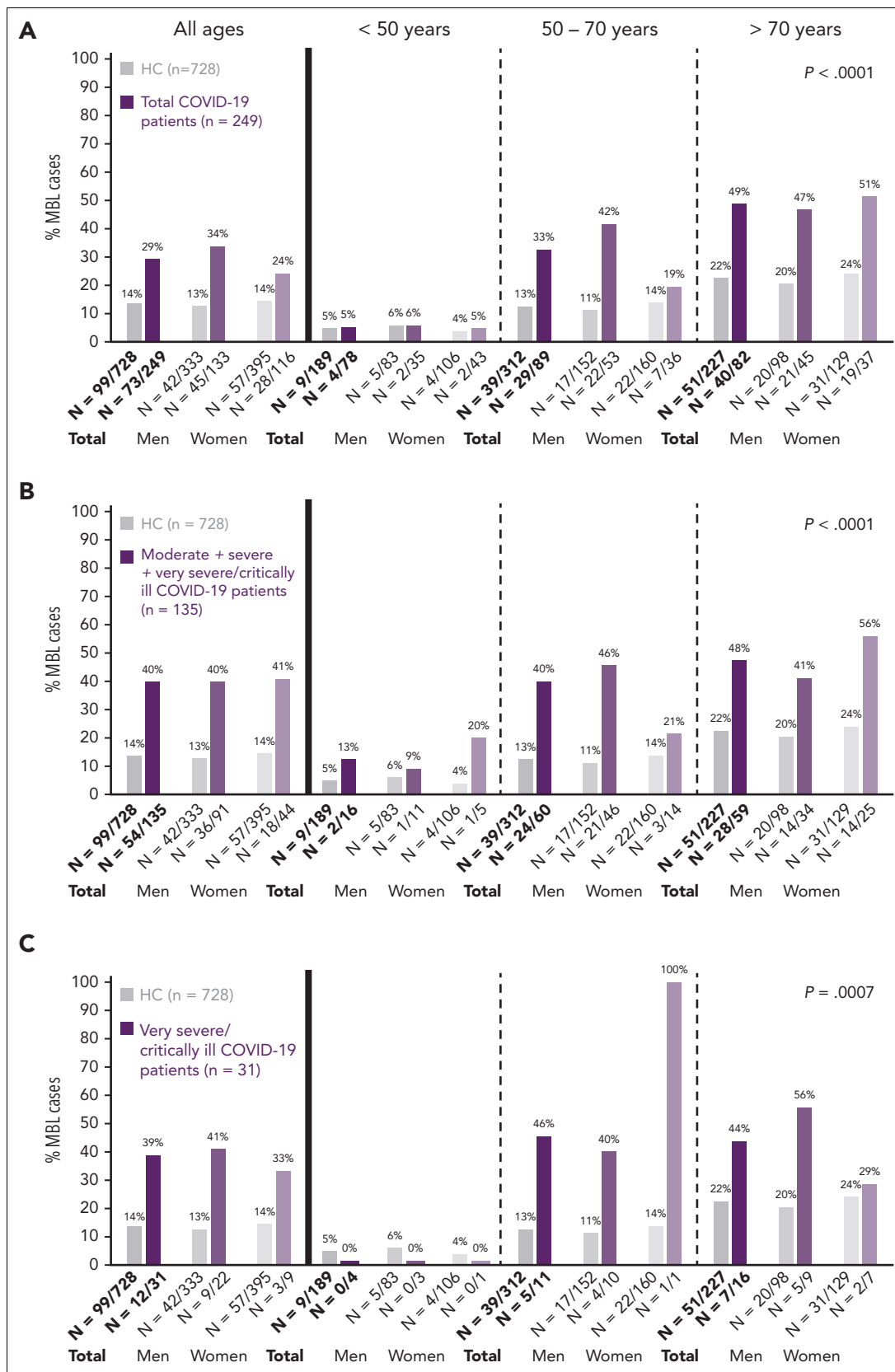
Figure 1. Frequency of MBL cases in COVID-19 patients vs the general population from the same geographic area studied before the SARS-CoV-2 pandemic. (A) Frequency of MBL among all COVID-19 patients, as well as (B) patients with moderate, severe, or very severe COVID-19, or (C) only very severe COVID-19, compared to healthy controls. (A-C) Further comparisons by sex and age groups. Gray bars represent the percentage of MBL cases in the general population, and dark bars represent the percentage of MBL cases among COVID-19 patients. Numbers over the bars are the percentage of MBL cases for each group. HC, healthy control.

prevalence of CLL-like MBL and non CLL-like MBL among COVID-19-infected patients of 27% (vs 12% in the general population aged >40 years, $P < .0001$)[6] and 2% (vs 2%, $P = .59$),[17] respectively. In all CLL-like MBL[lo] cases, a diagnosis of small lymphocytic lymphoma was ruled out by a hematologist at post-COVID-19 reassessment (38 of 38, 100%), based on the absence of organomegalies and other symptoms/signs of an underlying chronic lymphoproliferative disorder. The median (interquartile range) clone size of the MBL[lo] clones at diagnosis was 0.25 (0.07-3.83) cells/μL. Persistence of MBL[lo] at 1 year after onset of the disease was studied in 40 of 73 MBL[lo] patients, from which the vast majority (38 of 40; 95%) showed detectable clonal B-cells in blood at levels similar to those in the first analysis (median of 0.21 [0.1-1.6] cells/μL after 1 year, $P = .94$ vs the first analysis).

In line with these findings, MBL[lo] COVID-19 patients showed features of more severe COVID-19, including a higher frequency of dyspnea (67% vs 49%; $P = .02$), and a lower frequency of myalgia (18% vs 41%, $P = .001$; and 19% vs 37%, $P = .01$), nasal congestion/rhinorrhea (4% vs 23%, $P = .002$; and 4% vs 22%, $P = .005$), and nausea and/or vomiting (6% vs 18%, $P = .009$; and 4% vs 21%, $P = .002$), both in the whole cohort and in patients aged ≥50 years (supplemental Tables 4 and 6). Furthermore, MBL[lo] COVID-19 patients had lower oxygenation (oxygen saturation to fraction of inspired oxygen ratio [SpO$_2$/FiO$_2$] of 350 vs 443; $P = .001$), and higher serum levels of fibrinogen (600 vs 517 mg/dL; $P = .02$) and creatinine (1.05 vs 0.94 mg/dL; $P = .02$; supplemental Table 5). Consequently, MBL[lo] COVID-19 patients showed an increased need for hospitalization (85% vs 60%, $P < .0001$), oxygen therapy (70% vs 39%, $P < .0001$), and intensive care unit support (15% vs 6%, $P = .02$), together with longer hospitalization periods (median: 14 vs 10 days, $P = .03$; hazard ratio = 1.34). Despite this, the 2 patient groups showed similarly low death rates directly related to COVID-19 (4 of 132 non-MBL, 3% vs 2 of 73 MBL[lo], 3%; $P = .95$; supplemental Table 4). Three of these 6 patients died during the active phase of the infection, none of them carrying MBL clones, meaning that the 2 MBL[lo] subjects died after testing negative for SARS-CoV-2. CLL-like MBL[lo] and non-CLL-like MBL[lo] COVID-19 patients did not show differences in their clinical features, although the low number of non-CLL-like MBL[lo] cases does not allow a definitive conclusion in this regard. Altogether, these results support recent evidence indicating that CLL and MBL[hi] patients are at greater risk of severe COVID-19,[18] and they have poorer antibody responses to SARS-CoV-2 (and other viral and bacterial) vaccination,[19] which corroborates an increased risk for severe infections among MBL[lo] subjects.[10]

Controversial results have been reported in the literature, as regards the prevalence of MBL[lo] in men vs women in the general population.[6,7,20] Here, we observed a similar prevalence of MBL[lo] in the 2 groups of subjects from the general population (34% in men vs 24% in women, $P = .06$), in line with our previous observations (Figure 1).[6] In contrast, a clear predominance of MBL[lo] in men was found among COVID-19 patients within the 50- to 70-year age range (42% vs 19%, $P = .03$), in line with findings in previous reports.[7,20] Several studies have unveiled a disproportionately high rate of severe COVID-19 among adult men, compared to the rate in women, particularly in the elderly,[13,14] together with a greater prevalence of comorbidities,

which might partially explain the association with more severe disease in men aged ≥50 years.[12-15] In our cohort, MBL[lo] patients also exhibited more comorbidities than did non-MBL cases (70% vs 47%, $P = .001$; supplemental Table 4). However, except for the presence of cardiovascular disease (30% vs 19%; $P = .05$; supplemental Table 6), the greater frequency of all other comorbidities found in MBL[lo] COVID-19 patients appeared to be related to more advanced age among the former patients, as differences disappeared in older adults (supplemental Table 6).

To identify potential differences in the distribution of immune cells in blood between MBL[lo] and non-MBL COVID-19 patients that could be associated with the severity of the disease and reflect an immunodeficient state, we further investigated the distribution of major leukocyte (sub)populations in the blood of individuals with MBL[lo] vs without MBL during the acute phase of infection and after recovery from COVID-19. Overall, highly similar immune-cell profiles were found in the 2 groups of patients, reflecting changes that have been reported on extensively in COVID-19 patients (supplemental Tables 8-11).[16,21-23] In contrast, significant differences were observed in total B-cell counts of patients after recovery from COVID-19, associated with lower levels in blood among those who showed MBL[lo] (vs non-MBL; 143 vs 200 B-cells/μL; $P = .04$; supplemental Table 9). This finding suggests that MBL[lo] subjects have a defective ability to adequately recover B-cells after infection, which is consistent with our previous data suggesting that B-cell production is impaired, probably associated with a progressively reduced B-cell repertoire within the pre-germinal B-cell compartment in MBL[lo].[24] These findings prompted us to investigate the SARS-CoV-2–specific antibody responses in both group of patients.

Overall, most COVID-19 patients with or without MBL[lo] had already produced IgM, IgA, and IgG SARS-CoV-2–specific antibodies against either N or S viral proteins during the acute phase of infection (141 of 153, 92%). Subsequently, IgM and IgA levels declined, whereas IgG plasma levels remained elevated in most cases for at least 3 months after infection, with a similar pattern for antibodies against S and N viral proteins in the whole series (Figure 2). Yet, we observed important differences in the serologic responses of MBL[lo] vs non-MBL patients during the acute phase of infection that were independent of the specificity of the antibodies (anti-S or anti-N). These differences consisted of the following: a higher percentage of MBL[lo] (vs non-MBL) cases with detectable anti-SARS-CoV-2 IgM (136 of 144 [94%] vs 170 of 198 [86%], $P = .01$ for anti-S IgM; and 88 of 145 [61%] vs 94 of 198 [47%], $P = .02$ for anti-N IgM), IgG (132 of 144 [92%] vs 148 of 198 [75%], $P < .0001$ for anti-S IgG; and 134 of 145 [92%] vs 152 of 198 [77%], $P < .0001$ for anti-N IgG), and anti-N IgA (130 of 144 [90%] vs 156 of 198 [79%], $P = .005$ for anti-S IgA; and 131 of 145 [92%] vs 148 of 198 [75%], $P < .0001$ for anti-N IgA) antibodies, together with higher titres of SARS-CoV-2–specific anti-S IgM (3813 AU/ml vs 2965 AU/ml; $P = .0002$), anti-S IgG (97 AU/ml vs 89 AU/ml; $P = .03$), and anti-N IgA (186 AU/ml vs 149 AU/ml; $P = .009$) during the acute phase of the infection, and higher levels of anti-S IgA (97 AU/ml vs 37 AU/ml; $P = .04$) early after recovery, but lower anti-S IgA titres (9 AU/ml vs 55 AU/ml, $P = .006$) after later [median: 253 days] time points; Figure 2). Previous studies have found a direct relationship
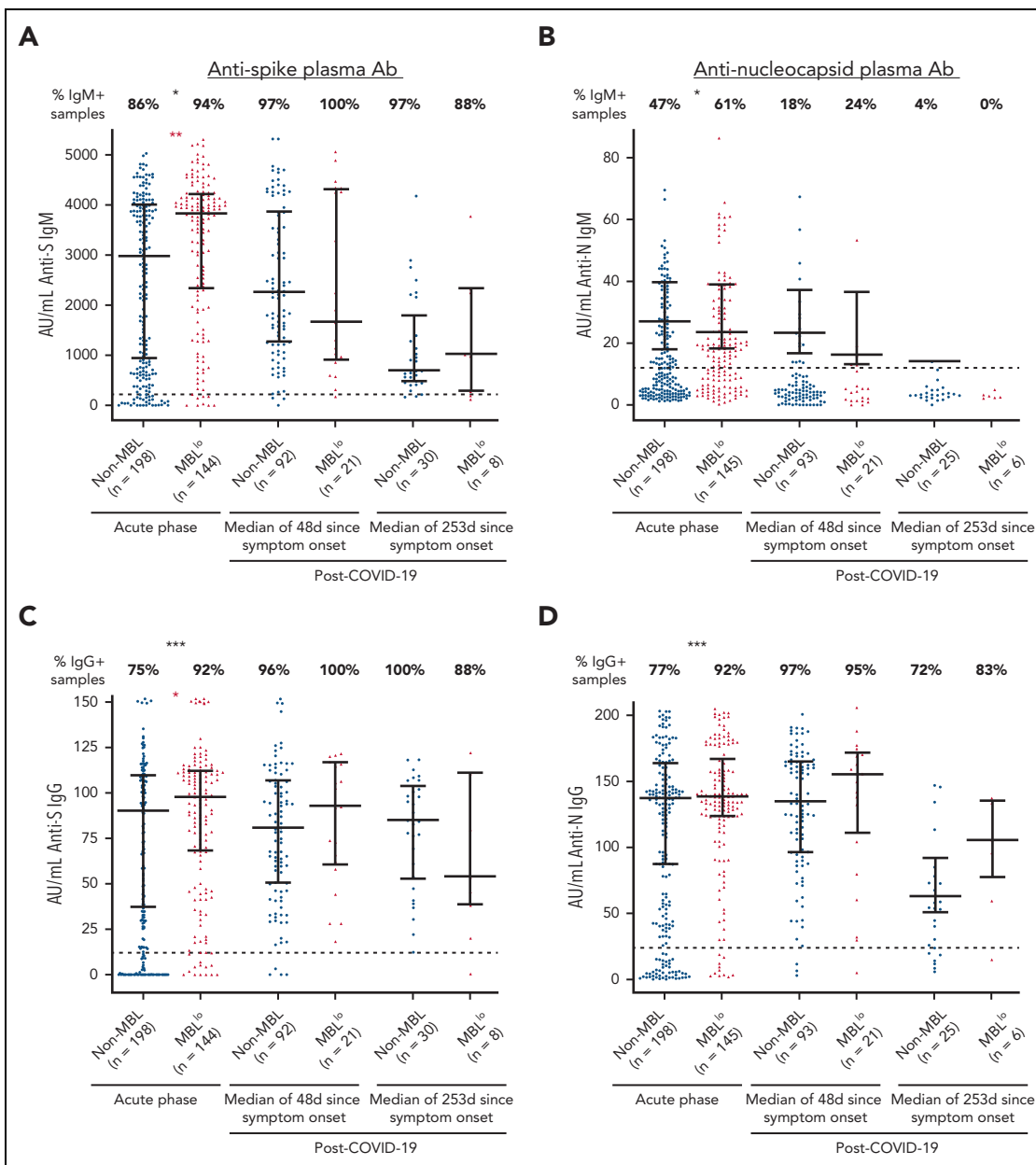
Figure 2. Levels of anti-SARS-CoV-2 antibodies (Abs) in plasma of COVID-19 patients according to the presence vs absence of MBL^lo. Levels (AU/mL) in plasma of COVID-19 patients of specific antibodies against the (left panels) spike and (right panels) nucleocapsid proteins of SARS-CoV-2, classified by isotype: (A-B) IgM, (C-D) IgG, and (E-F) IgA. COVID-19 patients without MBL are represented by blue dots, and those with MBL^lo by red triangles, and they are grouped according to the stage of infection (active vs early post-COVID-19 vs late post–COVID-19). Numbers on the top of the graphs indicate the percentage of positive samples for each group. The top and bottom lines represent the 25th and 75th percentiles, and the line in the middle represents median values of positive samples. Dashed lines represent the positivity cut-off for each antibody isotype (220 AU/mL for IgM, 12 AU/mL for IgG, and 2 AU/mL for IgA against spike, and 12 AU/mL for IgM and 24 AU/mL for both IgG and IgA against nucleocapsid). *P < .05, **P < .005, ***P < .0005 non-MBL vs MBL cases.

between the severity of the infection and higher levels of SARS-CoV-2–specific antibodies in serum/plasma, which might be required for complete clearance of the greater viral load in patients who are experiencing more severe disease, as observed in MBL^lo patients in this study.[22,25] Despite this relationship, recent reports indicate that both MBL^hi and CLL patients display decreased responses to vaccination against SARS-CoV-2 and other viral/bacterial agents.[19] Therefore, the higher levels of antibodies against SARS-CoV-2 found in our cohort of MBL^lo patients could reflect a delayed immune response to clear the virus in patients with more-severe

COVID-19. Altogether, these findings suggest that such impaired humoral responses might emerge at an earlier MBL^lo stage.

A multivariate analysis was subsequently performed to identify those clinical, laboratory, and biological variables that were independently associated with a higher risk of hospitalization for COVID-19. Thus, the presence of MBL^lo was selected as an independent marker associated with an adverse risk (odds ratio: 2.97; 95% confidence interval: 1.19-7.42; P = .02) of hospitalization, together with the presence of dyspnea (P < .0001) and
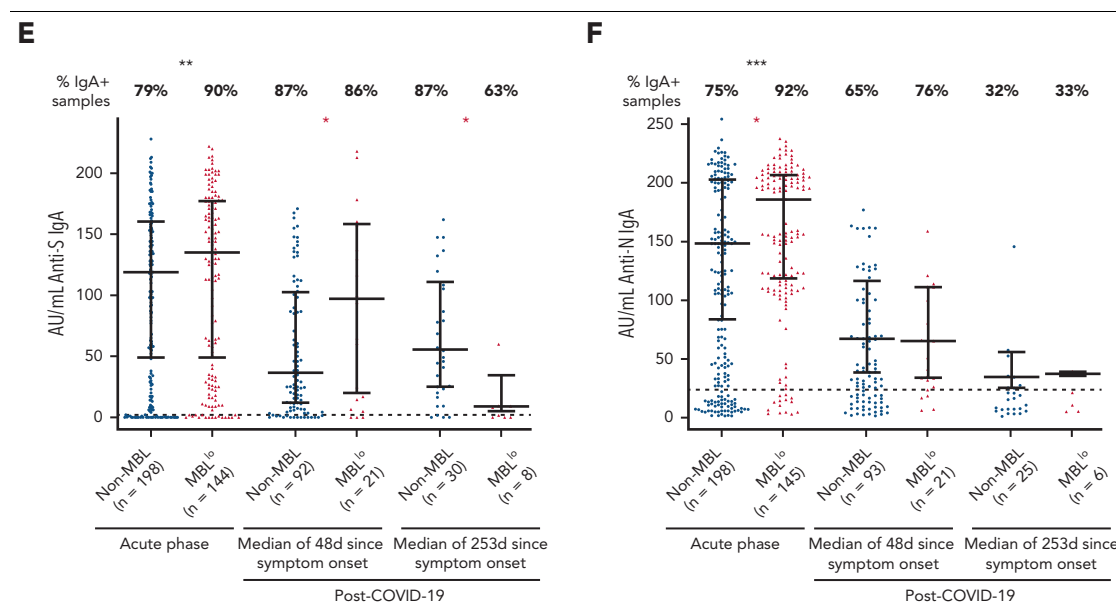
Figure 2 (continued)

fever (P = .004) at presentation, male sex (P = .01), more profound eosinopenia (P < .0001), and higher neutrophilia (P = .007), together with lower B-cell (P = .01) and NK cell (P = .02) levels, and a greater frequency of positivity for anti-N SARS-CoV-2 IgA (P < .0001) antibodies in plasma (supplemental Table 12). These results confirm the independent contribution of MBL[lo] to the development of severe COVID-19.

In summary, here we report for the first time a higher frequency of MBL[lo] among COVID-19 patients referred to a tertiary hospital during the first year of the SARS-CoV-2 pandemic, compared to that observed in the general population from the same geographic area, particularly among hospitalized patients with more-severe disease. Based on our results and previous data from the literature, MBL[lo] emerges as a new independent risk marker for more-severe COVID-19, and therefore, it might represent a major public health concern, as subjects with an MBL[lo]-associated impaired immunity are more likely to suffer from other (eg, respiratory) severe infections and to develop inadequate responses to vaccination.

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Authorship

Contribution: J.A., M.M., and A.O. contributed to the conceptualization, design, and supervision of the study, as well as to recruitment of funding; G.O.-A., B.F.-H., A.P.-P., A.T.-V., J.P., Ó.G.-L., M.B.-R., O.P.-E., F.J.G.P., M.S.S., and T.C.-S. performed the experiments; G.O.-A., B.F.-H., Q.L., A.P.-P., A.T.-V., M.B.-R., M.P.-A., F.J.M.-P., D.D., V.B., N.M.-G., R.F., J.A., and A.O. analyzed and interpreted data; C.C., J.Á.M.-O., A.L.-B., M.B.-G., L.V., G.H.-P., P.L., P.C.-A., E.P.-L., A.Y., M.G.-B., and M.M. selected cases for the study and collected their relevant clinical information; G.O.-A., B.F.-H., C.C., J.A., M.M., and A.O. coordinated the planning and execution of the experiments; G.O.-A., B.F.-H., J.A., and A.O. had full access to and verified the underlying data; G.O.-A., J.A., M.M., and A.O. wrote the paper; all authors critically reviewed the manuscript and approved the final version of the document.

Conflict-of-interest disclosure: A.O. and J.A. report being among the inventors of the EuroFlow-owned European patent 119646NL00 registered on November 2019 ("Means and methods for multiparameter flow cytometry-based leukocyte subsetting") and are also authors of the PCT patent WO 2010/ 140885A1 ("Methods, reagents and kits for flow cytometric immunophenotyping"). The Infinicyt software is based on intellectual property of the University of Salamanca in Spain. All above mentioned intellectual property and related patents are licensed to Cytognos (Salamanca, Spain) and Becton/Dickinson Biosciences (San José, California), and these companies pay royalties to the EuroFlow Consortium. These royalties are exclusively used for continuation of the EuroFlow collaboration and sustainability of the EuroFlow Consortium. The remaining authors declare no competing financial interests.

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Footnotes

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