Low birth weight as a potential risk factor for severe COVID-19 in adults

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The identification of factors predisposing to severe COVID-19 in young adults remains partially characterized. Low birth weight (LBW) alters cardiovascular and lung development and predisposes to adult disease. We hypothesized that LBW is a risk factor for severe COVID-19 in non-elderly subjects. We analyzed a prospective cohort of 397 patients (18–70 years) with laboratory-confirmed SARS-CoV-2 infection attended in a tertiary hospital, where 15% required admission to Intensive Care Unit (ICU). Perinatal and current potentially predictive variables were obtained from all patients and LBW was defined as birth weight ≤ 2.500 g. Age (adjusted OR (aOR) 1.04 [1–1.07], P = 0.012), male sex (aOR 3.39 [1.72–6.67], P < 0.001), hypertension (aOR 3.37 [1.69–6.72], P = 0.001), and LBW (aOR 3.61 [1.55–8.43], P = 0.003) independently predicted admission to ICU. The area under the receiver-operating characteristics curve (AUC) of this model was 0.79 [95% CI, 0.74–0.85], with positive and negative predictive values of 29.1% and 97.6% respectively. Results were reproduced in an independent cohort, from a web-based survey in 1822 subjects who self-reported laboratory-positive SARS-CoV-2 infection, where 46 patients (2.5%) needed ICU admission (AUC 0.74 [95% CI 0.68–0.81]). LBW seems to be an independent risk factor for severe COVID-19 in non-elderly adults and might improve the performance of risk stratification algorithms.

COVID-19 is a mild or asymptomatic condition in the majority of patients, but in up to 1–2% it may result in severe disease and death¹². Older age, male sex and coexisting conditions are the main risk factors described so far for severe COVID-19 disease³–⁸. However, a small proportion of young and apparently healthy adults may eventually require critical care. There is a need for comprehensive models that identify factors associated to the risk of severe forms of COVID-19⁹.

The association between low birth weight (LBW) and adult health has long been recognized¹⁰–¹². LBW, defined as ≤ 2500 g¹³,¹⁴, can result from fetal growth restriction, prematurity or both¹⁵. Fetal growth restriction has been associated with increased cardiovascular mortality¹⁶–¹⁸, lower lung functional capacity¹⁶–¹⁸ and increased respiratory morbidity¹⁶–¹⁸ in adulthood. Likewise, prematurity has been described as a risk factor for suboptimal cardiovascular²⁰ and lung²¹ development and a greater predisposition to heart failure²² and lung disease²³ later in life. For studies in adults, birth weight is an accessible and robust surrogate for fetal growth restriction and perinatal births, and a strong predictor of short and long-term morbidity²⁴.

From the above observations, we hypothesized that LBW could increase the risk of developing severe illness in non-elderly adults with COVID-19. To test this hypothesis, we designed a prospective study in confirmed COVID-19 patients (18–70 years) admitted to our institution, a public, tertiary, referral, university hospital in Spain (development dataset) and validated the model in an independent cohort of self-reported laboratory-confirmed COVID-19 subjects recruited through a web-based survey (validation dataset).
Results

Development dataset. Figure 1 (left panel) presents the CONSORT diagram of the testing cohort. Out of 516 potentially eligible patients (with laboratory-confirmed SARS-CoV-2 infection by real time polymerase chain reaction (RT-PCR) of nasopharyngeal swab samples) during the study period, the development cohort included 397 patients with available perinatal information (77%). Based on clinical assessment of severity, 98 patients (24.7%) followed home hospitalization care and 299 (75.3%) were hospitalized, 60 of whom (20%) were eventually taken care of in the Intensive Care Unit (ICU) (25 (42%) required mechanical ventilation and none died). Table 1 displays the characteristics of the 337 non-critically ill patients (home hospitalization (n = 98) or in hospital (n = 239)) with those treated in the ICU (n = 60). The latter were older, more frequently males, had a higher body mass index (BMI) and a higher prevalence of hypertension. Of note, they were also born with LBW (18.3 vs. 9.5%, p = 0.041) and suffered fetal growth restriction (25 vs. 14.8%, p = 0.043) more often. Individuals born with LBW had a higher probability for ICU admission as compared with those with normal birth weight (Fig. 2).

Table 2 displays crude and adjusted Odds Ratio (aOR) for ICU admission. In the multivariate model, age (aOR 1.04 [1–1.07], P = 0.012), male sex (aOR 3.3 [1.72–6.67], P < 0.001), hypertension (aOR 3.4 [1.69–6.72], P = 0.001), and LBW (aOR 3.61 [1.55–8.43], P = 0.003) remained independent predictors of ICU. As shown in Fig. 3 (left), the area under the receiver-operating characteristics curve (AUC) for predicting ICU admission was 0.79 (95% CI, 0.74–0.85). The model had a sensitivity of 91.7%, specificity of 60.2%, positive predictive value (PPV) of 29.1% and negative predictive value (NPV) of 97.6% (Table 3).

Validation dataset. Figure 1 (right panel) presents the CONSORT diagram of the validation dataset. We received 9320 responses of subjects aged 18 to 70 years who referred symptoms suggestive of COVID-19. Among them, 1822 self-reported COVID-19 confirmed by RT-PCR. A total of 1215 of them (67%) reported mild symptoms and did not require hospital admission whereas 607 (33%) were hospitalized of whom 46 (8%) patients required ICU admission (30 of them (65% of ICU patients) were mechanically ventilated, and one male patient (2% of ICU patients) died at the age 68 years as reported later by her daughter.

Table 4 shows the characteristics of the 1776 non-critically ill patients (treated at home (n = 1215) or in hospital (n = 561)) with those treated in the ICU (n = 46). Like we observed in the developing cohort, ICU patients in the validation dataset were older, more frequently males, had a higher BMI and a higher prevalence of hypertension. Importantly, again, they were born with LBW (19.6 vs. 7.3%, p = 0.006) and suffered fetal growth restriction (26.1 vs. 12.4%, p = 0.010) more often. In this validation dataset, the prevalence of prematurity was also higher in ICU patients (23.9 vs. 10.9%, p = 0.011).

The model obtained in development dataset was applied to the validation dataset, obtaining an AUC of 0.74 (95% CI 0.68–0.81) (Fig. 2, right panel), with a sensitivity of 73.9%, specificity of 67.3%, PPV of 5.5% and NPV of 99% (Table 3).

Discussion

This study provides evidence that recording birth weight might improve the prognostic stratification of COVID-19 in non-elder patients. Most young patients present mild forms of COVID-19, but a small proportion might require admission to ICU for severe complications3-4, which is clearly associated to non-obvious predisposing factors. Early interventions in COVID-19 have demonstrated to reduce mortality46. Consequently, the identification of predisposing factors –particularly in a priori non high-risk subjects- might allow early therapeutic measures eventually preventing serious evolution to serious illness. In this study we evaluated an innovative approach by studying early life risk factors not usually taken into account in current clinical practices. Birth weight is one of the most universally recorded information for any given individual and self-recalled birth weight has

Figure 1. CONSORT diagram of the study.

| Developing dataset | Validation dataset |
|--------------------|--------------------|
| 516 eligible patients with laboratory-confirmed SARS-CoV-2 infection | 9,320 responses with potential COVID-19 |
| No perinatal information available (n=119) | Validation dataset: 1,822 patients with laboratory-confirmed SARS-CoV-2 infection (13%) |
| Developing dataset: 397 patients (77%) | 1,215 home (67%) |
| 98 home (25%) | 607 hospitalized (33%) |
| 299 hospitalized (75%) | 561 non ICU admission (92%) |
| 239 non ICU admission (80%) | 46 ICU admission (8%) |

![CONSORT diagram of the study.](https://www.nature.com/scientificreports/)
|                                    | All population (N = 397) | No ICU admission (N = 337) | ICU admission (N = 60) | P value* |
|------------------------------------|--------------------------|---------------------------|------------------------|----------|
| Demographic and clinical characteristics in adulthood |                          |                           |                        |          |
| Mean age (± SD)—years              | 47 ± 12.2                | 46 ± 12.2                 | 53 ± 10.1              | <0.001   |
| Female—no. (%)                     | 197 (49.6)               | 183 (54.3)                | 14 (23.3)              | <0.001   |
| Mean body mass index (± SD)—kg/m²  | 26.9 ± 5                 | 26.6 ± 5                  | 28.6 ± 4.8             | 0.005    |
| Current smoker—no. (%)             | 27 (6.8)                 | 24 (7.1)                  | 3 (5)                  | 0.394    |
| Ex-smoker—no. (%)                  | 129 (32.5)               | 104 (30.9)                | 25 (41.7)              | 0.069    |
| Coexisting conditions—no. (%)      |                          |                           |                        |          |
| Hypertension                       | 66 (16.6)                | 40 (11.9)                 | 26 (43.3)              | <0.001   |
| Cardiovascular disease             | 16 (4)                   | 12 (3.6)                  | 4 (6.7)                | 0.211    |
| Diabetes mellitus                  | 32 (8.1)                 | 26 (7.7)                  | 6 (10)                 | 0.350    |
| Obesity                            | 98 (24.7)                | 84 (24.9)                 | 14 (23.3)              | 0.467    |
| Dyslipidemia                       | 31 (7.8)                 | 23 (6.8)                  | 8 (13.3)               | 0.077    |
| Chronic lung disease               | 37 (9.3)                 | 33 (9.8)                  | 4 (6.7)                | 0.312    |
| Chronic kidney disease             | 20 (5)                   | 14 (4.2)                  | 6 (10)                 | 0.064    |
| Autoimmune disease                 | 12 (3)                   | 10 (3)                    | 2 (3.3)                | 0.564    |
| Malignancy                         | 28 (7.1)                 | 22 (6.5)                  | 6 (10)                 | 0.235    |
| Thyroid disorders                  | 25 (6.3)                 | 21 (6.2)                  | 4 (6.7)                | 0.540    |
| Other viral infectionsa            | 11 (2.8)                 | 8 (2.4)                   | 3 (5)                  | 0.223    |
| Psychiatric disordersb             | 23 (5.8)                 | 19 (5.6)                  | 4 (6.7)                | 0.469    |
| Previous hospital admission within the last 12 months—no. (%) | 32 (8.1) | 27 (8) | 5 (8.3) | 0.548 |
| Drugs within last 15 days before COVID-19 diagnosis—no. (%) |          |       |        |          |
| NSAIDs                             | 142 (35.8)               | 120 (35.6)                | 22 (36.7)              | 0.492    |
| ACE inhibitors                     | 27 (6.8)                 | 21 (6.2)                  | 6 (10)                 | 0.208    |
| Corticoids                         | 12 (3)                   | 11 (3.3)                  | 1 (1.7)                | 0.436    |
| Perinatal and childhood characteristics |                      |                           |                        |          |
| Mean birth weight (± SD)—g         | 3302 ± 666               | 3296 ± 635                | 3335 ± 826             | 0.728    |
| Low birth weight—no. (%)           | 43 (10.8)                | 32 (9.5)                  | 11 (18.3)              | 0.041    |
| Fetal growth restriction—no. (%)   | 65 (16.4)                | 50 (14.8)                 | 15 (25)                | 0.043    |
| Prematurity—no. (%)                | 28 (7.1)                 | 23 (6.8)                  | 5 (8.3)                | 0.420    |
| Childhood lung disease—no. (%)     | 75 (18.9)                | 67 (19.9)                 | 8 (13.3)               | 0.155    |
| Asthma                             | 42 (10.6)                | 39 (11.6)                 | 3 (5)                  | 0.259    |
| Bronchitis                         | 20 (5)                   | 16 (4.7)                  | 4 (6.7)                | 0.126    |
| Other lung disease                 | 13 (3.3)                 | 12 (3.6)                  | 1 (1.7)                | 0.579    |

Table 1. Characteristics of participants in the development cohort by ICU admission. ICU intensive care unit, NSAIDs non-steroidal anti-inflammatory drugs, ACE angiotensin-converting enzyme. *P-value for the comparison of ICU admission vs. no ICU admission. aOther viral infections including HIV and/or hepatitis B or C. bPsychiatric disorders including depression, bipolar disorder, schizophrenia and anxiety requiring treatment.

Figure 2. Adjusted probability prediction for ICU admission in normal vs. low birth weight individuals computed with multivariate logistic regression model. For further explanations, see text.
demonstrated to be a reliable information, particularly in subjects born after the 1960s\textsuperscript{41}. If confirmed in future studies that LBW identifies high risk for complicated COVID-19, this should be included in initial assessment of non-elder infected subjects and would offer opportunities for early interventions to prevent complications.

Previous studies. Despite the large number of studies on prognostic factors for severe COVID-19\textsuperscript{3–8,25–36}, to our knowledge no previous study has investigated the predictive role of early life events as a risk factor for severe COVID-19 in adulthood. Results confirmed our working hypothesis, which was aligned with a long-standing research line in this field\textsuperscript{11,12,18,19,37}. Besides, results confirmed previous studies showing a strong predictive value for severe COVID-19 of older age, male sex and coexisting conditions such as hypertension\textsuperscript{3–8,25–31}. The fact that we studied non-elder adults (≤ 70 years) may have limited the identification of significant associations with other reported coexisting conditions such as chronic lung disease\textsuperscript{2,6–8,27}, diabetes\textsuperscript{2–5,7,8,25,26,30,32}, obesity\textsuperscript{8,31,33} or cancer\textsuperscript{3,34}. Current or previous smoking status\textsuperscript{35} and chronic treatment with ACE inhibitors\textsuperscript{36} were not asso-

| Table 2. Odds Ratios for ICU admission for COVID-19 in the developing cohort. To obtain ICU admission probability calculate $e^{\log_{e}}/(1 + e^{\log_{e}})$. ICU intensive care unit, OR odds ratio, aOR adjusted odds ratio, CI confidence interval. |
|----------------------------------|-------|------------------|-------|------------------|-------|
| Univariate analysis             | Multivariate analysis          |
| OR (95% CI)                     | $p$-value | aOR (95% CI)     | $p$-value | Beta coefficient |
| Age, in 1-year unit             | 1.06 (1.03–1.09)    | < 0.001          | 1.04 (1.01–1.07) | 0.012 | 0.03963 |
| Sex: male vs. female            | 3.9 (2.07–7.37)     | < 0.001          | 3.39 (1.72–6.67) | < 0.001 | 1.16734 |
| Body mass index, in 1 kg/m\textsuperscript{2} unit | 1.08 (1.02–1.13)   | 0.005            |                   |       |       |
| Smoker or ex-smoker: yes vs. no | 1.43 (0.82–2.48)    | 0.206            |                   |       |       |
| Hypertension: yes vs. no        | 5.68 (3.09–10.43)   | < 0.001          | 3.37 (1.69–6.72)  | 0.001 | 1.23937 |
| Cardiovascular disease: yes vs. no | 1.93 (0.6–6.21)    | 0.268            |                   |       |       |
| Diabetes mellitus: yes vs. no   | 1.33 (0.52–3.38)    | 0.550            |                   |       |       |
| Obesity: yes vs. no             | 0.9 (0.5–1.75)      | 0.792            |                   |       |       |
| Chronic lung disease: yes vs. no| 0.8 (0.1–6.61)      | 0.835            |                   |       |       |
| Malignancy: yes vs. no          | 1.59 (0.62–4.1)     | 0.337            |                   |       |       |
| Low birth weight: yes vs. no    | 2.14 (1.01–4.52)    | 0.046            | 3.61 (1.55–8.43)  | 0.003 | 1.10971 |
| Fetal growth restriction: yes vs. no | 1.91 (0.99–3.69) | 0.053            |                   |       |       |
| Prematurity: yes vs. no         | 1.24 (0.45–3.4)     | 0.675            |                   |       |       |
| Childhood lung disease: yes vs. no | 0.62 (0.28–1.37)  | 0.236            |                   |       |       |
| Constant                        |                   | $-4.95673$       |                   |       |       |

Figure 3. Receiver-operating characteristics curves for ICU admission in a multivariate model that includes age, sex, hypertension and low birth weight both in the development cohort (left) and validation dataset (right). For further explanations, see text.
associated with COVID-19 severity in our dataset. We acknowledge that other unstudied confounders may have interfered our results.

**Interpretation of novel findings.** Our results suggest that LBW is an independent risk factor for severe COVID-19 in adulthood. This finding is consistent with previous epidemiological and experimental studies supporting the developmental origin of adult diseases. Adverse in utero environment induces permanent changes in

| Developing cohort | Patients admitted to ICU | Patients not admitted to ICU | Total patients | Predictive value |
|-------------------|--------------------------|-----------------------------|---------------|------------------|
| N = 60            | N = 337                  | N = 397                     |               |                  |
| Criteria positive⁰| 55 true positive (29.1%) | 134 false positive (70.9%)  | 189           | PPV, 29.1%      |
| Criteria negative | 5 false negative (2.4%)  | 203 true negative (97.6%)   | 208           | NPV, 97.6%      |
| Sensitivity       | 91.7%                    |                             |               |                  |
| Specificity       | 60.2%                    |                             |               |                  |

**Validation dataset**

| N = 46 | N = 1780 | N = 1826 |                |
|--------|----------|----------|---------------|
| Criteria positive⁰| 34 true positive (5.5%) | 582 false positive (94.5%) | 616 | PPV, 5.5% |
| Criteria negative | 12 false negative (1.0%) | 1198 true negative (99.0%) | 1210 | NPV, 99.0% |
| Sensitivity       | 73.9%     |           |               |
| Specificity       | 67.3%     |           |               |

**Table 3.** Predictive accuracy of a multivariate model that includes age, sex, hypertension and low birth weight for ICU admission for COVID-19 in the developing cohort and validation dataset. **ICU intensive care unit, PPV positive predictive value, NPV negative predictive value.** ¹According to the logistic regression model, criteria positive is defined as a probability greater than 10.554%.

|                   | All population (N = 1822) | No ICU admission (N = 1776) | ICU admission (N = 46) | P-value * |
|-------------------|---------------------------|-----------------------------|------------------------|-----------|
| Demographic and clinical characteristics in adulthood |               |                             |                         |           |
| Mean age (± SD)—years | 46 ± 11.5               | 46 ± 11.5                   | 52 ± 9.1               | < 0.001   |
| Female—no. (%)      | 1255 (68.9)              | 1239 (69.8)                 | 16 (34.8)              | < 0.001   |
| Mean body mass index (± SD)—kg/m² | 25 ± 4.9 | 24.9 ± 4.8              | 28.9 ± 6.3              | < 0.001   |
| Current smoker—no. (%) | 132 (7.2) | 130 (7.3)                | 2 (4.3)                | 0.340     |
| Ex-smoker—no. (%)   | 702 (38.5)               | 682 (38.4)                  | 20 (43.5)              | 0.290     |
| Coexisting conditions—no. (%) |  |                             |                         |           |
| Hypertension        | 218 (12)                 | 208 (11.7)                  | 10 (21.7)              | 0.041     |
| Cardiovascular disease | 55 (3)                  | 55 (3.1)                    | 0 (0)                  | 0.240     |
| Diabetes mellitus   | 49 (2.7)                 | 46 (2.6)                    | 3 (6.5)                | 0.124     |
| Obesity             | 224 (12.3)               | 210 (11.9)                  | 14 (30.4)              | 0.001     |
| Dyslipidemia        | 97 (5.3)                 | 95 (5.3)                    | 2 (4.3)                | 0.552     |
| Chronic lung disease| 200 (11)                 | 196 (11)                    | 4 (8.7)                | 0.419     |
| Chronic kidney disease | 17 (0.9)              | 16 (0.9)                    | 1 (2.2)                | 0.354     |
| Autoimmune disease  | 93 (5.1)                 | 91 (5.1)                    | 2 (4.3)                | 0.580     |
| Malignancy          | 33 (1.8)                 | 32 (1.8)                    | 1 (2.2)                | 0.573     |
| Thyroid disorders   | 125 (6.9)                | 120 (6.8)                   | 5 (10.9)               | 0.204     |
| Psychiatric disorders⁰ | 61 (3.3)                | 61 (3.4)                    | 0 (0)                  | 0.205     |
| Perinatal and childhood characteristics |         |                             |                         |           |
| Mean birth weight (± SD)—g  | 3390 ± 606             | 3393 ± 595                  | 3283 ± 935             | 0.432     |
| Low birth weight—no. (%)   | 128 (7.6)               | 129 (7.3)                   | 9 (19.6)               | 0.006     |
| Fetal growth restriction—no. (%) | 233 (12.8)           | 221 (12.4)                  | 12 (26.1)              | 0.010     |
| Prematurity—no. (%)     | 205 (11.3)              | 194 (10.9)                  | 11 (23.9)              | 0.011     |
| Childhood lung disease—no. (%) | 237 (13)        | 233 (13.1)                  | 4 (8.7)                | 0.826     |
| Asthma                | 143 (7.8)               | 141 (7.9)                   | 2 (4.3)                | 0.309     |
| Bronchitis            | 47 (2.6)                | 46 (2.6)                    | 1 (2.2)                | 0.340     |
| Other lung disease    | 47 (2.6)                | 46 (2.6)                    | 1 (2.2)                | 0.666     |

**Table 4.** Characteristics of COVID-19 patients in the validation dataset by ICU admission. **ICU intensive care unit.** ⁰P-value for the comparison of ICU admission vs. no ICU admission. ⁰Psychiatric disorders including depression, bipolar disorder, schizophrenia and anxiety requiring treatment.
the structure, function and metabolism of the developing fetal organs. Most developmental changes of early life persist in the long term which leads to a greater risk of disease in adulthood\textsuperscript{10,11}. It is suggested that fetal adaptation to perinatal events represents a ‘first hit’ leading to latent susceptibility, which combined with a ‘second hit’ later in life could increase the risk for adult diseases\textsuperscript{10,11}. This notion has been consistently demonstrated in experimental research\textsuperscript{38}, but evidence in humans is limited. The COVID-19 pandemic represents a unique opportunity to study the response of a significant number of individuals born LBW to a specific and well-defined stressor.

LBW has been consistently associated with increased adult cardiovascular mortality, hypertension, metabolic syndrome, diabetes and lung morbidity\textsuperscript{10–12,15–23}. LBW can be a result of being born too small—fetal growth restriction and/or too early—prematurity. Fetal growth restriction is caused by placental insufficiency leading to a sustained reduction in fetal oxygen and nutrient supply\textsuperscript{11}. This triggers an adaptive fetal response including cardiovascular remodeling\textsuperscript{12,39}, increased blood pressure\textsuperscript{12}, altered lipoprotein profile, lost of nephrons, and disturbed pulmonary alveolarization and vascular growth\textsuperscript{11}. In prematurity, key developmental stages have to take place ex utero in non-physiological conditions\textsuperscript{40} leading to cardiovascular hypertrophy and impaired lung development, insulin sensitivity and bone density\textsuperscript{20–22,40}.

Strengths and limitations. This study has some strengths and limitations that merit comment. Among the strengths, we prospectively collected information spanning the full COVID-19 clinical spectrum, from mild to hospitalized and ICU patients. Likewise, we validated our observations in an independent dataset. Finally, we included only non-elderly subjects (<70 years) to avoid the potential confounding effect of age-related comorbidities. The study sample size was too small to assess the predictive value of LBW across age ranges. We acknowledge that evidence here presented should be validated in another prospective hospital cohort. We opted for an online survey to shorten validation time. We acknowledge also a potential selection bias since there were virtually no deaths in our study population. Firstly, mortality rate for COVID-19 was very low in our hospital (8%, 194/2425) with most cases occurring in subjects > 70 years-old. Secondly, we tried to contact all COVID-19 patients identified in the EMRs, but a few very severe cases were directly intubated and died preventing the interview for the study. In addition, we acknowledge the potential inaccuracy of the perinatal data obtained by interview or online survey. However, self-reported birth weight has demonstrated to be a good surrogate of adverse in utero environment, particularly in non-elderly subjects\textsuperscript{41}. Although the prevalence of LBW in our study populations lie within the range reported by recent international and national estimates\textsuperscript{42}, we acknowledge that a selection bias cannot be fully discarded. Finally, we acknowledge that future studies might unveil non-identified confounders not considered in the design of this study that might have affected the present results.

Conclusions

Our data suggest that low birth weight increases the risk of severe COVID-19 in non-elderly adults. This new information further supports the importance of early life events in adult diseases. If confirmed in future studies, LBW should be considered in risk stratification algorithms for COVID-19.

Methods

Development dataset. Study design, population and ethics. Prospective observational cohort that included non-elderly adults (aged 18 to 70 years) consecutively attended at Hospital Clinic of Barcelona from March 25 to April 25, 2020 with laboratory-confirmed SARS-CoV-2 infection by real time polymerase chain reaction (RT-PCR) of nasopharyngeal swab samples. Sample size was determined by the time window of opportunity of the study. Criteria for hospital admission (COVID-19 pneumonia) and therapeutic management while in hospital followed the in-house protocols. The primary outcome of the study was admission to the ICU, which was determined by the attending physician on a patient by patient basis following standard clinical assessment criteria\textsuperscript{43}. Follow-up time was censored on May 25, 2020 so that each patient had at least 30 days of observation. The study was approved by the Ethical Committee of Hospital Clinic (HC3B/2020/0353) and written informed consent was obtained from all patients. All research was performed in accordance with Regulation EU 2016/679 of the European Parliament and of the Council of April 27, 2016 on the protection of individuals.

Data collection. Cases were identified by daily review of hospital attendance logs in electronic medical records. Likewise, demographics, smoking exposure, coexisting conditions, treatment received during the last two weeks before hospitalization, need for ICU admission, complications or death during the clinical course, and therapeutic management interventions were obtained by reviewing electronic medical records. On the other hand, perinatal (birth weight and gestational age at delivery) and childhood (“asthma” or other respiratory disease in childhood) data were obtained by a face-to-face or telephone interview. Birth weight centiles were calculated adjusted by gender and gestational age at birth according to local standards\textsuperscript{14}. LBW was defined as birth weight equal or below 2500 g\textsuperscript{14}. Fetal growth restriction was defined as a birth weight below the 10th centile for gestational age\textsuperscript{45} and preterm delivery as born before 37 weeks of gestation\textsuperscript{46}.

Validation dataset. Study design, setting and population. To validate externally the performance of the prognostic algorithm created by the development cohort, we collected independent data from self-selected volunteers who declared laboratory-confirmed SARS-CoV-2 infection through an anonymous multilingual (Spanish, Catalan, Italian, English and French) online survey (Limey Survey GmbH, Germany). The survey was disseminated via email and social media, and it was open and free for all subjects who self-reported to have laboratory confirmed COVID-19. Demographic information, coexisting conditions, perinatal and childhood data were obtained by interview or online survey. We acknowledge also an incomplete ascertainment of LBW data and that a selection bias cannot be fully discarded. Finally, we acknowledge also an incomplete ascertainment of LBW data and that a selection bias cannot be fully discarded. Finally, we acknowledge also that the evidence here presented should be validated in another prospective hospital cohort. We acknowledge also that future studies might unveil non-identified confounders not considered in the design of this study that might have affected the present results.
data, COVID-19 related symptoms and need for hospitalization or admission to ICU were collected (voluntary sampling) using an anonymous web-based cross-sectional survey from April 1 to May 31, 2020.

Statistical analysis. Results are presented as counts (percentage) or mean (SD) as appropriate. Our aim was to determine whether being born LBW increases susceptibility to severe COVID-19 in non-elderly adults. Our main outcome measure was admission to ICU for COVID-19. Our main exposure measure was LBW defined as birth weight ≤ 2500 g. Other exposure measures were age, sex, body mass index, smoking status, presence of comorbidities (hypertension, cardiovascular disease, diabetes mellitus, obesity, chronic lung disease and malignancy), fetal growth restriction (defined as birth weight below 10th centile), prematurity (defined as delivery occurring before 37 weeks) and childhood lung disease. Variables with p < 0.05 on univariate analyses were entered in the multivariate logistic regression analysis to determine independent risk factors for ICU admission. A forward stepwise selection algorithm was applied to select the final model in the development dataset. Odds ratio and 95% confidence interval (95% CI) were calculated. Hosmer and Lemeshow test were used to assess the goodness of fit of the final model. Analysis of the Receiver Operating Curve (ROC) was used to evaluate the predictive performance of the model in the development datasets and the optimal cut-off was computed using Youden criteria. The model determined in the development dataset was used to predict ICU admission in the validation dataset and we report the statistical parameters for development and validation. All p-values are two-sided and considered statistically significant if p < 0.05. Data were analysed with SPSS v26 and R software version 3.6.2 (R project for statistical computing, Vienna, Austria).

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Author contributions

Fa.C. and Fr.C. postulated the hypothesis. Fa.C., Fr.C., E.G. and A.A. designed the study and wrote the study protocol. O.S., J.B., I.B., R.F., M.L. and K.V. contributed to the study protocol design. Fa.C., Fr.C., M.L., M.C. and M.T. recruited the patients and performed the data collection. F.G. designed the web-based survey. Fa.C. and Fr.C. postulated the hypothesis. Fa.C., Fr.C., E.G. and A.A. designed the study and wrote the study protocol. O.S., J.B., I.B., R.F., M.L. and K.V. contributed to the study protocol design. Fa.C., Fr.C., M.L., M.C. and M.T. recruited the patients and performed the data collection. F.G. designed the web-based survey.

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Competing interests

The authors declare no competing interests.

Additional information

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