LOW BIRTH WEIGHT AS A RISK FACTOR FOR SEVERE COVID-19 IN ADULTS

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ABSTRACT

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 (18-70y) 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 1,822 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.
INTRODUCTION

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 death.\textsuperscript{1,2} Older age, male sex and coexisting conditions are the main risk factors described so far for severe COVID-19 disease.\textsuperscript{3-8} 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-19.\textsuperscript{9}

The association between low birth weight (LBW) and adult health has long been recognized.\textsuperscript{10-12} LBW, defined as $\leq 2.500$ g,\textsuperscript{13-14} can result from fetal growth restriction, prematurity or both.\textsuperscript{13} Fetal growth restriction has been associated with increased cardiovascular mortality,\textsuperscript{10,15} lower lung functional capacity\textsuperscript{16-18} and increased respiratory morbidity\textsuperscript{18-19} in adulthood. Likewise, prematurity has been described as a risk factor for suboptimal cardiovascular\textsuperscript{20} and lung\textsuperscript{21} development and a greater predisposition to heart failure\textsuperscript{22} and lung disease\textsuperscript{23} later in life. For studies in adults, birth weight is an accessible and robust surrogate for fetal growth restriction and preterm births, and a strong predictor of short and long-term morbidity.\textsuperscript{24}

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 (Figure 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 Figure 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 9,320 responses of subjects aged 18 to 70 years who referred symptoms suggestive of COVID-19. Among them, 1,822 self-reported COVID-19 confirmed by RT-PCR. A total of 1,215 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 1,776 non-critically ill patients (treated at home (n=1,215) 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) (Figure 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 complications,\(^3\)-\(^8\) which is clearly associated to non-obvious predisposing factors. Early interventions in COVID-19 have demonstrated to reduce mortality.\(^4,6\) 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 demonstrated to be a reliable information, particularly in subjects born after the 1960s.\(^41\) If confirmed 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,\(^3,8,25-36\) 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.\(^11-12,18-19,37\) 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.\(^3,8,25-31\) The fact that we studied non-elderly adults (\(\leq 70\) years) may have limited the identification of significant
associations with other reported coexisting conditions such as chronic lung disease,\(^2,6-8,27\) diabetes,\(^2,5,7,8,25-26,30,32\) obesity\(^3,31,33\) or cancer.\(^3,34\) Current or previous smoking status\(^35\) and chronic treatment with ACE inhibitors\(^36\) were not associated with COVID-19 severity in our dataset.

**Interpretation of novel findings**

Our results show 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 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.\(^10,11\) 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.\(^10,11\) This notion has been consistently demonstrated in experimental research,\(^40\) 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.\(^10,11,12,15-21\) 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.\(^11\) This triggers an adaptive fetal response including cardiovascular remodeling,\(^12,36\) increased blood pressure,\(^12\) altered lipoprotein profile, lost of nephrons, and disturbed pulmonary alveolarization and vascular growth.\(^11\) In
prematurity, key developmental stages have to take place *ex utero* in non-physiological conditions\(^3\) leading to cardiovascular hypertrophy and impaired lung development, insulin sensitivity and bone density.\(^{20-22,39}\)

**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 the 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%, 194/2,425) 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. Finally, 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.\(^{41}\)

**Conclusions**
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 and should be considered in future risk stratification algorithms.

**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 Clínic 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. 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 our institution (HCB/2020/0353) and informed consent was obtained from all patients.

*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. LBW was defined as birth weight equal or below 2,500g. Fetal growth restriction was defined as a birth weight below the 10th centile for gestational age and preterm delivery as born before 37 weeks of gestation.

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, 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 (LimeSurvey®).

Statistical analysis

Results are presented as counts (percentage) or mean (SD) as appropriate. 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 2-sided and considered statistically significant if <0.05. Data were analysed with SPSS v26 and R software version 3.6.2 (R project for statistical computing, Vienna, Austria).
REFERENCES

1. Guan WJ, Ni ZY, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020;328:1708–20.

2. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020;8:475–81.

3. Guan WJ, Liang WH, Zhao Y, Liang H, Chen Z, Li Y. Comorbidity and its impact on 1590 patients with COVID-19 in China: A Nationwide Analysis [Internet]. The European respiratory journal. 2020. Available from: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L631357733%0Ahttp://dx.doi.org/10.1183/13993003.00547-2020

4. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients with 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA - J Am Med Assoc. 2020;323:1061–9.

5. Shi Y, Yu X, Zhao H, Wang H, Zhao R, Sheng J. Host susceptibility to severe COVID-19 and establishment of a host risk score: Findings of 487 cases outside Wuhan. Crit Care. 2020;24:2–5.

6. Cummings MJ, Baldwin MR, Abrams D, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. medRxiv [Internet]. 2020;6736: 2020.04.15.20067157

7. Zheng Z, Peng F, Xu B, et al. Risk factors of critical & mortal COVID-19 cases: A systematic literature review and meta-analysis. J Infect. 2020;(January).

8. Preliminary Estimates of the Prevalence of Selected Underlying Health Conditions Among Patients with Coronavirus Disease 2019 - United States, February 12-March 28,
9. Schnake-Mahl A, Carty MG, Sierra G, Toyin-Ajayi MP. Identifying Patients with Increased Risk of Severe COVID-19 Complications: Building an Actionable Rules-Based Model for Care Teams. N Engl J Med. 2020; DOI: 10.1056/CAT.20.0116

10. Barker D. The fetal and infant origins of adult disease. BMJ 1990;301:1111.

11. Crispi F, Miranda J, Gratacós E. Long-term cardiovascular consequences of fetal growth restriction: biology, clinical implications, and opportunities for prevention of adult disease. Am J Obstet Gynecol 2018;218:S869-S879.

12. Crispi F, Bijnens B, Figueras F, et al. Fetal growth restriction results in remodeled and less efficient hearts in children. Circulation 2010;121:2427-2436.

13. Kramer MS. Determinants of low birth weight: methodological assessment and meta-analysis. Bulletin of the World Health Organization.1987;65:663–737

14. Schieve LA, Meikle SF, Ferre C, Peternson HB, Jeng G, Wilcox LS. Low and Very Low Birth Weight in Infants Conceived with Use of Assisted Reproductive Technology. N Engl J Med 2002; 346:731-737

15. Leon DA, Lithell HO, Vågerö D, et al. Reduced fetal growth rate and increased risk of death from ischaemic heart disease: cohort study of 15 000 Swedish men and women born 1915-29. BMJ 1998;317:241-5.

16. den Dekker HT, Jaddoe V, Reiss IK, de Jongste JC, Duijts L. Fetal and Infant Growth Patterns and Risk of Lower Lung Function and Asthma The Generation R Study. Am J Respir Crit Care Med 2018;197:183–192.

17. Pike K, Jane Pillow J, Lucas JS. Long term respiratory consequences of intrauterine growth restriction. Semin Fetal Neonatal Med. 2012;17:92–8.

18. Agusti A, Faner R. Lung function trajectories in health and disease. The Lancet
Respiratory Medicine 2019;4:358-64.

19. Agustí A, Hogg JC. Update on the pathogenesis of chronic obstructive pulmonary disease. N Engl J Med. 2019;381:1248–56.

20. Telles F, McNamara N, Nanayakkara S, Doyle M, Williams M, Yaeger L, Marwick TH, Leeson P, Levy PT, Lewandowski A. Changes in the preterm heart from birth to young adulthood: a meta-analysis. Pediatrics 2020;146:e20200146.

21. Kotecha SJ, Edwards MO, Watkins WJ, et al. Effect of preterm birth on later FEV1: a systematic review and meta-analysis. Thorax 2013;68:760-6.

22. Carr H, Cnattingius S, Granath F, Ludvigsson JF, Edstedt Bonamy AK. Preterm Birth and Risk of Heart Failure Up to Early Adulthood. J Am Coll Cardiol. 2017;69:2634-2642.

23. Martinez FD. Early-Life Origins of Chronic Obstructive Pulmonary Disease. N Engl J Med 2016; 375:871-878

24. Hughes MM, Black RE, Katz J. 2500-g Low Birth Weight Cutoff: History and Implications for Future Research and Policy. Matern Child Health J 2017;21:283–289.

25. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395:497–506.

26. Wu C, Chen X, Cai Y, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med. 2020; doi:10.1001/jamainternmed.2020.0994

27. Caramelo F, Ferreira N, Oliveiros B. Estimation of risk factors for COVID-19 mortality - preliminary results. medRxiv [Internet]. 2020; doi.org/10.1101/2020.02.24.20027268

28. Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients with
coronavirus disease 2019: Retrospective study. BMJ. 2020;368.

29. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395:507–13

30. Li B, Yang J, Zhao F, et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. Clin Res Cardiol. 2020;531–8.

31. PriceHaywood EG, Burton J, Fort D, Seoane L. Hospitalization and Mortality among Black Patients and White Patients with COVID-19. N Engl J Med 2020; May27. DOI: 10.1056/NEJMsa2011686

32. Guo W, Li M, Dong Y, et al. Diabetes is a risk factor for the progression and prognosis of COVID-19. Diabetes Metab Res Rev. 2020;(March):1–9.

33. Lighter J, Phillips M, Hochman S, et al. Obesity in Patients Younger Than 60 Years Is a Risk Factor for Covid-19 Hospital Admission. Clin Infect Dis. 2020 Apr 9.

34. Robbilotti EV, Babady NE, Mead PA et al. Determinants of COVID-19 disease severity in patients with cancer. Nat Med 2020 June 24; doi: 10.1038/s41591-020-0979-0.

35. Vardavas CI, Nikitara K. COVID-19 and Smoking: A Systematic Review of the Evidence. Tob Induc Dis. 2020;18:20.

36. Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD. Renin-Angiotensin-Aldosterone System Inhibitors in Patients With COVID-19. N Engl J Med. 2020;382:1653-1659.

37. Lange P, Celli B, Agustí A, et al. Lung-function trajectories leading to chronic obstructive pulmonary disease. N Engl J Med. 2015;373:111–22.

38. Rodríguez-López M, Cruz-Lemini M, Valenzuela-Alcaraz B, et al. Descriptive analysis of different phenotypes of cardiac remodeling in fetal growth restriction.
Ultrasound Obstet Gynecol. 2017;50:207–214.

39. Luu TM, Katz SL, Leeson P, Thebaud B, Nuyt AM. Preterm Birth: Risk Factor for Early-Onset Chronic Diseases. CMAJ. 2016;188: 736–740.

40. Rueda-Clausen CF, Morton JS, Lopaschuk GD, Davidge ST. Long-term Effects of Intrauterine Growth Restriction on Cardiac Metabolism and Susceptibility to Ischaemia/Reperfusion. Cardiovasc Res. 2011;90:285-94.

41. Nilsen TS, Kutschke J, Brandt I, Harris JR. Validity of Self-Reported Birthweight: Results from a Norwegian Twin Sample. Twin Res Hum Genet 2017;20:406-413.

42. Nates JL, Nunnally M, Kleinpell R, et al. ICU Admission, Discharge, and Triage Guidelines: A Framework to Enhance Clinical Operations, Development of Institutional Policies, and Further Research. Crit Care Med. 2016;44:1553-1602.

43. Figueras F, Meler E, Iraola A, et al. Customized birthweight standards for a Spanish population. Eur J Obstet Gynecol Reprod Biol. 2008;136:20–4.

44. American College of Obstetricians and Gynecologists. Fetal growth restriction. ACOG Practice Bulletin No. 204. Obs Gynecol. 2019;133:e97–109.

45. American College of Obstetricians and Gynecologists. Definition of term pregnancy. ACOG Practice Bulletin No. 579. Obs Gynecol. 2013;122:1139-40.

46. Hosmer D W, Lemeshow S 2000. Applied Logistic Regression. New York, USA: John Wiley and Sons.

47. W. J. Youden. Index for rating diagnostic tests. Cancer 1950;3:32–35.
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### Table 1. Characteristics of participants in the development cohort by ICU admission.

|                                      | All population (N=397) | No ICU admission (N=337) | ICU admission (N=60) | P value* |
|--------------------------------------|------------------------|--------------------------|----------------------|----------|
| **Demographic and clinical characteristics in adulthood** |                        |                          |                      |          |
| Mean age (±SD) --yr                  | 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 infections§              | 11 (2.8)               | 8 (2.4)                  | 3 (5)                | 0.223    |
| Psychiatric disorders                | 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)                | 0.229    |
| 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    |

ICU denotes Intensive Care Unit, NSAIDs non-steroidal anti-inflammatory drugs, and ACE Angiotensin-converting enzyme.

§ Other viral infections including HIV and/or hepatitis B or C.

*P-value for the comparison of ICU admission vs. no ICU admission.
Table 2. Odds Ratios for ICU admission for COVID-19 in the developing cohort.

|                                    | Univariate analysis | Multivariate analysis | Beta Coefficient |
|------------------------------------|---------------------|-----------------------|------------------|
|                                    | OR (95% CI)         | p-value               | aOR (95% CI)     | p-value   |                                    |
| Age, in 1-yr unit                   | 1.06 (1.03-1.09)    | <0.001                | 1.04 (1.07-1.1)  | 0.012     | 0.03963                             |
| Sex: male vs. female                | 3.90 (2.07-7.37)    | <0.001                | 3.39 (1.72-6.67) | <0.001    | 1.16734                             |
| Body mass index, in 1 Kg/m² 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                 | 0.90 (0.5-1.75)     | 0.792                 |                  |           |                                    |
| Chronic lung disease: yes vs. no    | 0.80 (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         |           |                                    |

ICU denotes Intensive Care Unit, OR Odds Ratio, aOR adjusted Odds Ratio, and CI confidence interval. To obtain ICU admission probability calculate $\frac{e^{\text{logit}}}{1+e^{\text{logit}}}$. 
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.

| Developing cohort | Patients admitted to ICU (N=60) | Patients not admitted to ICU (N=337) | Total patients (N=397) | Predictive value |
|-------------------|----------------------------------|-------------------------------------|------------------------|------------------|
| Criteria positive§ | 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       |                                  |                                     |                        |
| Specificity       |                                  |                                     |                        |
| Validation dataset | (N=46)                           | (N=1,780)                           | (N=1,826)              |
| Criteria positive§ | 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       |                                  |                                     |                        |
| Specificity       |                                  |                                     |                        |

ICU denotes Intensive Care Unit, PPV positive predictive value, and NPV negative predictive value.

§According to the logistic regression model, criteria positive is defined as a probability greater than 10.554%
## Table 4. Characteristics of COVID-19 patients in the validation dataset by ICU admission.

ICU denotes Intensive Care Unit.

|                                | All population (N=1822) | No ICU admission (N=1776) | ICU admission (N=46) | P value* |
|--------------------------------|-------------------------|---------------------------|----------------------|----------|
| **Demographic and clinical characteristics in adulthood** |                         |                           |                      |          |
| Mean age (±SD) −yr             | 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 disorders          | 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    |

ICU denotes Intensive Care Unit.

*P-value for the comparison of ICU admission vs. no ICU admission.
FIGURE LEGENDS

**Figure 1.** CONSORT diagram of the study.

**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.

**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.
Developing dataset

516 eligible patients with laboratory-confirmed SARS-CoV-2 infection

No perinatal information available (n=119)

Developing dataset: 397 patients (77%)

98 home (25%)  299 hospitalized (75%)

239 non ICU admission (80%)  60 ICU admission (20%)

Validation dataset

9,320 responses with potential COVID-19

Validation dataset: 1,822 patients with laboratory-confirmed SARS-CoV-2 infection (13%)

1,215 home (67%)  607 hospitalized (33%)

561 non ICU admission (92%)  46 ICU admission (8%)
Developing dataset

AUC 0.79

Validation dataset

AUC 0.74