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Maternal and Perinatal Outcomes of Pregnant Women with SARS-COV-2 infection

The WAPM (The World Association of Perinatal Medicine) working group on COVID-19

Correspondence:

Daniele Di Mascio, MD.

Department of Maternal and Child Health and Urological Sciences, Sapienza University of Rome.

Via del Policlinico, 155. 00161 Rome, Italy. Email address: dani.dimascio@gmail.com

ORCID ID: 0000-0002-6560-3393

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What are the novel findings of this work?

Despite the increasing number of published studies, objective evidence is still needed to draw any conclusion on the course of SARS-COV-2 infection acquired during pregnancy.

What are the clinical implications of this work?

The study showed that in pregnancies complicated by SARS-COV-2, the risk of maternal mortality was 0.8%, but about 11% of women required admission to ICU. Pregnancies affected by SARS-COV-2 were also complicated by 23% rate preterm birth, and 4.1% rate of perinatal death. The risk of vertical transmission was negligible.

ABSTRACT

Objectives: To evaluate maternal and perinatal outcomes of pregnant women affected by SARS-COV-2.

Methods: This was a multinational retrospective cohort study including women with laboratory-confirmed SARS-COV-2 from 73 centers from 22 different countries in Europe, United States, South America, Asia and Australia from February 1, 2020 to April 30, 2020. Confirmed SARS-COV-2 infection was defined as a positive result on real-time reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assay of nasal and pharyngeal swab specimens. The primary outcome was a composite measure of maternal mortality and morbidity including admission to intensive care unit (ICU), use of mechanical ventilation, or death.

Results: 388 singleton pregnancies tested positive to SARS-COV-2 at RT-PCR nasal and pharyngeal swab were included in the study. The primary outcome was observed in 47/388 women (12.1%). 43/388 women (11.1%) were admitted to ICU, 36/388 (9.3%) required mechanical ventilation, and 3/388 women deceased (0.8%). Of the 388 women included in the study, 122 (31.4%) were still pregnant at the time of the study. Among the other 266 women, 6 had spontaneous first-trimester abortion, 3 had elective termination of pregnancy, 6 had stillbirth, and 251 delivered a live-born infant. The rate of preterm birth less than 37 weeks of gestation was 26.3% (70/266). Of the 251 live-born infants, 69/251 (27.5%) were admitted to NICU, with 5

neonatal deaths (2.0%). The overall rate of perinatal death was 4.1% (11/266). Only one infant (1/251, 0.4%) born from a mother tested positive during the third trimester, was found positive to SARS-COV-2 at RT-PCR.

Conclusions: SARS-COV-2 in pregnant women is associated with 0.8% rate of maternal mortality, but 11.1% rate of admission to ICU. The risk of vertical transmission seems to be negligible.

INTRODUCTION

In December 2019, a novel Coronavirus spread in China and identified as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-COV-2) was responsible of a cluster of respiratory disorders, the COVID-19 disease.¹

Coronaviruses are enveloped, non-segmented positive-sense RNA belonging to the Nidovirales order.² Although responsible of generally mild infections, including many common colds in adults and children, Coronavirus caused two important epidemics in the last decade: the severe acute respiratory syndrome and the Middle East respiratory syndrome, also known as SARS and MERS respectively. Despite the large and rapidly growing number of cases worldwide,³ there is limited data on COVID-19 in pregnancy, mainly coming from case series and small sample studies.⁴⁻⁷

Pregnant women are at increased risk for severe illness from influenza virus and other respiratory infections due to cardiopulmonary adaptive changes occurring during pregnancy, such as increased heart rate and stroke volume and reduced pulmonary residual capacity, that can increase the risk of hypoxemia and contribute to the increased severity. This may question whether the course of

COVID-19 in pregnant women can be associated with a higher burden of maternal mortality and morbidity compared to the general population.

A recent systematic review including all published reports on Coronaviruses (COVID-19, SARS and MERS) in pregnancy found that preterm birth was the most common adverse pregnancy outcome, and that COVID-19 was associated with an increased risk of preeclampsia, and cesarean delivery.^{5,8-10} Despite this, the small sample size, inclusion of cases mainly referred for severe acute respiratory symptoms, lack of information of pre-existing medical conditions complicating pregnancy, and heterogeneity in gestational age at infection and outcomes observed, does not allow to extrapolate any objective evidence on the course of the infection during pregnancy.

Objective

The primary aim of this study was to evaluate maternal and perinatal outcomes of pregnant women affected by SARS-COV-2.

METHODS

Study design and participants

This multinational, retrospective cohort study included all pregnant women with a laboratory-confirmed SARS-COV-2 infection, diagnosed between February 1, 2020 and April 30, 2020, in 73 centers from 22 different countries (Argentina, Australia, Belgium, Brazil, Colombia, Czech Republic, Finland, Germany, Greece, Israel, Italy, North Macedonia, Peru, Portugal, Republic of Kosovo, Romania, Russia, Serbia, Slovenia, Spain, Turkey, and United States) (Table S1). All infected women were diagnosed antepartum during pregnancy, and those with a positive test before conception or during post-partum were excluded from the study.

SARS-COV-2 was diagnosed on the basis of The World Health Organization (WHO) interim guidance.¹¹ A confirmed case of SARS-COV-2 was defined as a positive result on real-time reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assay of nasal and pharyngeal swab specimens.^{12,13} In the included centers, women were tested with RT-PCR assay of nasal and pharyngeal swab mostly due to symptoms or exposure at the time of triage. Neonates from mother positive to SARS-COV-2 were usually tested within 24 hours after delivery with RT-PCR assay of nasal and pharyngeal swab.

Data on recent exposure history, clinical symptoms or signs, laboratory findings, maternal and perinatal outcomes were collected. All medical records were anonymized and sent to the coordinator center at University of Naples Federico II (Naples, Italy) through The World Association of Perinatal Medicine (WAPM) data platform or via an encrypted Research Electronic Data Capture (REDCap) data management platform. Data were entered into a computerized database and cross-checked. In case of missing data, requests for clarification were sent to the coordinator of each participating center.

Outcomes

The primary outcome of the study was a composite measure of maternal mortality and morbidity including at least one of the following: admission to intensive care unit (ICU), use of mechanical ventilation, or death (defined as composite maternal adverse outcome). Secondary outcomes were abortion, stillbirth, neonatal death, perinatal death, intrauterine growth restriction (IUGR), preterm birth, cesarean delivery, low birth weight (LBW), admission to neonatal ICU (NICU), and vertical transmission confirmed at neonate RT-PCR assay.

Miscarriage was defined as pregnancy loss before 22 weeks of gestations. Stillbirth was defined as intrauterine fetal death at or after 22 weeks of gestation. Neonatal death was defined as death of a live-born infant within the first 28 days of life. Perinatal death was defined as either stillbirth or neonatal death. IUGR was defined as ultrasound estimated fetal weight less than 10th percentile.¹⁴

Preterm birth was defined as delivery before 37 completed weeks of gestation. LBW was defined as a birthweight less than 2,500 grams. Fever was defined as an axillary temperature of 37.5 °C or higher. Lymphocytopenia was defined as lymphocyte count of less than 1,500 cells per cubic millimeter. Thrombocytopenia was defined as a platelet count of less than 150,000 per cubic

millimeter. Increased Lactate Dehydrogenase (LDH) level was defined as LDH level higher than 443 U/L in the first trimester, 447 U/L in the second trimester, and 524 U/L in the third trimester of pregnancy. Computed tomography (CT) scan was performed at physicians' discretions. CT abnormalities related to SARS-CoV-2 included ground glass opacity with or without consolidation or visible intralobular lines. Acute respiratory distress syndrome (ARDS) was defined in accordance with the WHO interim guidance.¹¹

Common criteria for admission to ICU included all respiratory arrests, respiratory rate ≥ 40 or ≤ 8 breaths/min, oxygen saturation $< 90\%$ on $\geq 50\%$ oxygen, all cardiac arrests, pulse rate < 40 or > 140 beats/min, systolic blood pressure < 90 mm Hg, sudden fall in level of consciousness (fall in Glasgow coma score > 2 points), repeated or prolonged seizures, rising arterial carbon dioxide tension with respiratory acidosis, any patient giving cause for concern.

Common reasons for admission to NICU were prematurity, respiratory distress syndrome, sepsis, hypoglycemia, perinatal depression, or maternal chorioamnionitis.

Primary and secondary outcomes were evaluated in the overall cohort and in symptomatic and asymptomatic women.

Post-hoc subgroup analyses according to region (European versus non-European countries; high-income versus middle-income countries) were performed for the primary outcome, and for admission to ICU, admission to NICU, and cesarean delivery.

Statistical analysis

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) v. 19.0 (IBM Inc., Armonk, NY, USA) and using Stata, version 13.1 (Stata Corp., College Station, TX, 2014). Continuous variables were reported as means \pm standard deviation (SD), while categorical as

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numbers (percentage). Univariate comparisons of dichotomous data were performed with the use of the chi-square test with continuity correction. Comparisons between groups were performed with the use of the T-test to test group means by assuming equal within-group variances for parametric data, and with the use of Wilcoxon and Mann-Whitney tests for nonparametric data. Multivariate analysis was performed to evaluate potential predictors of the primary outcome. The final model was fit using a stepwise forward process, and including only the covariates with adjusted p-values <0.10 , with the exception of maternal age and pharmacological treatment, which were included a priori. The same approach was used to evaluate the potential independent predictors of perinatal deaths, and preterm deliveries. Logistic regression was reported as odds ratio (OR) and adjusted OR (aOR) with 95% confidence interval (CI). P value <0.05 was considered statistically significant.

Standard diagnostic procedures were adopted to check final models validity: influential observation analysis (Dbeta, change in Pearson chi-square), Hosmer-Lemeshow test for the goodness of fit and C statistic (area under the Receiving Operator Curve).

Women were followed-up from enrollment until 28-days postpartum or until the study end date, whichever came first. For the primary outcome, all enrolled women were analyzed. For the multivariate analysis, only women with completed pregnancies by the study end date were included. Neonatal death was only analyzed for liveborn infants with 28 days of follow-up data.

RESULTS

Characteristics of the included women

During the study period, 388 singleton viable pregnancies, positive to SARS-COV-2 at RT-PCR nasal and pharyngeal swab, in 73 centers from 22 different countries were included in the study.

The mean gestational age at diagnosis was 30.6 ± 9.5 weeks, with 8.0% (31/388) of women being diagnosed in the first, 22.2% (86/388) in the second and 69.8% (271/388) in the third trimester of pregnancy. The most common symptom at the time of triage was cough (52.1%), followed by fever (44.1%), and shortness of breath (15.5%), while 24.2% were asymptomatic. Chest computed tomography (CT) was performed in 56/388 women (14.4%). 45/56 (80.4%) presented bilateral multifocal involvement.

The most used pharmacologic therapy was hydroxychloroquine, used in 90 women (23.2%). Antiviral drugs were used in 72 women (18.6%), with combination of Lopinavir/Ritonavir being the most common used antiviral treatment (60/388, 15.5%) (Table 1). There were no variations in drug use by country.

Maternal outcomes

The primary outcome was reported in 47/388 women (12.1%) with 43/388 (11.1%) of women admitted to ICU, and 36/388 (9.3%) requiring mechanical ventilation. There were 3/388 cases of maternal deaths, accounting for a maternal mortality rate of 0.8% (Table 2). One death occurred in a 33-year old woman with type II diabetes mellitus. She presented at 33 weeks of gestation with stillbirth. She was febrile and unconscious. Chest radiography showed pulmonary infiltrates and atelectasis with elevated left hemidiaphragm. The woman was admitted to ICU and intubated but died with acute kidney injury and cardiac arrest. The second death occurred in a 27-year-old woman

who presented at 34 weeks of gestation with severe shortness of breath. She underwent urgent cesarean delivery and received continuous positive airway pressure (C-PAP) ventilation but died of respiratory failure before intubation. The third death occurred in a 31-year-old woman who presented at 38 weeks of gestation with myalgia, fatigue, sore throat, and severe hypertension. She underwent urgent cesarean delivery due to the uncontrolled high blood pressure and developed severe preeclampsia. After delivery, the woman was admitted to ICU, and received ECMO for acute respiratory failure complicated by pneumothorax and left lung hemorrhage and died 8 days after delivery. Details of women admitted to ICU are shown in Table S2.

Perinatal outcomes

Of the 388 women included in the study, 122 (31.4%) were still pregnant at the time of the study data analysis. Among the other 266 women, 3 (1.1%) had elective termination of pregnancy, 6 (2.3%) had stillbirth, 6 had spontaneous first-trimester abortion (19.4% of the 31 women with first trimester infection), and 251 (94.4%) delivered a live-born infant (Table 2; Figure 1). The most common mode of delivery was the cesarean delivery, performed in 136/251 (54.2%) women. Preterm birth at less than 37 weeks of gestation occurred in 70/266 women (26.3%), of them 56/70 (80.0%) were indicated preterm deliveries and 14/70 (20.0%) were spontaneous preterm deliveries. Of the 251 live-born infants, 69 (27.5%) were admitted to NICU.

There were 5/251 (2.0%) neonatal deaths. Of them, 3 were born preterm, and the other two died after they developed a late-onset sepsis. Only one of the 251 live-born neonates (0.4%) was found positive at RT-PCR pharyngeal swabs performed after delivery. The mother was tested positive during the third trimester of pregnancy.

Among the 266 women with completed pregnancies, the overall number of perinatal deaths was 11 (4.1%). Ten of their mothers had COVID-19 symptoms at presentation, and one was asymptomatic.

Predictors of primary outcome

In the multivariable analysis restricted to the women with completed pregnancy (n=266; Table 3), the only independent predictors of primary outcome (composite measure of maternal mortality and morbidity) were COVID-19 symptoms at presentation versus no symptoms (aOR 5.11, 95% CI 1.11 to 23.6), shortness of breath at presentation (aOR 3.68, 95% CI 1.58 to 8.58), and increased levels of LDH (aOR 4.13, 95% CI 1.54 to 11.1).

Post-hoc analyses

Post-hoc subgroup analyses according to region showed no statistically significant differences in the primary outcome (Table S3).

DISCUSSION

Main findings

This multicenter study, including 388 pregnant women from 72 different centers, aimed to evaluate maternal and perinatal outcomes of pregnant women with confirmed SARS-COV-2. The study showed that in pregnancies complicated by SARS-COV-2, the risk of maternal mortality was 0.8%, but about 11% of women required admission to ICU. Pregnancies affected by SARS-COV-2 were also complicated by 26.3% rate preterm birth, and 4.1% rate of perinatal death. The risk of vertical transmission was negligible, with only one case confirmed positive after the delivery. Multivariate analyses showed that the only independent predictors of primary outcome (composite measure of maternal mortality and morbidity) were COVID-19 symptoms at presentation.

Strengths and limitations

To the best of our knowledge, this is one of the largest cohort of SARS-COV-2 infection during pregnancy published so far.⁵ The enrollment of only of women with laboratory-confirmed SARS-COV-2, the large sample, the inclusion of both University Hospitals and Community Hospitals from different countries, and multitude of outcomes explored, represent the major strengths of the study. Moreover, no patients were lost to follow up and no data were missing for the primary outcome. The major limitation of the study is the inclusion of only high-income and middle-income countries. Therefore, data from this study may not be applicable to low-income countries, where maternal and perinatal outcomes may be even worse. Data on maternal therapy were limited by the

non-randomized approach, and we also acknowledge a potential heterogeneity in management, since a very large number of centers participated in this study. Our population came mostly from women referred for suspected COVID-19, due to symptoms or exposure, and consequently tested with RT-PCR nasal and pharyngeal swab. Therefore, the percentage of asymptomatic women in our cohort was low. Maternal and perinatal outcomes may be better in cohort of women that received universal screening for SARS-COV-2, where the rate of asymptomatic women can be as high as 88%.¹⁵ We may not have included all positive women referred to our centers. Indeed, an asymptomatic woman with COVID-19 undiagnosed early in pregnancy and then tested negative late in pregnancy may not have been included. A lack of control group of pregnant women without COVID-19 make difficult to evaluate the increased risk of adverse maternal and perinatal outcome in women with COVID-19. Data on treatment side effects and on indication for cesarean delivery were not collected. Therefore, it was not possible to evaluate whether the high rate of cesarean delivery was indirectly related to COVID-19, e.g. fear of vertical transmission during vaginal delivery, or fear of providers to stand near a positive woman for many hours during labor and delivery. The multicenter study design raises the question of the different criteria for maternal ICU admission. Another major limitation as the use of a composite score of maternal mortality and morbidity as a primary outcome. This choice was due to the fact that each individual component of the primary and secondary outcome had a low prevalence in the sub-group of women with COVID-19 infection and thus analyzing each outcome separately would have significantly reduced the power of the analysis and therefore the robustness of the results. Unfortunately, this did not allow us to perform meaningful sub-group analysis in view of the very low prevalence of each component of the primary outcome in the study population. Finally, the very large number of centers

participating in this study made difficult to ascertain whether each investigator retrieved the information of each outcome independently or by record linkage.

Implications for clinical practice and research

Since December 2019, the outbreak of COVID-19 has become a major epidemic worldwide.² Patients infected with the virus may either be asymptomatic or experience mild to severe symptoms, including pneumonia, respiratory failure, and death.¹⁶⁻¹⁸

Physiologic maternal adaptations to pregnancy may predispose pregnant women to a more severe course of viral pneumonia, with higher risk of maternal mortality and morbidity as reported for influenza or varicella infections.¹⁹ Therefore, prevention and control of COVID-19 among pregnant women have become a major concern for obstetricians. In the last few months, several recommendations have been published,^{4,20,21} but evidence is limited,²² and is mostly based on case reports,²³⁻²⁶ and expert opinions.^{4,20,21} Data published so far^{5,27,28} showed that COVID-19 in pregnant women was associated with a relatively high rate of preterm birth, and cesarean delivery, but no evidence of vertical transmission or maternal death.^{4,5,29}

In the present cohort, the mortality rate was low. In our cohort we reported three cases of maternal deaths among three symptomatic pregnant women. Very few cases of maternal death related to COVID-19 have been reported so far.¹⁷ Evidence from non-pregnant populations showed that among critically ill patients with laboratory-confirmed COVID-19 admitted to ICUs, mortality is about 25%.^{29,30} In our cohort, the rate of maternal death was 0.8% with 11% rate of admission to ICU. Conversely, the 1918 Spanish flu had a mortality rate of 3% in the general population, and

37% among pregnant women,^{31,32} and in the 2003 pregnant women with SARS-COV-1 reported a mortality rate of 25%.⁴

Our cohort included a case of suspected vertical transmission, with a neonate tested positive soon after birth at RT-PCR test on nasopharyngeal swab. The newborn was asymptomatic and had negative RT-PCR test after 14 days of life. Unfortunately, amniotic fluid was not tested, and specimens from placenta were not obtained, thus questioning whether the infection occurred in utero (antenatal vertical transmission) or immediately prior or after birth (perinatal vertical transmission). Don et al. reported a case of a primiparous woman positive to SARS-COV-2 at RT-PCR on nasopharyngeal swab who delivered by cesarean section in a negative-pressure isolation room.³³ Results from 5 RT-PCR tests on nasopharyngeal swab taken from 2 hours to 16 days of age were negative, but the infant had elevated antibody levels and abnormal cytokine test results 2 hours after birth. The elevated IgM antibody level may suggest that the neonate could be infected in utero, given that IgM antibodies are not transferred to the fetus via the placenta.³⁴ Anyway, no infant specimen had a positive RT-PCR test result, so there was no virologic evidence for congenital infection in this case to support the serologic suggestion of in utero transmission.³⁵ Notably, IgM may also reach fetal circulation in case of placental inflammation.³⁶ Moreover, sensitivity and specificity of IgM tests vary by disease, but usually are less reliable than molecular diagnostic tests based on nucleic acid amplification and detection.³⁷ Congenital infections, indeed, are usually not diagnosed based on IgM detection because IgM assays can be prone to false-positive and false-negative results, along with cross-reactivity and testing challenges.^{36,37} Another potential perinatal vertical transmission occurring during vaginal delivery in a pregnant women with rectal and stool maternal swab positive for COVID-19 has been recently reported by Carosso et al.²⁹ The authors

concluded that SARS-COV-2 can enter the neonatal nasopharynx and potentially trigger neonatal infection.^{29,38}

Different therapies have been proposed for treatment of COVID-19. Agents previously used to treat SARS and MERS are potential candidates to treat SARS-COV-2, but meta-analysis of SARS and MERS therapies found no clear benefit of any specific regimen.³⁹⁻⁴¹ Published clinical experiences showed that hydroxychloroquine, azithromycin, and antiviral drugs, including as Kaletra (Lopinavir/Ritonavir), Darunavir/Cobicistat or other antiretrovirals, Arbidol (Umifenovir), Remdesivir, or Favipiravir are the most promising drugs of COVID-19.^{39,42} In the present study, 42.8% (166/388) of the women received a pharmacologic treatment, such as hydroxychloroquine, azithromycin, antiviral drug, or low molecular weight heparin. The very small number of events, inclusion of an heterogeneous population of pregnant women and lack of randomized study design did not allow to extrapolate any evidence of the effectiveness of pharmacologic therapy in our cohort. In the absence of proven therapy, currently the care of patients with SARS-COV-2 should be mostly based on supportive care, and further evidence is needed before drawing any robust conclusion.⁴³

Conclusions

In summary, SARS-COV-2 in pregnant women is associated with 0.8% rate of maternal mortality, but 11.1% rate of admission to ICU. The risk of vertical transmission seems to be negligible.

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Gabriele Saccone MD,¹ Cihat Sen MD,² Daniele Di Mascio MD,³ Alberto Galindo MD,⁴ Amos Grünebaum MD,⁵ Jun Yoshimatsu MD,⁶ Milan Stanojevic MD,⁷ Asım Kurjak MD,⁷ Frank Chervenak MD,⁵ María José Rodríguez Suárez MD,⁸ Zita Maria Gambacorti-Passerini MD,⁹ María de los Angeles Anaya Baz MD,^{9,10} Esther Vanessa Aguilar Galán MD,^{9,10} Yolanda Cuñarro López MD,¹¹ Juan Antonio De León Luis MD,¹¹ Ignacio Cueto Hernández MD,¹¹ Ignacio Herraiz MD,⁴ Cecilia Villalain MD,⁴ Roberta Venturella MD,¹² Giuseppe Rizzo MD,^{13,14} Ilenia Mappa MD,¹³ Giovanni Gerosolima MD,¹⁵ Lars Hellmeyer MD,¹⁶ Josefina Königsbauer MD,¹⁶ Giada Ameli MD,¹⁶ Tiziana Frusca MD,¹⁷ Nicola Volpe MD,¹⁷ Giovanni Battista Luca Schera MD,¹⁷ Stefania Fieni MD,¹⁷ Eutalia Esposito MD,¹⁸ Giuliana Simonazzi MD,¹⁹ Gaetana Di Donna MD,¹⁹ Aly Youssef MD,¹⁹ Anna Nunzia Della Gatta MD,¹⁹ Mariano Catello Di Donna MD,²⁰ Vito Chiantera MD,²⁰ Natalina Buono MD,²⁰ Giulio Sozzi MD,²⁰ Pantaleo Greco MD,²¹ Danila Morano MD,²¹ Beatrice Bianchi MD,²¹ Maria Giulia Lombana Marino MD,²¹ Federica Laraud MD,²² Arianna Ramone MD,²² Angelo Cagnacci MD,²² Fabio Barra MD,²² Claudio Gustavino MD,²² Simone Ferrero MD,²² Fabio Ghezzi MD,²³ Antonella Cromi MD,²³ Antonio Simone Laganà MD,²³ Valentina Laurita Longo MD,^{24,25,26} Francesca Stollagli MD,²⁵ Angelo Sirico MD,²⁴ Antonio Lanzone MD,^{24,25} Lorenza Driul MD,²⁷ Fabiana Cecchini MD,²⁷ Serena Xodo MD,²⁷ Brian Rodriguez MD,²⁸ Felipe Mercado-Olivares MD,²⁸ Deena Elkafrawi MD,²⁸ Giovanni Sisti MD,²⁸ Rosanna Esposito MD,¹ Antonio Coviello MD,¹ Marco Cerbone MD,¹ Maddalena Morlando MD,²⁹ Antonio Schiattarella MD,²⁹ Nicola Colacurci MD,²⁹ Pasquale De Francis MD,²⁹ Iliana Cataneo MD,³⁰ Marinella Lenzi MD,³⁰ Fabrizio Sandri MD,³⁰ Riccardo Buscemi MD,³¹ Giorgia Gattei MD,³¹ Francesca della Sala MD,³¹ Eleonora Valori MD,^{31,32} Maria Cristina Rovellotti MD,³¹ Elisa Done MD,³³ Gilles Faron MD,³³ Leonardo Gucciardo MD,³³ Valentina Esposito MD,³⁴ Flaminia Vena MD,³ Antonella Giancotti MD,³ Roberto Brunelli MD,³ Ludovico Muzii MD,³ Luigi Nappi MD,³⁵ Felice Sorrentino MD,³⁵ Marco Liberati MD,³⁶ Danilo Buca MD,³⁶ Martina Leombroni MD,³⁶ Francesca Di Sebastiano MD,³⁶ Massimo Franchi MD,³⁷ Quintino Cesare Ianniciello MD,³⁷ Simone Garzon MD,³⁷ Giuliano Petriglia MD,³⁸ Leonardo Borrello MD,³⁸ Alvaro José Nieto-Calvache MD,^{39,40} Juan Manuel Burgos-Luna MD,^{39,40} Caroline Kadji MD,⁴¹ Andrew Carlin MD,⁴¹ Elisa Bevilacqua MD,⁴¹ Marina Moucho MD,⁴² Pedro Viana Pinto MD,⁴² Rita Figueiredo MD,⁴² José Morales Roselló MD,⁴³ Gabriela Loscalzo MD,⁴³ Alicia Martinez-Varea MD,⁴³ Vincente Diago MD,⁴³ Jesús S Jimenez Lopez MD,⁴⁴ Alicia Yeliz Aykanat MD,⁴⁵ Stefano Cosma MD,⁴⁶ Andrea Carosso MD,⁴⁶ Chiara Benedetto MD,⁴⁶ Amanda Bermejo MD,⁴⁷ Otto Henrique May Feuerschuette MD,⁴⁸ Ozlem Uyaniklar MD,⁴⁹ Sakine Rahimli Ocakoglu MD,⁴⁹ Zeliha Atak MD,⁴⁹ Reyhan Gündüz MD,⁵⁰ Esra Tustas Haberal MD,⁵¹ Bernd Froessler MD,⁵² Anupam Parange MD,⁵² Peter Palm MD,⁵² Igor Samardjiski MD,⁵³ Chiara Tacaliti MD,⁵⁴ Erhan Okuyan MD,⁵⁵ George Daskalakis MD,⁵⁶ Renato Augusto Moreira de Sa MD,⁵⁷ Alejandro Pittaro MD,⁵⁸ Maria Luisa Gonzalez-Duran MD,⁵⁹ Ana Concheiro Guisan MD,⁵⁹ Şerife Özlem Genç MD,⁶⁰ Blanka Zlatohlávková MD,⁶¹ Anna Luengo Piqueras MD,⁶² Dolores Esteban Oliva MD,⁶² Aylin Pelin Cil MD,⁶³ Olus Api MD,⁶³ Panos Antsaklis MD,⁵⁶ Liana Ples MD,⁶⁴ Ioannis Kyvernitis MD,⁶⁵ Holger Maul MD,⁶⁵ Marcel Malan MD,⁶⁵ Albert Lila MD,⁶⁶ Roberta Granese MD,⁶⁷ Alfredo Ercoli MD,⁶⁷ Giuseppe Zoccali MD,⁶⁷ Andrea Villasco MD,⁶⁸ Nicoletta Biglia MD,⁶⁸ Ciuhodaru Madalina MD,⁶⁹ Elena Costa MD,⁷⁰ Caroline Daelemans MD,⁷⁰ Axelle Pintiaux MD,⁷⁰ Elif Gül Yapar Eyi MD,⁷¹ Elisa Cueto MD,⁷² Eran Hadar MD,⁷³ Sarah Dollinger MD,⁷³ Noa A. Brzezinski-Sinai MD,⁷³ Erasmo Huertas MD,⁷⁴

Pedro Arango MD,⁷⁴ Amadeo Sanchez MD,⁷⁴ Javier Alfonso Schwartzman MD,⁷⁵ Liviu Cojocaru MD,⁷⁶ Sifa Turan MD,⁷⁶ Ozhan Turan MD,⁷⁶ Maria Carmela Di Dedda MD,⁷⁷ Rebeca Garrote Molpeceres MD,⁷⁸ Snezana Zdjelar MD,⁷⁹ Tanja Premru-Srsen MD,⁸⁰ Lilijana Kornhauser-Cerar MD,⁸⁰ Mirjam Drušković MD,⁸⁰ Valentina De Robertis MD,⁸¹ Vedran Stefanovic MD,⁸² Irmeli Nupponen MD,⁸² Kaisa Nelskylä MD,⁸² Zulfiya Khodjaeva MD,⁸³ Ksenia A. Gorina MD,⁸³ Gennady T. Sukhikh MD,⁸³ Giuseppe Maria Maruotti MD,¹ Silvia Visentin MD,⁸⁴ Erich Cosmi MD,⁸⁴ Jacopo Ferrari MD,⁸⁴ Alessandra Gatti MD,⁸⁵ Daniela Luvero MD,⁸⁵ Roberto Angioli MD,⁸⁵ Ludovica Puri MD,²⁵ Marco Palumbo MD,⁸⁶ Giusella D'Urso MD,⁸⁶ Francesco Colaleo MD,⁸⁶ Agnese Maria Chiara Rapisarda MD,⁸⁶ Ilma Floriana Carbone MD,⁸⁷ Lamberto Manzoli MD,⁸⁸ Maria Elena Flacco MD,⁸⁸ Giovanni Nazzaro MD,¹ Mariavittoria Locci MD,¹ Maurizio Guida MD,¹ Attilio Di Spiezio Sardo MD,⁸⁹ Pierluigi Benedetti Panici MD,³ Asma Khalil MD,^{90,91} Vincenzo Berghella MD,⁹² Giuseppe Bifulco MD,¹ Giovanni Scambia MD,²⁴ Fulvio Zullo MD,¹ Francesco D'Antonio MD³⁶

¹Department of Neuroscience, Reproductive Sciences and Dentistry, School of Medicine, University of Naples Federico II, Naples, Italy

²Perinatal Medicine Foundation and Department of Perinatal Medicine, Memorial Hospital, Istanbul, Turkey

³Department of Maternal and Child Health and Urological Sciences, Sapienza University of Rome, Rome, Italy

⁴Fetal Medicine Unit, Maternal and Child Health and Development Network, Department of Obstetrics and Gynecology, University Hospital 12 de Octubre, Complutense University of Madrid, Madrid, Spain

⁵Department of Obstetrics and Gynecology, Lenox Hill Hospital, Zucker School of Medicine at Hofstra/Northwell, NY, USA

⁶Department of Perinatology and Gynecology, National Cerebral and Cardiovascular Center, Osaka, Japan

⁷Department of Obstetrics and Gynecology, Medical School University of Zagreb, Sveti Duh University Hospital, Zagreb, Croatia

⁸Hospital Universitario Central de Asturias, Spain

⁹Department of Obstetrics and Gynecology, Ciudad Real University General Hospital, Ciudad Real, Spain

¹⁰University of Castilla-La Mancha, Ciudad Real, Spain

¹¹Fetal Medicine Unit, Maternal and Child Health and Development Network, Department of Obstetrics and Gynecology, Gregorio Marañón Hospital, Complutense University of Madrid, Madrid, Spain

¹²Department of Obstetrics and Gynaecology, School of Medicine, Magna Graecia University of Catanzaro, Catanzaro, Italy.

¹³University of Roma Tor Vergata, Division of Maternal Fetal Medicine, Ospedale Cristo Re Roma, Rome, Italy

¹⁴Department of Obstetrics and Gynecology The First I.M. Sechenov Moscow State Medical University, Moscow, Russia

¹⁵Department of Obstetrics and Gynecology, Ospedale AOSG Moscati, Avellino, Italy

¹⁶Department of Gynecology and Obstetrics, Vivantes Klinikum im Friedrichshain, Berlin, Germany

¹⁷Department of Obstetrics and Gynecology, University of Parma, Parma, Italy

¹⁸Department of Obstetrics and Gynecology, Ospedale di San Leonardo, Castellammare di Stabia, Italy

¹⁹Department of Obstetrics and Gynecology, University of Bologna, Sant'Orsola- Malpighi University Hospital, Bologna, Italy.

²⁰Department of Gynecologic Oncology, University of Palermo, Palermo, Sicilia, Italy

²¹Department of Medical Sciences, Section of Obstetrics and Gynecology, Azienda Ospedaliera-Universitaria Sant' Anna, University of Ferrara, Ferrara, Italy

²²Academic Unit of Obstetrics and Gynaecology, IRCCS Ospedale Policlinico San Martino, Genova, Italy

²³Department of Obstetrics and Gynecology, "Filippo Del Ponte" Hospital, University of Insubria, Varese, Italy

²⁴Department of Obstetrics and Gynaecology, Fondazione Policlinico Universitario A Gemelli IRCCS - Università Cattolica del Sacro Cuore, Rome, Italy

²⁵Istituto di Clinica Ostetrica e Ginecologica, Università Cattolica del Sacro Cuore, Rome, Italy

²⁶Queen Margaret University, Institute for Global Health and Development, Edinburgh, U.K.

²⁷Clinic of Obstetrics and Gynecology, University of Udine, Udine, Italy

²⁸Department of Obstetrics and Gynecology, New York Health and Hospitals/Lincoln Bronx, NY, USA

²⁹Department of Woman, Child and General and Specialized Surgery, University of Campania Luigi Vanvitelli, Naples, Italy

³⁰Unit of Obstetrics and Gynecology, Ospedale Maggiore, Bologna, Italy

³¹Department of Translational Medicine, University of Eastern Piedmont, Novara, Italy

³²Hospital Castelli, Verbania, Italy

³³UZ Brussel, Universitair Ziekenhuis, Brussel, Belgium

³⁴University of Milan, Milan, Italy

³⁵Department of Obstetrics and Gynecology, Department of Medical and Surgical Sciences, University of Foggia, Foggia, Italy

³⁶Centre for High Risk Pregnancy and Fetal Care, Department of Obstetrics and Gynecology, University of Chieti, Chieti Italy

- ³⁷Department of Obstetrics and Gynecology, AOUI Verona, University of Verona, Verona, Italy
- ³⁸Maternal and Child Health Department, Santa Maria Hospital, Terni, Italy
- ³⁹Fundación Valle del Lili, Tertiary Obstetric Unit, Cali, Colombia
- ⁴⁰Universidad Icesi, Postgraduate Department, Cali, Colombia
- ⁴¹Department of Obstetrics and Gynecology, University Hospital Brugmann, Université Libre de Bruxelles, Brussels, Belgium
- ⁴²Department of Obstetrics and Gynecology, Centro Hospitalar e Universitário São João, Porto, Portugal
- ⁴³Servicio de Obstetricia y Ginecología, Hospital Universitario y Politécnico La Fe, Valencia, Spain
- ⁴⁴Hospital Regional Universitario de Málaga, Malaga, Spain
- ⁴⁵Department of Obstetrics and Gynecology, Istanbul University-Cerrahpasa Medical School, Istanbul, Turkey
- ⁴⁶Department of Obstetrics and Gynecology, Sant'Anna Hospital, University of Turin, Turin, Italy
- ⁴⁷Hospital Universitario de Mostoles, Mostoles, Spain
- ⁴⁸Departamento de Ginecologia e Obstetrícia, Hospital Universitário Polydoro Ernani, Santiago, Brazil
- ⁴⁹Bursa City Hospital, Bursa, Turkey
- ⁵⁰Department of Obstetrics and Gynecology, University of Dicle, Diyarbakır, Turkey
- ⁵¹Hisar Intercontinental Hospital, Istanbul, Turkey
- ⁵²Department of Anaesthesia, Lyell McEwin Hospital, Adelaide, Australia
- ⁵³University Clinic of Obstetrics and Gynecology, Skopje, North Macedonia
- ⁵⁴Ospedale Generale Regionale "F. Miulli", Acquaviva delle Fonti, Italy
- ⁵⁵Batman Maternity and Child Health Hospital, Batman, Turkey
- ⁵⁶Alexandra Hospital – National and Kapodistrian, University of Athens, Athens, Greece
- ⁵⁷Assistência Obstétrica do Grupo Perinatal, Rio de Janeiro, Brazil
- ⁵⁸Hospital Raul F. Larcade, Buenos Aires, Argentina
- ⁵⁹Alvaro Cunqueiro University Hospital Of Vigo, Vigo, Spain
- ⁶⁰Karaman Public Hospital, Karaman, Turkey
- ⁶¹Department of Obstetrics and Gynecology, Division of Neonatology, General Hospital in Prague and First Faculty of Medicine, Charles University, Prague, Czech Republic
- ⁶²Hospital Universitari Germans Trias i Pujol, Barcelona, Spain
- ⁶³American Hospital, Istanbul, Turkey
- ⁶⁴Department of Obstetrics and Gynecology, Saint John Hospital, UMF Carol Davila Bucharest, Romania
- ⁶⁵Asklepios Hospital Barmbek, Hamburg, Germany
- ⁶⁶Regional Hospital Gjakova, Kosovo, Republic of Kosovo
- ⁶⁷Department of Obstetrics and Gynecology, University of Messina, Messina, Italy
- ⁶⁸Academic Division of Obstetrics and Gynecology, Maurizio Umberto I Hospital, University of Turin, Turin, Italy
- ⁶⁹Universitatea de Medicină și Farmacie Grigore T. Popa Iași, Iasi, Romania
- ⁷⁰Department of Obstetrics and Gynecology, Hospital Erasme, Cliniques Universitaires de Bruxelles, Brussels, Belgium
- ⁷¹Ankara Bilkent City Hospital, Ankara, Turkey
- ⁷²Hospital Virgen De La Luz, Cuenca, Spain
- ⁷³Helen Schneider Hospital for Women, Rabin Medical Center, Petach-Tikva and Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel
- ⁷⁴Instituto Nacional Materno Perinatal, Lima, Peru
- ⁷⁵Centro de Educación Médica e Investigaciones Clínicas "Norberto Quirno", Buenos Aires, Argentina
- ⁷⁶Department of Obstetrics, Gynecology and Reproductive Science, University of Maryland Medical Center, Baltimore, MD, USA
- ⁷⁷Department Gynecology and Obstetrics, Fornaroli Hospital, Magenta, Italy
- ⁷⁸University Clinic Hospital Of Valladolid, Valladolid, Spain
- ⁷⁹Kbc Dr Dragisa Misovic Dedinje Belgrade, Serbia
- ⁸⁰Department of Perinatology, University Medical Center, Medical Faculty, University of Ljubljana, Ljubljana, Slovenia
- ⁸¹Fetal Medicine Unit, Di Venere Hospital, Bari, Italy
- ⁸²Department of Obstetrics and Gynecology, Neonatology and Intensive Care, Helsinki University Hospital and University of Helsinki, Helsinki, Finland
- ⁸³National Medical Research Center for Obstetrics, Gynecology and Perinatology, Moscow, Russia
- ⁸⁴Department of Woman' and Child's Health, University of Padova, Padova, Italy
- ⁸⁵Campus Bio Medico, University of Rome, Rome, Italy
- ⁸⁶Department of General Surgery and Medical Surgical Specialties, University of Catania, Catania, Italy
- ⁸⁷Ospedale Maggiore Policlinico Milano, Milan, Italy
- ⁸⁸Department of Medical Sciences, University of Ferrara, Italy.
- ⁸⁹Department of Public Health, School of Medicine, University of Naples Federico II, Naples, Italy
- ⁹⁰Fetal Medicine Unit, Saint George's Hospital, London, United Kingdom
- ⁹¹Vascular Biology Research Centre, Molecular and Clinical Sciences Research Institute, St George's University of London

⁹²Maternal Fetal Medicine Division, Obstetrics and Gynecology Department, Sidney Kimmel Medical College at Thomas Jefferson University, Philadelphia, PA, United States.

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FIGURE LEGEND

Figure 1. Study flowchart

SUPPLEMENTARY TABLES

Table S1. List of the centers included in the study

Table S2. Details of women admitted to intensive care unit

Table S3. Post hoc subgroup analyses according to region

Table 1. Characteristics of the included women

	(N=388)
Demographics, n (%)	
Living in high income countries	337 (86.9)
Living in European countries	295 (76.0)
Healthcare workers	28 (7.2)
Smoking	54 (13.9)
Chronic disease pre-existing pregnancy*	156 (40.2)
Obesity**	28 (7.2)
Infection in the first trimester of pregnancy	31 (8.0)
Infection in the second trimester of pregnancy	86 (22.2)
Infection in the third trimester of pregnancy	271 (69.8)
Chest CT scan	56 (14.4)
Bilateral CT abnormalities	45/56 (80.4)
Mean age in years \pm SD	32.2 \pm 6.1
Mean gestational age at infection (weeks) \pm SD	30.6 \pm 9.5
COVID-19 Symptoms at diagnosis, n (%)	
Fever	171 (44.1)
Cough	202 (52.1)
Rhinorrhea	29 (7.5)
Myalgia	56 (14.4)
Anosmia	21 (5.4)
Shortness of breath	60 (15.5)
Diarrhea	16 (4.1)
Conjunctivitis	9 (2.3)
Symptoms, any	294 (75.8)
Laboratory findings, n (%)	
Lymphopenia	156 (40.2)
Thrombocytopenia	40 (10.3)
Increased LDH levels	32 (8.2)
Pharmacologic Treatments, n (%)	
No specific pharmacologic treatments	222 (57.2)
Hydroxychloroquine	90 (23.2)
Any antibiotics	79 (20.4)
Azithromycin	58 (14.9)
Low molecular weight heparin	87 (22.4)
Antiviral drug,	
Any	72 (18.6)
- Darunavir/Cobicistat	4 (1.0)

- Oseltamivir	2 (0.5)
- Lopinavir/Ritonavir	60 (15.5)
- Darunavir/Ritonavir	2 (0.5)
- Remdesivir	2 (0.5)

Data are presented as number (percentage) or as mean \pm standard deviation (SD)

**including diabetes, hypertension, or asthma*

***defined as body mass index of 30 or greater*

LDH, Lactate Dehydrogenase; CT, computed tomography

Table 2. Maternal and perinatal outcomes, overall and by symptoms at diagnosis.

	Total Sample	(N=388)	Symptomatic	(N=294)	Asymptomatic	(N=94)	
	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	p
Maternal outcomes							
Primary outcome ^A	12.1 (9.2-15.7)	47	15.3 (11.6-19.9)	45	2.1 (0.6-7.4)	2	0.001
Admission to ICU	11.1 (8.3-14.6)	43	14.3 (10.8-18.8)	42	1.1 (0.2-5.8)	1	<0.001
Any type of mechanical ventilation	9.3 (6.8-12.6)	36	11.9 (8.7-16.1)	35	1.1 (0.2-5.8)	1	0.002
Intubation	6.4 (4.4-9.3)	25	8.5 (5.8-12.3)	25	0.0 (0.0-3.9)	0	0.003
ARDS	1.8 (0.9-3.7)	7	2.4 (1.2-4.8)	7	0.0 (0.0-3.9)	0	0.13
ECMO	0.5 (0.1-1.9)	2	0.7 (0.2-2.5)	2	0.0 (0.0-3.9)	0	0.4
Maternal death	0.8 (0.3-2.2)	3	1.0 (0.4-3.0)	3	0.0 (0.0-3.9)	0	0.3
Ongoing pregnancies	31.4 (27.0-36.2)	122	35.7 (30.5-41.3)	105	18.1 (11.6-27.1)	17	0.001
Completed pregnancies	68.6 (63.8-73.0)	266	64.3 (58.7-69.6)	189	81.9 (72.9-88.4)	77	0.001
Perinatal outcomes							
<i>Women with completed pregnancies</i>		(N=266)		(N=189)		(N=77)	
Elective termination of pregnancy	1.1 (0.4-3.3)	3	1.1 (0.3-3.8)	2	1.3 (0.2-7.0)	1	0.9
Stillbirth	2.3 (1.0-4.8)	6	2.7 (1.1-6.1)	5	1.3 (0.2-7.0)	1	0.8
Perinatal death	4.1 (2.3-7.3)	11	5.3 (2.9-9.5)	10	1.3 (0.2-7.0)	1	0.14
IUGR	3.8 (2.1-6.8)	10	4.8 (2.5-8.8)	9	1.3 (0.2-7.0)	1	0.2
Preterm birth	26.3 (21.4-	70	31.8 (25.5-38.7)	60	13.0 (7.2-22.3)	10	0.002

	31.9)						
Live-born infants	94.4 (90.9-96.6)	251	93.7 (89.2-96.3)	177	96.1 (89.2-98.7)	74	0.8
<i>Women with live-born infants</i>		(N=251)		(N=177)		(N=74)	
Possible vertical transmission	0.4 (0.07-2.2)	1	0.6 (0.1-3.1)	1	0.0 (0.0-4.9)	0	0.5
Neonatal death ^B	2.0 (0.9-4.6)	5	2.8 (1.2-6.4)	5	0.0 (0.0-4.9)	0	0.14
Admission to NICU	27.5 (22.3-33.3)	69	28.3 (22.1-35.3)	50	25.7 (17.1-36.7)	19	0.7
Breastfeeding	40.2 (34.4-46.4)	101	41.2 (34.3-48.6)	73	37.8 (27.7-49.3)	28	0.2
Skin to skin	27.5 (22.3-33.3)	69	28.8 (22.6-35.9)	51	24.3 (16.0-35.2)	18	0.3
Low birth weight	20.7 (16.2-26.2)	52	24.3 (18.6-31.1)	43	12.2 (6.5-21.5)	9	0.022
Cesarean delivery	54.2 (48.0-60.2)	136	56.5 (49.1-63.6)	100	48.7 (37.6-59.8)	36	0.5
Spontaneous first-trimester abortion ^C	19.4 (9.2-36.3)	6/31	21.7 (9.7-41.9)	5/23	12.5 (2.2-47.1)	1/8	0.7
Gestational age at delivery Mean \pm SD	37.2 \pm 3.9		36.6 \pm 4.3		38.6 \pm 2.2		<0.001
Birth weight (grams) Mean \pm SD	2919 \pm 772		2821 \pm 846		3149 \pm 496		0.004

ICU, intensive care unit; NICU; neonatal intensive care unit; IUGR, intrauterine growth restriction; ARDS, acute respiratory distress syndrome; ECMO, Extra Corporeal Membrane Oxygenation

^A defined as at least one of the following: admission to ICU, use of mechanical ventilations, or maternal death

^B Including only live-born infants with 28 days follow-up

^C Including only women with first trimester infection

Table 3. Potential predictors of primary outcome (maternal death, admission to ICU, or maternal mechanical ventilation) among the women with completed pregnancy (n=266).

	No primary outcome	Primary outcome	Crude OR (95% CI)	Adjusted OR (95% CI) ^A	Adjusted p ^A
	(N=227)	(N=39)			
Demographics, % (n)					
Living in high (vs middle) income countries	87.7 (199)	87.2 (34)	0.96 (0.35-2.65)	--	--
Living in European countries	79.3 (180)	76.9 (30)	0.87 (0.39-1.96)	--	--
Healthcare workers	7.9 (18)	2.6 (1)	0.31 (0.04-2.36)	--	--
Smoking	14.5 (33)	5.1 (2)	0.32 (0.07-1.38)	--	--
Chronic disease pre-existing	43.6 (99)	12 (30.8)	0.57 (0.28-1.19)	--	--

pregnancy*					
Obesity	10.1 (23)	2.6 (1)	0.23 (0.03-1.78)	--	--
Infection in the first trimester of pregnancy	4.4 (10)	0.0 (0)	--	--	--
Infection in the second trimester of pregnancy	9.7 (22)	23.1 (9)	2.80 (1.18-6.64)	--	--
Infection in the third trimester of pregnancy	85.9 (122)	76.9 (30)	0.55 (0.24-1.26)	--	--
Maternal mean age in years \pm SD	32.6 \pm 6.2	31.5 \pm 6.6	0.97 (0.92-1.03)	0.95 (0.89-1.01)	0.10
Mean gestational age at infection (weeks) \pm SD	34.6 \pm 7.5	32.1 \pm 5.8	0.96 (0.92-1.00)	--	--
Symptoms at diagnosis, % (n)					
Fever	41.4 (94)	59.0 (23)	2.03 (1.02-4.06)	--	--
Cough	45.4 (103)	59.0 (23)	1.73 (0.87-3.45)	--	--
Rhinorrhea	6.6 (15)	0.0 (0)	--	--	--
Myalgia	13.2 (30)	12.8 (5)	0.97 (0.35-2.66)	--	--
Anosmia	5.3 (12)	2.6 (1)	0.47 (0.06-3.73)	--	--
Shortness of breath	11.0 (25)	43.6 (17)	6.24 (2.93-13.3)	3.68 (1.58-8.58)	0.003
Diarrhea	2.6 (6)	2.6 (1)	0.97 (0.11-8.28)	--	--
Conjunctivitis	1.3 (3)	0.0 (0)	--	--	--
Symptoms, any	67.0 (152)	94.9 (37)	9.13 (2.14-38.9)	5.11 (1.11-23.6)	0.037
Laboratory findings, % (n)					
Lymphopenia	37.9 (86)	66.7 (26)	3.28 (1.60-6.72)	2.26 (0.99-5.16)	0.053
Thrombocytopenia	8.8 (20)	23.1 (9)	3.10 (1.29-7.44)	--	--

Increased lactate dehydrogenase levels	7.0 (16)	30.8 (12)	5.86 (2.51-13.7)	4.13 (1.54-11.1)	0.005
Pharmacologic Treatments, % (n)					
No specific pharmacologic treatments	57.7 (131)	35.9 (14)	0.41 (0.20-0.83)	0.58 (0.26-1.29)	0.18
Hydroxychloroquine	21.6 (49)	35.9 (14)	2.03 (0.98-4.21)	--	--
Any antibiotics	21.2 (48)	25.6 (10)	1.29 (0.59-2.82)	--	--
Azithromycin	18.1 (41)	10.3 (4)	0.52 (0.17-1.54)	--	--
Low molecular weight heparin	19.4 (44)	43.6 (17)	3.21 (1.57-6.56)	--	--
Antiviral drug, any	16.7 (38)	33.3 (13)	2.49 (1.17-5.27)	--	--
- Lopinavir/Ritonavir	14.1 (32)	28.2 (11)	2.39 (1.08-5.28)	--	--

^A Logistic regression model including 266 observations; Area under the ROC curve 0.81. With the exception of maternal age and any pharmacological treatment, which were included a priori, the variables that were not significant at 0.1 level in the final model were not included to reduce overfitting. **including diabetes, hypertension, or asthma*

Figure 1. Flow-chart of the study population

