Laboratory Analysis of Symptomatic and Asymptomatic Pregnant Patients with SARS-CoV-2 Infection

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Condensation

Inflammatory biomarkers in pregnant patients with SARS-CoV-2 infection exhibit poor discriminatory ability in differentiating symptomatic from asymptomatic infection and severe-critical disease from mild-moderate disease.

Short title: Lab Analysis of SARS-CoV-2 in Pregnant Patients

AJOG at a Glance

A. Why was the study conducted?

- We aimed to compare laboratory findings among pregnant patients with severe acute respiratory syndrome coronavirus (SARS-CoV-2) by symptom status and disease severity to elucidate which inflammatory biomarkers may be most associated with clinical phenotype in pregnant patients.

B. What are the key findings?

- Elevated high-sensitivity C-reactive protein was significantly associated with symptomatic (versus asymptomatic) infection, although the low specificity (43%, 95% CI 26-63) limits its clinical utility. Among symptomatic pregnant patients, elevated liver enzymes, procalcitonin, and lactate hydrogenase were significantly associated with severe-critical (versus mild-moderate) disease. However, again, poor test characteristics limit their clinical applicability.

C. What does this study add to what is already known?

- Inflammatory biomarkers in pregnant patients with SARS-CoV-2 infection exhibit vast heterogeneity, poor discriminative ability, and thereby limited clinical utility in distinguishing symptomatic and severe disease from asymptomatic and mild disease, respectively.

Keywords: inflammatory biomarkers in pregnancy, SARS-CoV-2 infection in pregnancy

ABSTRACT

Background:

Inflammatory biomarkers have been utilized to portend disease severity in non-pregnant individuals with SARS-CoV-2 infection. However, currently limited data are available, and with mixed results, to elucidate which inflammatory biomarkers may be most associated with clinical phenotype in pregnant patients.

Objective:

We aimed to compare laboratory findings among pregnant patients with severe acute respiratory syndrome coronavirus (SARS-CoV-2) by symptom status and disease severity.

Study Design:

We retrospectively evaluated pregnant patients at an urban academic U.S. hospital with positive polymerase-chain reaction SARS-CoV-2 testing between March and October 2020, performed for reported symptoms or universal screening on admission. In our hospital, all patients with SARS-CoV-2 were recommended to have baseline laboratory testing, including leukocyte, neutrophil and lymphocyte counts; aspartate and alanine aminotransferase; high sensitivity C-reactive protein (hsCRP); procalcitonin (PCT); lactate dehydrogenase (LDH); D-dimer; and ferritin. We performed multivariable logistic regression to evaluate peak laboratory abnormalities significantly associated with symptomatic SARS-CoV-2 infection and disease severity with gestational age at diagnosis, maternal age, and obesity as covariates. The sensitivity

and specificity of laboratory abnormalities to identify symptomatic versus asymptomatic infection, and severe to critical disease versus mild to moderate disease, were calculated.

Results:

We identified 175 pregnant patients with SARS-CoV-2, of whom 100 (57%) were symptomatic; 17 (17%) of those who were symptomatic had severe to critical disease. Laboratory data was available for 128 patients, of whom 67 (52%) were symptomatic. Compared to asymptomatic people, symptomatic people were more likely to exhibit elevated hsCRP after adjusting for gestational age (aOR 5.67, 95% CI 1.42-22.52, sensitivity 81%, specificity 43%). In symptomatic individuals, transaminitis (aOR 5.67, 95% CI 1.27-25.43), elevated PCT (aOR 16.60, 95% CI 2.61-105.46), and elevated LDH (aOR 17.55, 95% CI 2.51-122.78) were independently associated with severe to critical disease compared to mild to moderate disease after adjusting for maternal age and obesity. Sensitivity for transaminitis, PCT elevation and LDH elevation was 47%, 87% and 53%, while specificity was 89%, 63% and 90%, respectively, for differentiating disease severity.

Conclusion:

Inflammatory biomarkers in pregnant patients with SARS-CoV-2 exhibit vast heterogeneity, poor discriminative ability, and thereby limited clinical utility. Larger registry studies should evaluate which inflammatory biomarkers, accounting for pregnancy physiology, may be most useful for risk stratification and prognostication of pregnant patients with SARS-CoV-2 infection.

MAIN TEXT

Introduction

Pregnant individuals are more likely to experience severe sequelae after infection with severe acute respiratory syndrome coronavirus (SARS-CoV-2), presumably due to physiologic changes in pregnancy that alter immune function.[1-4] In the United States, from March to August 2020, approximately one in four reproductive-aged patients who were hospitalized for SARS-CoV-2 infection was pregnant, and as of October 29, 2020, SARS-CoV-2 has infected nearly 35,000 pregnant individuals resulting in 50 maternal deaths.[5,6] In the midst of a rapidly evolving pandemic, several small case series have determined that the majority of pregnant individuals with SARS-CoV-2 infection will have a mild clinical phenotype, but a clinically significant minority will develop severe illness.[3,7-10]

In the non-pregnant population, several inflammatory biomarkers show promise in facilitating risk stratification and prognostication of patients with severe SARS-CoV-2 infection, including leukocyte, neutrophil and lymphocyte counts; aspartate and alanine aminotransferase; C-reactive protein (CRP); procalcitonin (PCT); lactate dehydrogenase (LDH); D-dimer; and ferritin.[11-15] However, several of these biomarkers, especially white blood cell count and differential, D-dimer, CRP and ferritin, are physiologically altered in pregnancy, challenging the clinical integration of these results. While some studies have evaluated subsets of biomarkers to clinically distinguish pregnant individuals based on symptoms or severity of symptoms, the small sample sizes have precluded meaningful conclusions. [16-21] As such, we remain without a clear laboratory-based approach to evaluate pregnant patients with SARS-CoV-2.

As inflammatory biomarkers may provide insight into disease severity in individuals with SARS-CoV-2 infection, they have the potential to predict a clinical trajectory and thereby impact

clinical care in pregnant patients with SARS-CoV-2 infection. Given the limited data currently available to elucidate which inflammatory biomarkers may be most associated with clinical phenotype in pregnant patients, we aimed to compare laboratory findings among symptomatic and asymptomatic pregnant patients infected with SARS-CoV-2. We further examine differences in biomarkers among pregnant patients with symptomatic SARS-CoV-2 infection according to disease severity.

Materials and Methods

In this retrospective cohort study conducted at Northwestern Memorial Hospital, an urban academic tertiary care center in Chicago, IL, we evaluated pregnant patients with positive SARS-CoV-2 polymerase-chain reaction (PCR) testing between March and October 2020. Pregnant patients were included if they had a positive SARS-CoV-2 test during the study period, were currently pregnant (determined by a positive pregnancy test or ultrasound), and presented to our hospital for care. Testing was performed as part of routine clinical care 1) in the ambulatory and inpatient setting either for reported symptoms consistent with SARS-CoV-2 infection, 2) known exposure to individuals with SARS-CoV-2 infection, or 3) by universal screening protocol at time of inpatient admission for labor or antepartum management. All individuals who underwent testing were systematically queried regarding symptoms and exposure to sick contacts using a standardized review of symptoms at time of presentation for testing and were coded as symptomatic if any of the following symptoms was present: headache; anosmia; ageusia; fever; chills; fatigue; malaise; myalgias; chest pain or discomfort; cough; congestion; sore throat; shortness of breath, dyspnea, respiratory distress or wheezing; or nausea, vomiting, diarrhea, or abdominal pain (unrelated to contractions or other labor symptoms).

Symptomatic people were admitted if they had unstable vital signs, required oxygen supplementation, reported significant shortness of breath or respiratory symptoms, or were felt to be at risk for subsequent clinical deterioration. Otherwise clinically stable pregnant individuals not warranting admission had outpatient telehealth follow-up for monitoring of symptoms. In our hospital, all patients who tested positive for SARS-CoV-2, irrespective of pregnancy, were recommended to have baseline labs with a complete blood cell count with differential to assess neutrophil and lymphocyte percentage as well as leukocyte counts; chemistry panel to evaluate aspartate aminotransferase (AST) and alanine aminotransferase (ALT); and additional testing for the following biomarkers that were selected *a priori* based on their potential to stratify disease severity: high-sensitivity C-reactive protein (hsCRP), PCT, LDH, D-dimer, and ferritin. Labs were repeated daily if hospital admission was required, and providers were recommended to trend all inflammatory markers on symptomatic patients throughout the study period until they demonstrated clinical improvement. If patients were not hospitalized, then only laboratory values from a single outpatient office, emergency room, or triage visit at the time of SARS-CoV-2 testing were available. Notably, for many asymptomatic patients with positive SARS-CoV-2 testing, laboratory assessment was not performed. A chest x-ray was not routinely obtained on admission for SARS-CoV-2; rather, the clinical suspicion of worsening pulmonary disease or concern for superimposed bacterial pneumonia were used to guide the decision for radiographic evaluation.

Disease severity was classified with guidance from the National Institute of Health's SARS-CoV-2 Treatment Guidelines into asymptomatic infection (individuals who test positive for SARS-CoV-2, but with no current symptoms consistent with SARS-CoV-2), mild illness (individuals with any of the various signs and symptoms of SARS-CoV-2, but who do not have

shortness of breath, dyspnea or abnormal chest imaging), moderate illness (individuals who show evidence of lower respiratory disease on clinical assessment or imaging and with oxygen saturation ≥94% on room air), severe illness (individuals with oxygen saturation <94% on room air, respiratory rate >30 breaths per minute, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen [PaO_2/FiO_2] <300 mmHg, or lung infiltrates >50%), and critical illness (individuals who have respiratory failure, septic shock and/or multiple organ dysfunction).[22] However, as the threshold for oxygen supplementation in pregnancy is to maintain oxygen saturation ≥95% on room air, we classified any woman requiring oxygen supplementation as having severe illness (i.e. oxygen saturation <95% on room air), with moderate illness thereby encompassing evidence of lower respiratory disease with oxygen saturation ≥95% on room air.

Pregnant patients were stratified by the presence of symptoms and by severity of illness. Pregnant patients with mild to moderate disease were compared to those with severe-critical disease. If patients initially presented with mild to moderate disease, but subsequently demonstrated progression to severe to critical disease, they were assigned to and analyzed among the severe to critical disease group. Maternal baseline sociodemographic and clinical characteristics were compared by both the presence and severity of symptoms in bivariable analyses. Obesity was defined as body mass index ≥30kg/m^2. Independent samples t-tests and Mann Whitney U tests compared normally and nonnormally distributed continuous variables, respectively. Chi-square and Fisher's exact tests were used to compare categorical variables. A p-value less than 0.05 was considered statistically significant.

Median peak laboratory values, among all laboratory data available for the patient within fourteen days of a positive COVID-19 test result, were also compared according to symptom

status and the severity of illness using independent samples t-tests and Mann Whitney U tests in bivariable analyses. As SARS-CoV-2 infection has been associated with leukopenia in non-pregnant patients, we also compared the nadir of neutrophil percentage, lymphocyte percentage and leukocyte count between groups.[23] The data included were cross-sectional; only the highest (or lowest) biomarker level was analyzed for each patient. Analysis of laboratory values obtained at initial presentation was similarly performed. Multiple lab values for the same patient were not analyzed. No corrections were made for multiple comparison testing.

Peak (vs. nadir) laboratory values as well as laboratory values on initial presentation were then dichotomized based on whether they fell within the normal clinical range as defined by our laboratory's standard reference ranges. The prevalence of an abnormal laboratory finding was compared between 1) pregnant patients who were symptomatic versus asymptomatic and 2) symptomatic pregnant patients with mild to moderate disease versus those with severe to critical disease. Chi-square and Fisher's exact tests determined biomarker abnormalities significantly associated with symptomatic infection and disease severity. Peak (vs. nadir) laboratory values as well as laboratory values on initial presentation that were significantly associated with 1) symptomatic SARS-CoV-2 or 2) severity of symptoms were evaluated with multivariable logistic regression. These multivariable regressions controlled for significant covariates to identify whether the identified laboratory abnormalities were independently associated with either symptoms or more severe illness.

The remainder of our analysis involved analysis of only peak (vs. nadir) laboratory values. Sensitivity and specificity of each laboratory abnormality identified in multivariable regression to be a significant predictor of clinical phenotype (i.e. symptomatic versus asymptomatic infection; mild to moderate disease versus severe to critical disease) were

calculated. Sensitivity analysis excluding pregnant patients treated with dexamethasone, which is known to contribute to leukocytosis, was also performed for neutrophilia, lymphopenia and leukopenia among pregnant patients with symptomatic SARS-CoV-2 infection according to disease severity. Of note, at our institution, any patient with a positive COVID test result warranting antenatal corticosteroid administration for fetal benefit received dexamethasone, not betamethasone. Additional sensitivity analyses among symptomatic patients excluded patients who had laboratory assessment during labor or within 48 hours postpartum, as biomarker levels can be altered by physiologic changes intrapartum and immediately postpartum.

Statistical analyses were conducted using Stata version 16.1.844 (College Station, TX). The study was approved by the Northwestern University Feinberg School of Medicine Institutional Review Board (IRB# STU00212232) prior to its initiation and obtained a waiver of written consent.

Results

During the study period, 175 pregnant patients were identified to have a positive PCR test confirming SARS-CoV-2 infection, of whom 100 (57%) were symptomatic (Figure 1). Only one asymptomatic individual was tested solely due to exposure to a known positive case contact; all other asymptomatic individuals were tested per universal screening protocol. Median gestational age at diagnosis was 39 weeks in symptomatic individuals compared to 29.6 weeks asymptomatic individuals ($p < 0.001$), with 43% of people with symptomatic disease identified prior to the third trimester (Table 1). Of note, 46% and 23% of symptomatic and asymptomatic people, respectively, reported known exposure to a positive case contact ($p=0.003$). There were no statistically significant differences in parity, race, ethnicity or maternal co-morbidities

between those who were symptomatic versus asymptomatic. Among symptomatic individuals, pregnant patients with severe to critical disease were older (p=0.03) and more likely to be obese (p=0.004) compared to those with mild to moderate disease; baseline characteristics were otherwise similar between those with mild to moderate disease and those with severe to critical disease. The most common medical comorbidities reported by disease severity are described in Table 1.

Among symptomatic pregnant patients, 60% had mild disease, 23% had moderate disease, 16% had severe disease and one person (1%) had critical disease. The most commonly reported symptoms were cough (63%), fever (41%), and shortness of breath (40%, Figure 2). Thirty symptomatic pregnant individuals (30%) were hospitalized for supportive care and further management of SARS-CoV-2 infection, 13 (43%) of whom had mild to moderate disease and the remaining 17 (57%) with severe to critical disease. The majority of asymptomatic women (94.6%) were identified during a hospitalization for delivery, whereas only 26.5% of symptomatic women were identified during a hospitalization for delivery.

Laboratory data was available for 128 patients, of whom 61 (48%) were asymptomatic and 67 (52%) were symptomatic. When peak (vs. nadir) laboratory markers as continuous variables were compared between symptomatic and asymptomatic pregnant patients, those with symptomatic infection had decreased leukocyte nadir and increased peak ferritin, ALT, AST, hsCRP, D-dimer, and PCT (Table 2). When peak (vs. nadir) laboratory markers as continuous variables were compared between pregnant patients with mild to moderate disease and those with severe to critical disease, pregnant patients with severe to critical disease had reduced lymphocyte percentage and leukocyte nadir, and increased peak neutrophil percentage, ferritin,

ALT, AST, hsCRP, PCT and LDH (Table 2). Supplementary Table 1 demonstrates similar analysis for laboratory values obtained at initial presentation.

Laboratory markers were then dichotomized as normal versus abnormal. For both peak (vs nadir) laboratory values and those obtained at initial presentation, only leukocytosis (compared to the absence of leukocytosis, with leukocytosis defined as white blood cell count greater than 10.5K/µL); leukopenia (compared to the absence of leukopenia, with leukopenia defined as white blood cell count less than 4K/µL); and an elevated hsCRP (compared to a normal hsCRP, defined as less than 10 mg/L) were significantly associated with symptomatic infection (Table 3, Supplementary Table 2). Neutrophil percentage, lymphocyte percentage, transaminitis, and elevations in ferritin, D-Dimer, LDH and PCT were not associated with symptomatic disease. After adjusting the peak value for gestational age at diagnosis, pregnant patients with an elevated hsCRP had an over four-fold odds of having symptomatic disease. Within the subgroup of pregnant patients who had symptoms, lymphopenia (compared to the absence of lymphopenia, with lymphopenia defined as lymphocyte percentage less than 20%); transaminitis (compared to normal liver transaminases, with elevated ALT defined as greater than 52 units/L and elevated AST defined as greater than 39 units/L); an elevated PCT (compared to normal PCT, defined as less than 0.065 ng/mL); and an elevated LDH (compared to normal LDH, defined as less than 271 units/L), were associated with severe to critical disease (Table 4) in analysis by peak (vs. nadir) laboratory values. Neutrophil percentage, leukocyte count, and an elevated ferritin, D-dimer, and hsCRP levels were not associated with disease severity among pregnant patients with symptomatic SARS-CoV-2 infection. After adjusting for age and obesity in analysis by peak (vs. nadir) laboratory values, transaminitis, an elevated PCT, and an elevated LDH were each associated with having severe to critical disease. In analysis of

253 laboratory values obtained at initial presentation, elevated procalcitonin was no longer significant
254 (Supplementary Table 3).

255 Regarding test characteristics for peak laboratory values, hsCRP showed moderate
256 sensitivity (81%), but poor specificity (43%) for distinguishing symptomatic versus
257 asymptomatic infection. The sensitivity and specificity for each of these biomarkers to
258 differentiate disease severity among symptomatic patients were also suboptimal, with a
259 sensitivity of 47%, 87% and 53% for transaminitis, procalcitonin elevation and LDH elevation,
260 while specificity was 89%, 63% and 90%, respectively (Table 5).

261 In a planned sensitivity analysis of peak (vs. nadir) laboratory values excluding three
262 individuals treated with dexamethasone, neutrophilia (OR 5.11, 95% CI 0.59-43.85),
263 lymphopenia (OR 7.28, 95% CI 0.86-61.67) and leukopenia (OR 2.73, 95% CI 0.53-14.04) were
264 not significant in bivariable analysis of biomarkers according to disease severity in pregnant
265 patients with symptomatic SARS-CoV-2 infection. In additional sensitivity analysis among
266 symptomatic patients excluding those who had laboratory assessment done intrapartum or
267 postpartum, only an elevated PCT (aOR 10.85, 95% CI 1.44-81.88) and an elevated LDH (aOR
268 8.90, 95% CI 1.06-75.10) were significantly associated with severe to critical disease;
269 transaminitis was no longer significantly associated with disease severity (OR 3.0, 95% CI 0.57-
270 15.87).

271

272 **Comment**

273 *Principal Findings*

274 In our cohort of 175 pregnant patients with SARS-CoV-2 infection, we identified a
275 relatively low, but clinically important subset of patients with severe and critical disease (17%).

Among our analytic cohort of 128 patients with data on inflammatory biomarkers available, we observed vast heterogeneity in measured biomarker levels among pregnant patients with SARS-CoV-2 infection even within cohorts (e.g. among those who were asymptomatic or among those with mild to moderate disease). This pronounced heterogeneity decreases the discriminatory strength of any one specific inflammatory marker to differentiate clinical phenotypes of disease. Of all inflammatory markers analyzed, only hsCRP was independently associated with symptomatic disease. However, 55% of people with asymptomatic disease had an abnormally elevated hsCRP, making the specificity of this as a discriminatory test clinically not useful.

Among symptomatic pregnant patients, elevated liver enzymes, PCT, and LDH for peak laboratory values were all significantly associated with severe or critical disease. Transaminitis and LDH both demonstrated poor performance as a screening test with high false negative rates, but demonstrated greater diagnostic ability for distinguishing severe to critical disease from mild to moderate disease with specificity approaching 89-90%. Elevated peak PCT demonstrated improved performance as a screening test, but poor performance as a diagnostic test for more severe disease as reflected by the test sensitivity and specificity. Overall, the discriminatory ability of these laboratory tests to distinguish disease severity in symptomatic pregnant patients is poor and suggests they have limited utility in clinical practice.

Results

While the obstetric literature on inflammatory biomarkers associated with SARS-CoV-2 infection demonstrates mixed results, several studies evaluating nonpregnant individuals with SARS-CoV-2 infection have noted elevated D-dimer levels, neutrophil counts, ferritin, liver enzymes, LDH and CRP levels as well as decreased lymphocyte counts to have utility in

differentiating morbidity and mortality risk resulting from widespread systemic inflammation.[11-15,20,24] However, we must consider that normal reference ranges for laboratory results may be altered by physiologic changes in pregnancy.[24] In particular, D-dimer is typically elevated during pregnancy, albeit with inconsistent reference ranges.[21,24-26] Normal reference ranges for hsCRP and PCT have not been identified for pregnancy, although PCT is basally expressed at very low levels in pregnancy while median CRP values in normal pregnancies appear to be higher than standardized values for nonpregnant individuals. [21,24-28] Pregnancy itself does not affect LDH levels or liver enzymes, though these can be elevated in the setting of pre-eclampsia or other liver diseases associated with pregnancy.[29-31] Leukocytosis, primarily related to increased circulation of neutrophils, without significant alteration in lymphocyte count is also associated with the normal pregnancy state.[32,33,34] Finally, although elevated ferritin level can be an indicator of infection in pregnancy, ferritin levels can also be reduced as a result of hemodilution that is characteristic of pregnancy.[35] Therefore, it is possible certain biomarker levels in our cohort may be labeled "normal" or "abnormal"' merely due to pregnancy physiology and not solely due to SARS-CoV-2 infection. We must interpret the trends in laboratory markers identified and their clinical significance with caution in our pregnant cohort given baseline alterations due to normal pregnancy physiology.

Prior evaluation of inflammatory biomarkers in pregnant patients with SARS-CoV-2 infection according to symptomatology and disease severity is limited and demonstrates mixed results (Table 6).[17,18,20,21,25,26]. Two studies compared biomarkers in pregnant versus nonpregnant women with SARS-CoV-2 infection, though these did not include subgroups for symptomatic disease or disease severity.[17,18] Shi et al. published a meta-analysis of 173 people in eleven studies evaluating biomarkers among pregnant women dichotomized as elevated versus normal

and did not find elevated CRP or LDH to be associated with SARS-CoV-2 infection in pregnant women, although without attention to symptomatic disease or disease severity.[20] Grechukina et al. evaluated CRP and D-dimer levels in nineteen asymptomatic and symptomatic pregnant women, with no significant difference identified between groups.[21] In contrast, we identified abnormally elevated hsCRP to be independently associated with symptomatic disease.

Two studies have evaluated biomarker abnormalities in pregnant women according to disease severity, the largest with 64 people; both identified elevated CRP to be associated with greater disease severity, but neither identified a significant association between liver enzymes and disease severity.[25,26] While we did not identify hsCRP to be independently associated with more severe disease in pregnant patients, we identified liver enzymes to be significantly associated with disease severity. Furthermore, Pierce-Williams et al. identified elevated PCT and LDH to be associated with greater disease severity, while Pereira et al. did not find LDH to be associated with disease severity. [25,26] Similar to Pierce-Williams et. al, we identified elevated PCT and LDH for peak laboratory values to be independently associated with more severe disease. Prior studies have not evaluated test characteristics such as the sensitivity and specificity of these biomarkers for risk stratification and prognostication among pregnant individuals with SARS-CoV-2 infection; the poor discriminatory ability of these tests as we have identified among our cohort may account for the variable differences in significant laboratory markers identified in the aforementioned studies.

Clinical and Research Implications

While the inflammatory biomarkers evaluated in our cohort of pregnant patients do not appear to be clinically useful for discriminating between symptomatic and asymptomatic

infection nor particularly indicative of disease severity, other clinical applications of these biomarkers remain unclear. Prior studies have commented on the use of elevated D-Dimer levels to guide prophylactic anticoagulation in patients with more severe SARS-COV-2 infection either during inpatient admission or following delivery.[36-39] Additionally, elevated procalcitonin has been demonstrated to be a marker for increased risk of bacterial infection in patients with SARS-CoV-2 infection, and more specifically superimposed bacterial pneumonia, that may support antibiotic therapy.[40] However, evaluation of the ability of these inflammatory biomarkers to predict coagulopathy or bacterial superinfection and guide treatment in pregnant patients is beyond the scope of this manuscript. Future studies should further evaluate the clinical applications of inflammatory biomarkers in pregnant patients with SARS-CoV-2 infection accounting for pregnancy physiology.

Strengths and Limitations

Our study is strengthened by the diverse patient population and comprehensive array of inflammatory biomarkers evaluated. Our results are likely generalizable to other pregnant individuals in the U.S. Additionally, our large cohort afforded us the ability to control for potential confounders, notably gestational age at diagnosis, maternal age and presence of obesity. Each of these factors could influence the laboratory values assessed.

While this cohort is the largest cohort to our knowledge to analyze laboratory markers of disease in pregnant individuals with clinically phenotyped SARS-CoV-2 infection, the small sample size and missing data, particularly within smaller subgroups and among asymptomatic patients, may lead to type II error. Missing data, specifically as it is not missing at random, further introduces additional selection bias, limiting our ability to firmly conclude the frequency

of abnormal lab results and the validity of comparisons between groups. Changes in criteria for testing over the course of the pandemic also limit our ability to determine the proportion of pregnant individuals tested who will have symptomatic infection. Changes in the care and management of patients with SARS-CoV-2 infection also occurred throughout the study period with different treatments having the potential to affect peak biomarker levels; however, our study conclusions are less likely to be impacted by the evolving treatment methods given the relative consistency in findings in our analysis of laboratory values obtained on initial presentation with that of peak laboratory values.

It is important to note this is an epidemiologic, cross-sectional analysis evaluating peak laboratory values, or nadir in the case of leukocyte count and differential, based on available laboratory data captured among pregnant patients in the hospital setting as a proxy for the most severe point in the clinical course of patients' disease. We cannot comment on biomarker trends overtime throughout the course of a patient's disease, nor are we able to fully capture laboratory data for pregnant patients managed primarily in the outpatient setting. Particularly in asymptomatic patients identified on admission, but also among symptomatic individuals, the actual timing of infection is unknown and it is plausible that peak biomarker levels could have occurred prior to, or even after, admission.

Conclusions

Inflammatory biomarkers used to differentiate morbidity in non-pregnant patients with SARS-CoV-2 infection demonstrate poor diagnostic ability and thereby limited clinical utility in pregnant patients. Given the severity of infection in pregnant individuals, ongoing large registry studies are needed to further evaluate which inflammatory biomarkers, accounting for pregnancy

391 physiology, may be most useful for risk stratification and prognostication of pregnant patients
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REFERENCES

1. Ellington S, Strid P, Tong VT, Woodworth K, Galang RR, Zambrano LD, et al. Characteristics of people of reproductive age with laboratory-confirmed SARS-CoV-2 infection by pregnancy status—United States, January 22, June 7, 2020. MMWR Morb Mortal Wkly Rep 2020;69:769-775.
2. Panagiotakopoulos L, Myers TR, Gee J, Lipkind HS, Kharbanda EO, Ryan DS, et al. SARS-CoV-2 infection among hospitalized pregnant women: reasons for admission and pregnancy characteristics—eight U.S. health care centers, March 1-May 30, 2020. MMWR Morb Mortal Wkly Rep 2020;69(38);1355-1359
3. Chen H, Guo J, Wang C, Luo F, Yu X, Zhang W, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. Lancet 2020;395(10226):809–815.
4. Mor G, Cardenas I. The immune system in pregnancy: a unique complexity. *Am J Reprod Immunol*. 2010;63(6):425-433. doi: 10.1111/j.1600-0897.2010.00836.x
5. Delahoy MJ, Whitaker M, O'Halloran A, Chai SH, Kirley PD, Alden N, et al. Characteristics and Maternal and Birth Outcomes of Hospitalized Pregnant Women with Laboratory-confirmed COVID-19—COVID-NET, 13 States, March 1-August 22, 2020. MMWR Morb Mortal Wkly Rep 2020;69:1347-1354.
6. Centers for Disease Control and Prevention. Data on COVID-19 during pregnancy: severity of maternal illness. Accessed Oct. 31, 2020. https://www.cdc.gov/coronavirus/2019-ncov/cases-updated/special-populations/pregnancy-data-on-covid-19.html

7. Andrikopoulou M, Madden N, Wen T, Aubey JJ, Aziz A, Baptiste CD, et al. Symptoms and critical illness among obstetric patients with coronavirus disease 2019 (COVID-19) infection. Obstet Gynecol. 2020 Aug;136(2):291-299. doi: 10.1097/AOG.0000000000003996
8. Breslin N, Baptiste C, Gyamfi-Bannerman C, Miller R, Martinez R, Bernstein K, et al. Coronavirus disease 2019 infection among asymptomatic and symptomatic pregnant women: two weeks of confirmed presentations to an affiliated pair of New York City hospitals. Am J Obstet Gynecol MFM. 2020;2(2):100118. doi:10.1016/j.ajogmf.2020.100118
9. Li N, Han L, Peng M, Lv Y, Ouyang Y, Liu K, et al. Maternal and neonatal outcomes of pregnant women with COVID-19 pneumonia: a case-control study. Clin Infect Dis. 2020;71(6):2035-2041. doi: 10.1101/2020.03.10.20033605
10. Chen S, Liao E, Cao D, Gao Y, Sun G, Shao Y. Clinical analysis of pregnant women with 2019 novel coronavirus pneumonia. J Med Virol. 2020;92:1556-1561.
11. Kermali M, Khalsa RK, Pillai K, Ismail Z, Harky A. The role of biomarkers in diagnosis of COVID-19 – A systematic review. Life Sci. 2020;254:117788. doi: 10.1016/j.lfs.2020.117788
12. Malik P, Patel U, Mehta D, Patel N, Kelkar R, Akrmah M, et al. Biomarkers and outcomes of COVID-19 hospitalisations: systematic review and meta-analysis. BMJ Evid Based Med. Published online ahead of print September 15, 2020. Accessed October 29, 2020. 10.1136/bmjebm-2020-111536

13. Danwang C, Endomba FT, Nkeck JR, Wouna DLA, Robert A, Noubiap JJ. A meta-analysis of potential biomarkers associated with severity of coronavirus disease 2019 (COVID-19). Biomark Res. 2020;8:37. doi: 10.1186/s40364-020-00217-0

14. Ponti G, Maccaferri M, Ruini C, Tomasi A, Ozben T. Biomarkers associated with COVID-19 disease progression. Crit Rev Clin Lab Sci. 2020;57(6):389-399. doi: 10.1080/10408363.2020.1770685

15. Aboughdir M, Kirwin T, Abdul Khader A, Wang B. Prognostic Value of Cardiovascular Biomarkers in COVID-19: A Review. Viruses. 2020;12(5):527. doi: 10.3390/v12050527

16. Koumoutsea EV, Vivanti AJ, Shehata N, Benachi A, Le Gouez A, Desconclois C, et al. COVID-19 and acute coagulopathy in pregnancy. J Thromb Haemost. 2020;18:1648–1652.

17. Wang Z, Wang Z, Xiong G. Clinical characteristics and laboratory results of pregnant women with COVID-19 in Wuhan, China. Int J Gynaecol Obstet. 2020;150(3):312–7. doi: 10.1002/ijgo.13265

18. Liu H, Liu F, Li J, Zhang T, Wang D, Lan W. Clinical and CT imaging features of the COVID-19 pneumonia: Focus on pregnant women and children. J Infect 2020;80(05):e7–e13. doi: https://doi.org/10.1016/j.jinf.2020.03.007

19. Chen L, Li Q, Zheng D, et al. Clinical characteristics of pregnant women with COVID-19 in Wuhan, China. N Engl J Med 2020;382:e100. doi: 10.1056/NEJMc2009226

20. Shi L, Wang Y, Yang H, Duan G, Wang Y. Laboratory abnormalities in pregnant women with novel coronavirus disease 2019. Am J Perinatol. 2020;37(10):1070-1073. doi: 10.1055/s-0040-1712181

21. Grechukhina O, Greenberg V, Lundsberg LS, Deshmukh U, Cate J, Lipkind HS, et al. Coronavirus disease 2019 pregnancy outcomes in a racially and ethnically diverse population. Am J Obstet Gynecol MFM. 2020;100246. doi: 10.1016/j.ajogmf.2020.100246

22. Clinical Presentation of People with SARS-CoV-2 Infection. NIH COVID-19 Treatment Guidelines. https://www.covid19treatmentguidelines.nih.gov/overview/clinical-presentation.

23. Goyal P, Choi JJ, Pinheiro LC, Schenck EJ, Chen R, Jabri A, et al. Clinical Characteristics of Covid-19 in New York City. N Engl J Med. 2020;382(24):2372-2374. doi: 10.1056/NEJMc2010419

24. Abbassi-Ghanavati, Mina MD; Greer, Laura G. MD; Cunningham, F Gary MD Pregnancy and Laboratory Studies: A Reference Table for Clinicians. Obstetrics & Gynecology. 2009;114(6):1326-1331 doi: 10.1097/AOG.0b013e3181c2bde8

25. Pierce-Williams RAM, Burd J, Felder L, Khoury R, Bernstein PS, Avila K, et al. Clinical course of severe and critical coronavirus disease 2019 in hospitalized pregnancies: a United States cohort study. Am J Obstet Gynecol MFM. 2020 Aug;2(3):100134. doi: 10.1016/j.ajogmf.2020.100134

26. Pereira A, Cruz-Melguizo, Adrien M, Fuentes L, Marin E, Perez-Medina T. Clinical course of coronavirus disease-2019 in pregnancy. Acta Obstet Gynecol Scand. 2020;99:839–847. doi: 10.1111/aogs.13921

27. Henry BM, de Oliveira MHS, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in

coronavirus disease 2019 (COVID-19): a meta-analysis. Clin Chem Lab Med. 2020;58(7):1021-1028. doi: 10.1515/cclm-2020-0369

28. Watts DH, Krohn MA, Wener MH, Eschenbach DA. C-reactive protein in normal pregnancy. Obstet Gynecol. 1991 Feb;77(2):176-80. doi: 10.1097/00006250-199102000-00002

29. Mangogna A, Aogstinis C, Ricci G, Romano F, Bulla R. Overview of procalcitonin in pregnancy and pre-eclampsia. Clin Exp Immunol. 2019;198(1):37-46. doi: 10.1111/cei.13311

30. Vazquez-Alaniz F, Salas-Pacheco JM, Sandoval-Carrillo AA, La-llave-Leon O, Hernande EMM, Barraza-Salas M, et al. Lactate dehydrogenase in hypertensive disorders of pregnancy: severity or diagnostic marker? J Hypertens Manag. 2019;5:040. Doi: 10.23937/2474-3690/1510040.

31. Hak J, Nisa NU, Gupta S. LDH levels in pregnancy and its association with severity of the disease and feto-maternal outcome in pre-eclampsia and eclampsia. JK Science. 2015;17(3):110-113.

32. Mikolasevic, I, Filipec-Kanizaj T, Jakopcic I, Majurec I, Brncic-Fischer A, Sobocan N, et al. Liver Disease During Pregnancy: A Challenging Clinical Issue. *Med Sci Monit. 2018;*24:4080–4090. doi: 10.12659/MSM.907723

33. Kuvin SF, Brecher G. Differential neutrophil counts in pregnancy. N Engl J Med 1962;266:877

34. Kühnert M, Strohmeier R, Stegmüller M, Halberstadt E. Changes in lymphocyte subsets during normal pregnancy. Eur J Obstet Gynecol Reprod Biol. 1998;76:147

35. Theresa O. Scholl, Thomas Reilly, Anemia, Iron and Pregnancy Outcome. J Clin Nutr. 2000;130(2):443-447S. doi: 10.1093/jn/130.2.443S

36. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost. 2020;18(5):1094-1099. doi: 10.1111/jth.14817

37. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost*. 2020;2020:844-847. doi: 10.1111/jth.14768

38. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2020;395:507-513. doi: 10.1016/S0140-6736(20)30211-7

39. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan. *China. Lancet*. 2020;395:497-506. Doi:10.1016/S0140-6736(20)30183-5

40. Hu R, Han C, Pei S, Yin M, Chen X. Procalcitonin levels in COVID-19 patients. *Int J Antimicrob Agents*. 2020;56(2):106051. doi:10.1016/j.ijantimicag.2020.106051

545 **TABLES**

546 **Table 1. Baseline sociodemographic and clinical characteristics of pregnant patients with SARS-CoV-2 infection**

Variable	Asymptomatic n=75	Symptomatic n=100	p-value	Mild-Moderate n=83	Severe-Critical n=17	p-value
Maternal age, years	29.3 ± 6.06	30.2 ± 6.2	0.39	29.5 ± 5.9	33.2 ± 6.9	0.03
Gestational age at diagnosis	39 (16.3-41.1)	29.6 (3.6-41)	<0.001	29.1 (3.6-41)	31.1 (16-36.4)	0.81
By trimester:						
1st trimester	0 (0.0)	5 (5)	<0.001	5 (6)	0 (0)	0.83
2nd trimester	1 (1.4)	38 (38)		31 (37)	7 (41)	
3rd trimester	74 (99)	57 (57)		47 (57)	10 (59)	
Nulliparous	28 (37)	34 (34)	0.65	31 (37)	3 (18)	0.16
Self-reported race						
Black	21 (28)	23 (23)	0.74	18 (22)	5 (29)	0.85
White	19 (26)	30 (30)		25 (30)	5 (29)	
Asian	2 (3)	5 (5)		5 (6)	0 (0)	
Other*	32 (43)	42 (42)		35 (42)	34 (41)	
Hispanic ethnicity	35 (47)	55 (55)	0.32	43 (52)	12 (71)	0.16
Maternal comorbidities						
Asthma/pulmonary disease	10 (13)	21 (21)	0.18	16 (19)	5 (29)	0.35
Obesity (body mass index ≥30kg/m^2)	40 (53)	57 (57)	0.63	42 (51)	15 (88)	0.004
Chronic hypertension	4 (5)	12 (12)	0.19	9 (11)	3 (18)	0.42
Immunosuppressive disease/medication	4 (5)	3 (3)	0.46	2 (2)	1 (6)	0.43
Pregestational diabetes	3 (4)	6 (6)	0.73	5 (6)	1 (6)	0.99
Gestational diabetes	8 (11)	14 (14)	0.46	9 (13)	5 (29)	0.05

547 Data presented as mean ± standard deviation, median (range) or n (%)
548 *The standard reported race categories within our electronic medical record system include White, Black, Asian, American Indian or
549 Alaskan Native, Native Hawaiian or Other Pacific Islander, or "Other." We have condensed American Indian or Alaskan Native and
550 Native Hawaiian or Other Pacific Islander into "Other." Several patients of Hispanic ethnicity also selected "Other" as their identified
551 race.
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554 **Table 2. Peak (vs. nadir) laboratory characteristics in pregnant patients stratified by the presence or absence of symptoms and**
555 **disease severity**

Variable	n	Asymptomatic	n	Symptomatic	p-value	n	Mild-Moderate	n	Severe-Critical	p-value
Neutrophils (%)										
Highest	42	75.5 (58-90)	56	77 (44-94)	0.29	39	75 (44-93)	17	82 (72-94)	<0.001
Lowest	42	72 (0-90)	56	67.5 (42-86)	0.02	39	70 (42-80)	17	66 (61-86)	0.39
Lymphocytes (%)										
Highest	42	18 (6-45)	56	21 (7-49)	0.09	39	20 (7-49)	17	24 (12-30)	0.70
Lowest	42	18 (5-34)	56	16 (0-33)	0.21	39	17 (3-33)	17	11 (0-18)	<0.001
Leukocytes										
Highest	61	10.8 (5.7-24.4)	67	8.8 (3.1-64.4)	<0.001	44	8.3 (3.1-14.9)	17	10.4 (4.2-64.4)	0.26
Lowest	61	9.3 (7.7, 11.4)	67	6.1 (4.8, 8.3)	<0.001	44	6.9 (2.9-16.1)	17	5.1 (3.5-8.3)	0.004
Ferritin	27	16.5 (6.2-817.6)	40	44.3 (8.5-15695.4)	0.001	26	23.8 (8.5-175.6)	14	81.8 (17.9-15695.4)	0.003
ALT	50	12 (5-99)	53	18 (5-4997)	<0.001	36	17.5 (5-670)	17	31 (10-4997)	0.03
AST	50	21 (9-96)	53	27 (12-10000)	0.005	36	25 (12-327)	17	36 (17-10000)	0.01
hsCRP	30	11.0 (1.3-163.6)	42	37.1 (0.9-219.5)	0.005	27	12.9 (0.9-219.5)	15	76.2 (36.4-203.6)	<0.001
D-dimer	37	774 (242-6907)	47	613 (187-17106)	0.03	31	564 (187-3411)	16	689 (262-17106)	0.50
PCT	38	0 (0-3.5)	47	0.08 (0-19.0)	0.02	32	0.05 (0-2.7)	15	0.25 (0-19.0)	<0.001
LDH	47	224 (123-521)	47	221 (112-12000)	0.60	30	193 (112-10851)	17	267 (151-12000)	<0.001

556 Data presented as median (range)
557 *ALT—alanine aminotransferase, AST—aspartate aminotransferase;*
558 *hsCRP—high-sensitivity C-reactive protein, PCT—procalcitonin, LDH—lactate dehydrogenase*
559 Reference range: Neutrophils (55-70%), Lymphocytes (20-40%), Leukocytes (4.0-10.5 K/μL), ferritin (11-307 ng/mL), ALT (0-52
560 unit/L), AST (0-39 unit/L), high-sensitivity C-reactive protein (0-10 mg/L), D-dimer (0-230 D-DU ng/mL), PCT (0.0-0.065 ng/mL),
561 LDH (0-271 unit/L)
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Table 3. Peak (vs. nadir) laboratory abnormalities identified among pregnant patients with SARS-CoV-2 infection stratified by the presence or absence of symptoms

Variable	n	Asymptomatic	n	Symptomatic	p-value	OR (95% CI)	aOR (95% CI)
Neutrophilia	42	28 (66.7)	56	45 (80.4)	0.12	2.05 (0.82-5.13)	-
Neutropenia	42	1 (2.4)	56	3 (5.4)	0.42	2.32 (0.23-23.14)	-
Lymphocytosis	42	1 (2.4)	56	2 (3.6)	0.62	1.48 (0.13-16.91)	-
Lymphopenia	42	27 (64.3)	56	42 (75.0)	0.25	1.67 (0.70-3.99)	-
Leukocytosis	61	34 (67.1)	67	18 (26.9)	**0.02**	**0.41 (0.20-0.84)**	0.48 (0.19-1.18)
Leukopenia	61	0 (0.0)	67	7 (10.4)	**0.01**	**8.42 (1.01-70.6)**	4.97 (0.37-66.65)
Elevated ferritin	27	1 (3.7)	40	2 (5.0)	0.65	1.37 (0.12-15.89)	-
Transaminitis	50	6 (11.8)	53	12 (21.8)	0.16	2.15 (0.74-6.25)	-
Elevated hsCRP	30	17 (56.7)	42	34 (81.0)	**0.03**	**3.25 (1.13-9.34)**	**4.51 (1.11-18.40)**
Elevated D-dimer	37	37 (100.0)	47	45 (95.7)	0.20	0.63 (0.05-7.17)	-
Elevated PCT	38	17 (44.7)	47	25 (53.2)	0.44	1.40 (0.59-3.31)	-
Elevated LDH	47	10 (21.3)	47	12 (25.5)	0.63	1.27 (0.49-3.31)	-

Data presented as n (%)

OR—unadjusted odds ratio, aOR—odds ratio adjusted for gestational age, CI—confidence interval; hsCRP—high-sensitivity C-reactive protein, PCT—procalcitonin, LDH—lactate dehydrogenase

Table 4. Peak (vs. nadir) laboratory abnormalities identified among pregnant patients with symptomatic SARS-CoV-2 infection stratified by disease severity

Variable	n	Mild-Moderate	n	Severe-Critical	p-value	OR (95% CI)	aOR (95% CI)
Neutrophilia	39	28 (71.8)	17	17 (100.0)	0.06	6.29 (0.74-53.28)	-
Neutropenia	39	3 (7.7)	17	0 (0.0)	0.33	0.75 (0.07-7.77)	-
Lymphocytosis	39	2 (5.1)	17	0 (0.0)	0.48	1.16 (0.10-13.68)	-
Lymphopenia	39	25 (64.1)	17	17 (100.0)	**0.003**	**8.96 (1.07-74.91)**	7.08 (0.80-62.62)
Leukocytosis	44	11 (25.0)	17	7 (41.2)	0.21	2.10 (0.64-6.85)	-
Leukopenia	44	4 (9.1)	17	3 (17.7)	0.30	2.14 (0.43-10.78)	-
Elevated ferritin	26	0 (0.0)	14	2 (14.3)	0.12	4.17 (0.34-50.61)	-
Transaminitis	36	4 (11.1)	17	8 (47.1)	**0.006**	**7.11 (1.74-29.1)**	**5.67 (1.27-25.43)**
Elevated hsCRP	27	19 (70.4)	15	15 (100.0)	0.09	5.89 (0.66-52.70)	-
Elevated D-dimer	31	29 (93.6)	16	16 (100.0)	0.43	1.03 (0.09-12.35)	-
Elevated PCT	32	12 (62.5)	15	13 (86.7)	**0.002**	**10.83 (2.08-56.51)**	**16.60 (2.61-105.46)**
Elevated LDH	30	3 (10.0)	17	9 (52.9)	**0.002**	**10.13 (2.20-46.59)**	**17.55 (2.51-122.78)**

Data reported as n (%)

OR—unadjusted odds ratio, aOR—odds ratio adjusted for maternal age and obesity, CI—confidence interval; hsCRP—high-sensitivity C-reactive protein, PCT—procalcitonin, LDH—lactate dehydrogenase

613 **Table 5. Test characteristics of identified peak laboratory abnormalities in pregnant patients**
614 **associated with clinical phenotype**

	Sensitivity (95% CI)	Specificity (95% CI)
ASYMPTOMATIC VERSUS SYMPTOMATIC INFECTION		
Elevated hsCRP	81.0% (65.9-91.4)	43.3% (25.5-62.6)
MILD-MODERATE VERSUS SEVERE-CRITICAL DISEASE		
	Sensitivity (95% CI)	**Specificity (95% CI)**
Transaminitis	47.1% (23.0-72.2)	88.9% (73.9-96.9)
Elevated PCT	86.7% (59.5-98.3)	62.5% (43.7-78.9)
Elevated LDH	52.9% (27.8-77.0)	90.0% (73.5-97.9)

615 *hsCRP—high-sensitivity C-reactive protein, PCT—procalcitonin, LDH—lactate dehydrogenase*
616 *CI—confidence interval*
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620 **Table 6. Literature review of studies evaluating laboratory markers in pregnant patients**

STUDY AUTHOR	NUMBER OF SUBJECTS		NON-PREGNANT VERSUS PREGNANT PATIENTS								
	Non-pregnant	**Pregnant**	**Neutrophils**	**Lymphocytes**	**Leukocytes**	**D-Dimer**	**ALT**	**AST**	**CRP**	**PCT**	**LDH**
Liu et al.[18]	14	16	↑	X	↑				X		
Wang et al.[17]	42	30	↑	X	↑	↑	X	X	↑	↑	X
			ASYMPTOMATIC VERSUS SYMPTOMATIC PREGNANT PATIENTS								
	Asymptomatic	**Symptomatic**	**Neutrophils**	**Lymphocytes**	**Leukocytes**	**D-Dimer**	**ALT**	**AST**	**CRP**	**PCT**	**LDH**
Grechikuna et al.[21]	12	7				X			X		
Fisher et al.	61	67	X	X	X	X	X	X	↑	X	X
			PREGNANT PATIENTS STRATIFIED BY SEVERE VERSUS CRITICAL DISEASE								
	Severe	**Critical**	**Neutrophils**	**Lymphocytes**	**Leukocytes**	**D-Dimer**	**ALT**	**AST**	**CRP**	**PCT**	**LDH**
Pierce-Williams et al.[26]	44	20				X	X	X	↑	↑	↑
			PREGNANT PATIENTS STRATIFIED BY MILD-MODERATE VERSUS SEVERE DISEASE								
	Mild-Moderate	**Severe**	**Neutrophils**	**Lymphocytes**	**Leukocytes**	**D-Dimer**	**ALT**	**AST**	**CRP**	**PCT**	**LDH**
Pereira et al.[27]	10	2	↑	X		↑	X	X	↑		X
Fisher et al.	39	17	X	X	X	X	↑	↑	X	↑	↑

621 X—*no significant difference identified between group,* ↑—*significant increase in laboratory value identified,*
622 *ALT—alanine aminotransferase, AST—aspartate aminotransferase, CRP—C-reactive protein, PCT—procalcitonin, LDH—lactate dehydrogenase*
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627 **FIGURE LEGENDS**

Figure 1. Patient flow diagram

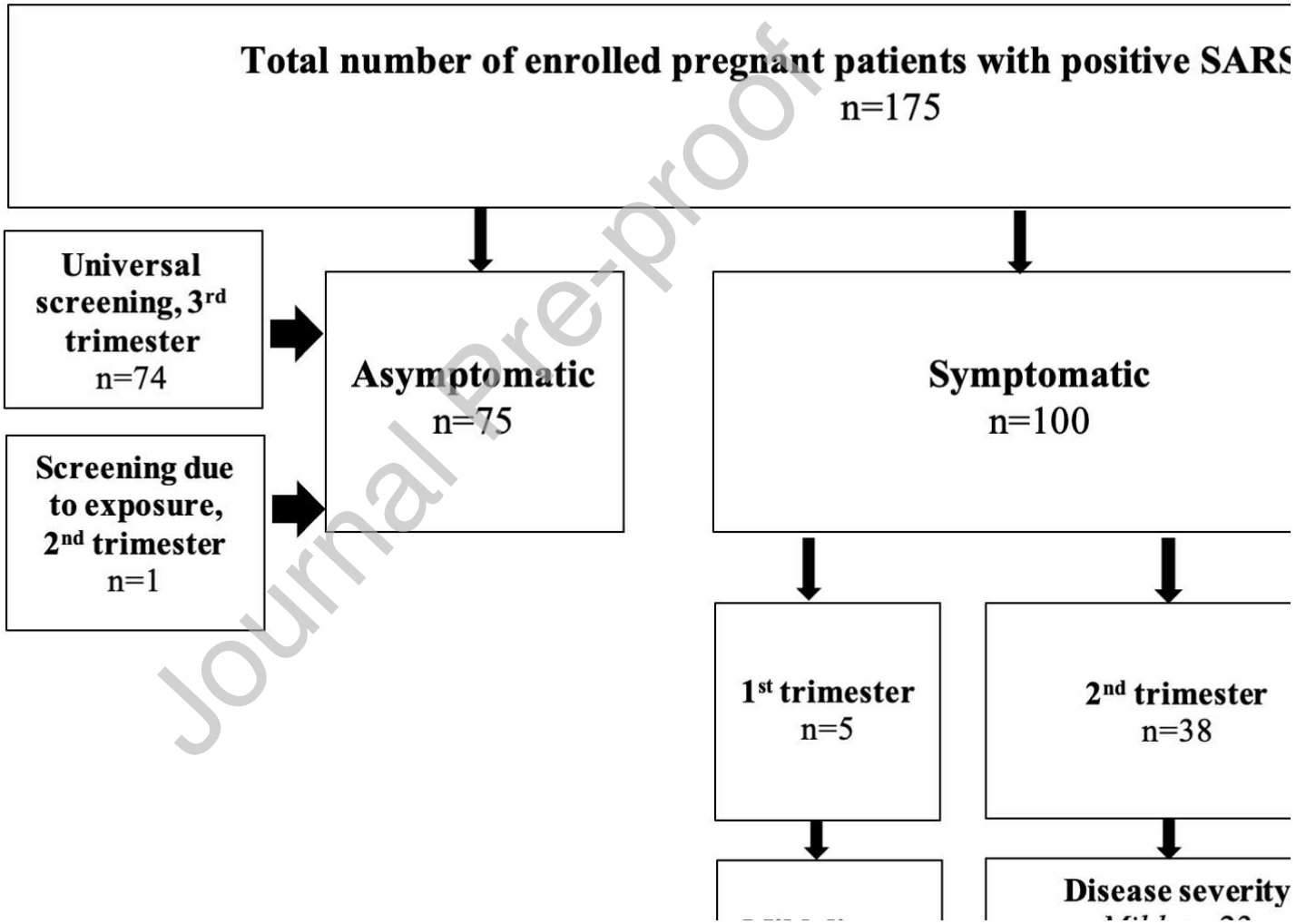

Figure 1. Flow diagram of asymptomatic and symptomatic pregnant patients with SARS-CoV-2 infection by gestational age and disease severity.

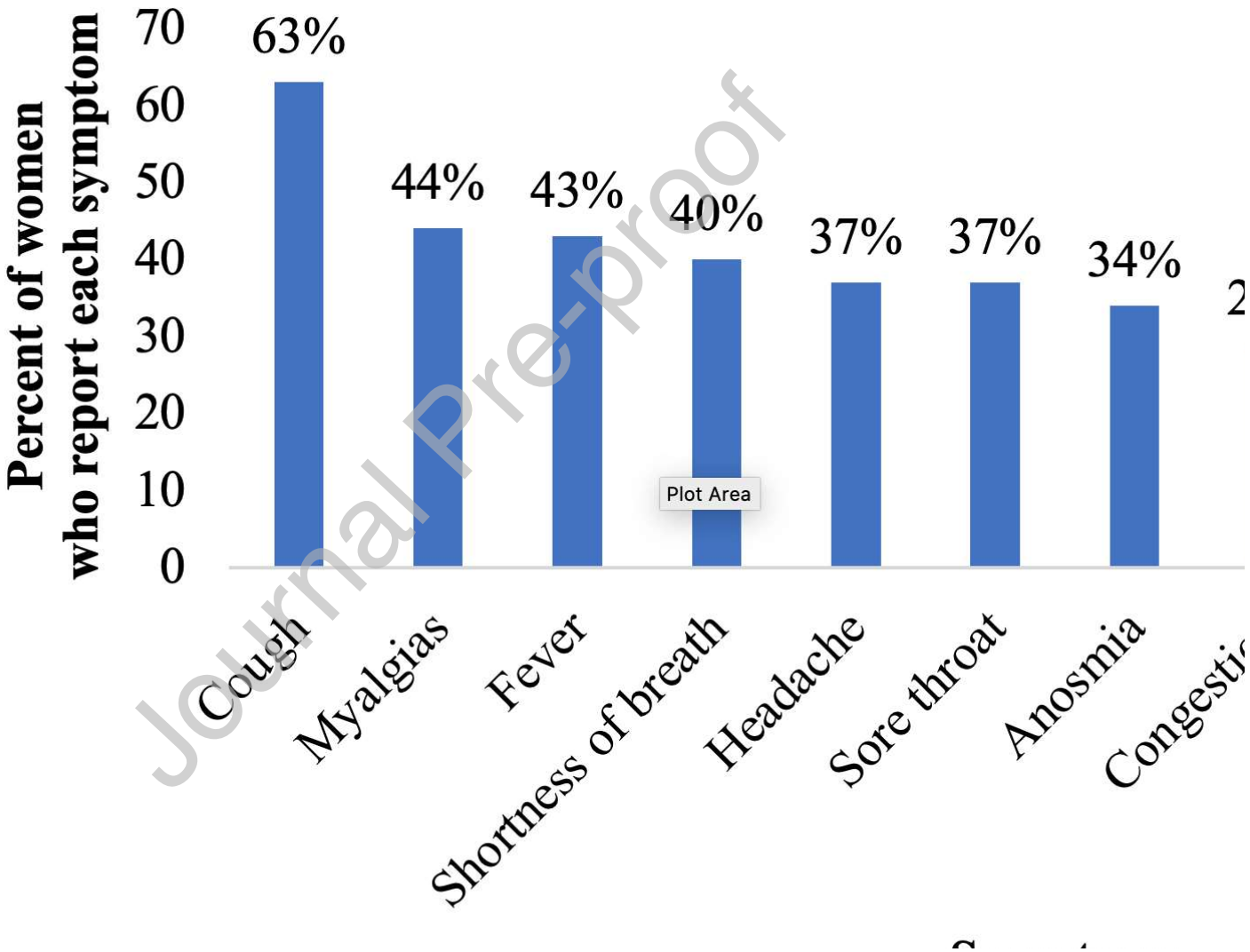

Figure 2. The most commonly reported symptoms among symptomatic pregnant patients with SARS-CoV-2 infection.

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