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Laboratory analysis of symptomatic and asymptomatic pregnant patients with SARS-CoV-2 infection

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BACKGROUND: Inflammatory biomarkers have been used to portend disease severity in nonpregnant 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 SARS-CoV-2 infection by symptom status and disease severity.

STUDY DESIGN: We retrospectively evaluated pregnant patients with positive SARS-CoV-2 infection, confirmed through polymerase chain reaction testing, at an urban academic US hospital between March 2020 and October 2020, performed for reported symptoms or universal screening on admission. In our hospital, all patients with SARS-CoV-2 infection were recommended to have baseline laboratory testing, including leukocyte, neutrophil, and lymphocyte counts; aspartate aminotransferase and alanine aminotransferase; high-sensitivity C-reactive protein; procalcitonin; lactate dehydrogenase; 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 were calculated to identify symptomatic vs asymptomatic infection and severe to critical disease vs mild to moderate disease.

RESULTS: We identified 175 pregnant patients with SARS-CoV-2 infection, of whom 100 (57%) were symptomatic; 17 (17%) of those who were symptomatic had a severe to critical disease. Laboratory data were available for 128 patients, of whom 67 (52%) were symptomatic. Compared with asymptomatic individuals, symptomatic individuals were more likely to exhibit elevated high-sensitivity C-reactive protein levels after adjusting for gestational age (adjusted odds ratio, 5.67; 95% confidence interval, 1.42−22.52; sensitivity, 81%; specificity, 43%). In symptomatic individuals, transaminitis (adjusted odds ratio, 5.67; 95% confidence interval, 1.27−25.43), elevated procalcitonin levels (adjusted odds ratio, 16.60; 95% confidence interval, 2.61−105.46), and elevated lactate dehydrogenase levels (adjusted odds ratio, 17.55; 95% confidence interval, 2.51−122.78) were independently associated with severe to critical disease rather than mild to moderate disease after adjusting for maternal age and obesity. For differentiating disease severity, sensitivity rates for transaminitis, procalcitonin elevation, and lactate dehydrogenase elevation were 47%, 87%, and 53%, respectively, whereas the specificity rates were 89%, 63%, and 90%, respectively.

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

Key words: inflammatory biomarkers in pregnancy, SARS-CoV-2 infection in pregnancy

Introduction

Pregnant women are more likely to experience severe sequelae after SARS-CoV-2 infection, presumably because of physiological changes in pregnancy that alter immune function.[1−4] In the United States, from March 2020 to August 2020, approximately 1 in 4 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 women, resulting in 50 maternal deaths.[5,6] Amid a rapidly evolving pandemic, several small case series have determined that most pregnant women with SARS-CoV-2 infection will have a mild clinical phenotype, but a clinically significant minority of pregnant women with SARS-CoV-2 infection will develop a severe illness.[3,7−10]

EDITOR'S CHOICE

In the nonpregnant 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. Although some studies have evaluated subsets of biomarkers to clinically distinguish pregnant women based on symptoms or severity of symptoms, the small sample sizes have precluded meaningful conclusions.[16−21] As such, we do not have a clear laboratory-based approach to evaluate pregnant patients with SARS-CoV-2 infection.

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

Cite this article as: Fisher SA, Goldstein JA, Mithal LB, et al. Laboratory analysis of symptomatic and asymptomatic pregnant patients with SARS-CoV-2 infection. Am J Obstet Gynecol MFM 2021;3:100458.

2589-9333/$36.00

http://dx.doi.org/10.1016/j.ajogmf.2021.100458

AJOG MFM at a Glance

Why was this study conducted?

We aimed to compare laboratory findings among pregnant patients with SARS-CoV-2 infection by symptom status and disease severity to elucidate the inflammatory biomarkers that may be most associated with clinical phenotype in pregnant patients.

Key findings

An elevated high-sensitivity C-reactive protein level was significantly associated with symptomatic (vs asymptomatic) infection, although the low specificity (43%; 95% confidence interval, 26−63) limits its clinical use. Among symptomatic pregnant patients, elevated liver enzymes, procalcitonin, and lactate hydrogenase were significantly associated with severe to critical (vs mild to moderate) disease. However, poor test characteristics limit their clinical applicability.

What does this add to what is 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 diseases from asymptomatic and mild diseases, respectively.

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 examined the differences in biomarkers among symptomatic pregnant patients with 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, Illinois, we evaluated pregnant patients with positive SARS-CoV-2 infection, confirmed through polymerase chain reaction (PCR) testing, between March 2020 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 in the ambulatory and inpatient settings for reported symptoms consistent with SARS-CoV-2 infection, known exposure to individuals with SARS-CoV-2 infection, or as a universal screening protocol at the 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 the 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 individuals were admitted if they had unstable vital signs, required oxygen supplementation, reported significant shortness of breath or respiratory symptoms, or felt to be at risk of subsequent clinical deterioration. Apart from that, clinically stable pregnant women 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 laboratory test results with a complete blood cell count with differential to assess neutrophil and lymphocyte percentages and 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 on the basis of their potential to stratify disease severity: high-sensitivity CRP (hsCRP), PCT, LDH, D-dimer, and ferritin. Laboratory test results 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 department, 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 infection; alternatively, the clinical suspicion of worsening pulmonary disease or concern for superimposed bacterial pneumonia was used to guide the decision for radiographic evaluation.

Disease severity was classified with guidance from the National Institutes of Health's COVID-19 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 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 of ≥94% on room air), severe illness (individuals with oxygen saturation of <94% on room air, respiratory rate of >30 breaths per minute, a ratio of arterial partial pressure of oxygen to the fraction of inspired oxygen of <300 mm Hg, or lung infiltrates of >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 an oxygen saturation of ≥95% on room air, we classified any woman requiring oxygen supplementation as having a severe illness (ie, oxygen saturation of <95% on room air), with moderate illness thereby encompassing evidence of lower respiratory disease with an oxygen saturation of ≥95% on room air.

Pregnant patients were stratified by the presence of symptoms and severity of illness. Pregnant patients with mild to moderate disease were compared with those with severe to critical disease. If patients initially presented with mild to moderate disease, but subsequently demonstrated progression to a 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 a body mass index of ≥30 kg/m^2. Independent samples *t* tests and Mann-Whitney *U* tests compared normally and abnormally distributed continuous variables, respectively. Chi-square test and the Fisher exact test were used to compare categorical variables. A *P* value of <.05 was considered statistically significant.

Median peak laboratory values, among all laboratory data available for the patient within 14 days of a positive SARS-CoV-2 test result, were 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 nonpregnant patients, we compared the nadir of neutrophil percentage, lymphocyte percentage, and leukocyte count between the groups.[23] The data included were cross-sectional; only the highest (or the lowest) biomarker level was analyzed for each patient. The analysis of laboratory values obtained at initial presentation, was similarly performed. Multiple laboratory values for the same patient were not analyzed. No correction was made for multiple comparison testing.

Peak (vs nadir) laboratory values and laboratory values on initial presentation were dichotomized on the basis of whether or not 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 pregnant patients who were symptomatic vs asymptomatic and symptomatic pregnant patients with mild to moderate disease vs those with severe to critical disease. Chi-square test and the Fisher exact test determined biomarker abnormalities significantly associated with symptomatic infection and disease severity. Peak (vs nadir) laboratory values and laboratory values on initial presentation that were significantly associated with symptomatic SARS-CoV-2 or 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 a more severe illness.

The remainder of our analysis involved analysis of only peak (vs nadir) laboratory values. The sensitivity and specificity of each laboratory abnormality identified in multivariable regression to be a significant predictor of clinical phenotype (ie, symptomatic vs asymptomatic infection; mild to moderate disease vs severe to critical disease) were calculated. Moreover, sensitivity analysis, excluding pregnant patients treated with dexamethasone, which is known to contribute to leukocytosis, was 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 SARS-CoV-2 test result warranting antenatal corticosteroid administration for fetal benefit received dexamethasone, not betamethasone. Additional sensitivity analyses among symptomatic patients excluded patients who had laboratory assessments during labor or within 48 hours after delivery, as biomarker levels can be altered by physiological changes during labor and immediately after delivery.

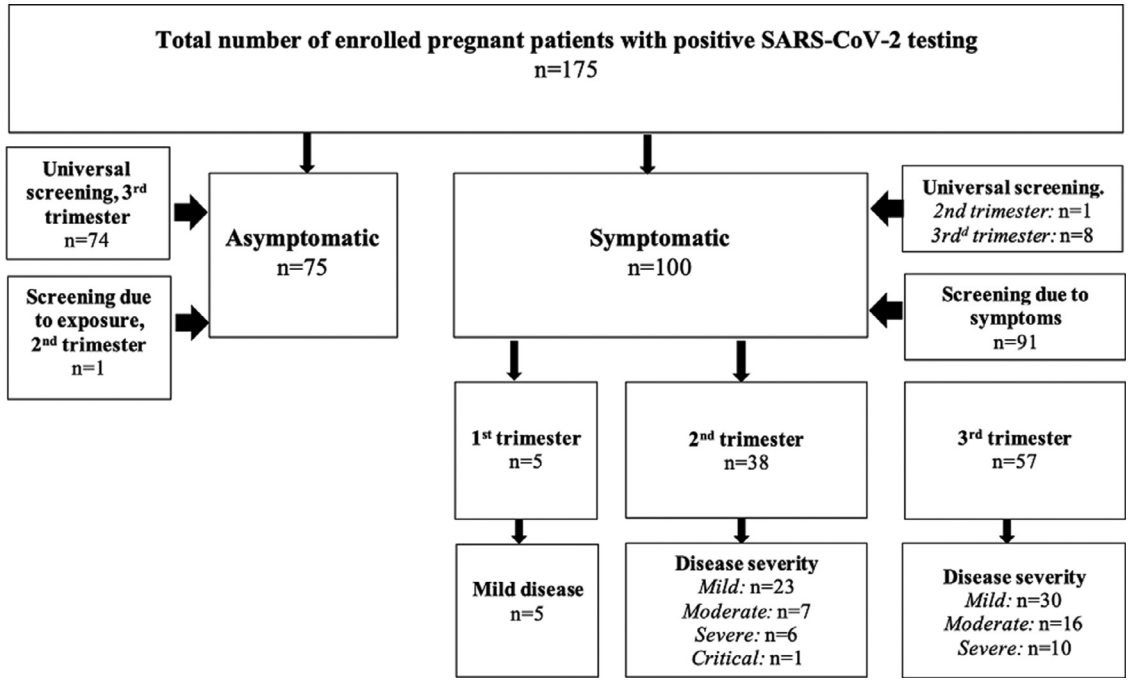
Statistical analyses were conducted using Stata (version 16.1.844; StataCorp LLC, College Station, TX). The study was approved by the Northwestern University Feinberg School of Medicine Institutional Review Board (IRB number, STU00212232) before its initiation and obtained a waiver of written consent.

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 1 asymptomatic patient was tested solely because of exposure to a known positive case contact; all other asymptomatic patients were tested per universal screening protocol. The median gestational age at diagnosis was 39 weeks in symptomatic patients and 29.6 weeks in asymptomatic patients (*P*<.001), with 43% of patients with a symptomatic disease identified before the third trimester of pregnancy (Table 1). Of note, 46% and 23% of symptomatic and asymptomatic patients, respectively, reported known exposure to a positive case contact (*P*=.003). There was no statistically significant difference in parity, race, ethnicity, or maternal comorbidities between those who were symptomatic and those who were asymptomatic. Among symptomatic individuals, pregnant patients with severe to critical disease were older (*P*=.03) and more likely to be obese (*P*=.004) than those with mild to moderate disease; baseline characteristics were 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 1% (1 person) had a critical disease. The commonly reported symptoms were cough (63%), fever (41%), and shortness of breath (40%) (Figure 2). Moreover, 30 symptomatic

FIGURE 1
Flow diagram



Asymptomatic and symptomatic pregnant patients with SARS-CoV-2 infection by gestational age and disease severity.

Fisher. Laboratory analysis of SARS-CoV-2 in pregnant patients. Am J Obstet Gynecol MFM 2021.

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. Most 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 were 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). A similar analysis for laboratory values obtained at initial presentation, has been demonstrated in Supplemental Table 1.

Laboratory markers were dichotomized as normal vs abnormal. For peak (vs nadir) laboratory values and those obtained at initial presentation, only leukocytosis (compared with the absence of leukocytosis, with leukocytosis defined as white blood cell count of >10.5 K/μL), leukopenia (compared with the absence of leukopenia, with leukopenia defined as white blood cell count of <4 K/μL), and an elevated hsCRP level (compared with a normal hsCRP level, defined as <10 mg/L) were significantly associated with symptomatic infection (Table 3; Supplemental Table 2). Neutrophil percentage, lymphocyte percentage, transaminitis, and elevations in ferritin, D-dimer, LDH, and PCT levels were not associated with a symptomatic disease. After adjusting the peak value for gestational age at diagnosis, pregnant patients with an elevated hsCRP level had more than a 4-fold odds of having a symptomatic disease. Within the subgroup of pregnant patients who had symptoms, lymphopenia (compared with the absence of lymphopenia, with lymphopenia defined as lymphocyte percentage of <20%), transaminitis (compared with normal liver transaminases, with elevated ALT defined as >52 units/L and elevated AST defined as >39 units/L), an elevated PCT level (compared with normal PCT level, defined as <0.065 ng/mL), and an elevated LDH level (compared with normal LDH level, defined as <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 elevated ferritin, D-dimer, and hsCRP levels were not

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 to moderate (n=83)	Severe to critical (n=17)	*P* value
Maternal age (y)	29.30±6.06	30.20±6.20	.39	29.50±5.90	33.20±6.90	.03
Gestational age at diagnosis	39.0 (16.3–41.1)	29.6 (3.6–41.0)	<.001	29.1 (3.6–41.0)	31.1 (16.0–36.4)	.81
By trimester						
First trimester	0 (0)	5 (5.0)	<.001	5 (6.0)	0 (0)	.83
Second trimester	1 (1.4)	38 (38.0)		31 (37.0)	7 (41.0)	
Third trimester	74 (99.0)	57 (57.0)		47 (57.0)	10 (59.0)	
Nulliparous	28 (37.0)	34 (34.0)	.65	31 (37.0)	3 (18.0)	.16
Self-reported race						
Black	21 (28.0)	23 (23.0)	.74	18 (22.0)	5 (29.0)	.85
White	19 (26.0)	30 (30.0)		25 (30.0)	5 (29.0)	
Asian	2 (3.0)	5 (5.0)		5 (6.0)	0 (0)	
Other[a]	32 (43.0)	42 (42.0)		35 (42.0)	34 (41.0)	
Hispanic ethnicity	35 (47.0)	55 (55.0)	.32	43 (52.0)	12 (71.0)	.16
Maternal comorbidities						
Asthma or pulmonary disease	10 (13.0)	21 (21.0)	.18	16 (19.0)	5 (29.0)	.35
Obesity (body mass index ≥30 kg/m^2)	40 (53.0)	57 (57.0)	.63	42 (51.0)	15 (88.0)	.004
Chronic hypertension	4 (5.0)	12 (12.0)	.19	9 (11.0)	3 (18.0)	.42
Immunosuppressive disease or medication	4 (5.0)	3 (3.0)	.46	2 (2.0)	1 (6.0)	.43
Pregestational diabetes mellitus	3 (4.0)	6 (6.0)	.73	5 (6.0)	1 (6.0)	.99
Gestational diabetes mellitus	8 (11.0)	14 (14.0)	.46	9 (13.0)	5 (29.0)	.05

Data are presented as mean±standard deviation, median (interquartile range), or number (percentage), unless otherwise indicated.

[a] The standard reported race categories within our electronic medical record system include White, Black, Asian, American Indian or Alaskan Native, Native Hawaiian or Other Pacific Islander, or "other." We have condensed American Indian or Alaskan Native and Native Hawaiian or Other Pacific Islander into "other." Several patients of Hispanic ethnicity selected "other" as their identified race.

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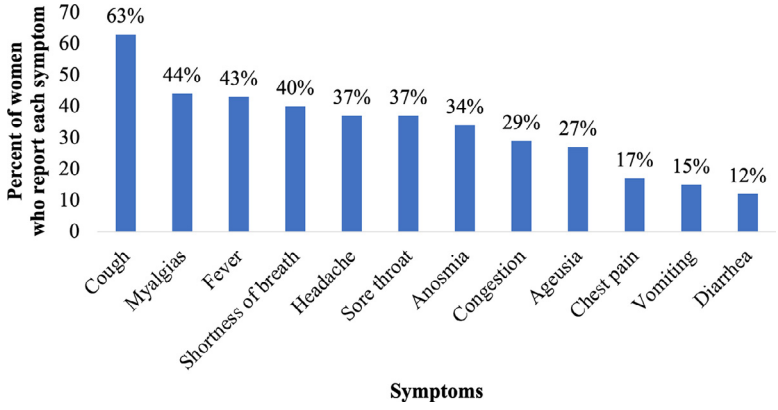
associated with disease severity among pregnant patients with symptomatic SARS-CoV-2 infection. After adjusting for age and obesity in analysis by peak (vs nadir) laboratory values, transaminitis, an elevated PCT level, and an elevated LDH level were each associated with having a severe to critical disease.

FIGURE 2
Most common symptoms among symptomatic pregnant patients with SARS-CoV-2 infection



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In the analysis of laboratory values obtained at initial presentation, an elevated PCT level was no longer significant (Supplemental Table 3).

Regarding test characteristics for peak laboratory values, hsCRP showed moderate sensitivity (81%) but poor specificity (43%) for distinguishing symptomatic vs asymptomatic infection. Moreover, the sensitivity and specificity for each of these biomarkers to differentiate disease severity among symptomatic patients were suboptimal, with a sensitivity of 47%, 87%, and 53% for transaminitis, PCT elevation, and LDH elevation, respectively, and a specificity of 89%, 63%, and 90%, respectively (Table 5).

In a planned sensitivity analysis of peak (vs nadir) laboratory values, excluding 3 individuals treated with dexamethasone, neutrophilia (odds ratio [OR], 5.11; 95% confidence interval [CI], 0.59–43.85), lymphopenia (OR, 7.28; 95% CI, 0.86–61.67), and

TABLE 2
Peak (vs nadir) laboratory characteristics in pregnant patients stratified by the presence or absence of symptoms and disease severity

Variable	n	Asymptomatic	N	Symptomatic	*P* value	n	Mild to moderate	n	Severe to critical	*P* value
Neutrophils (%)										
Highest	42	75.5 (58–90)	56	77.0 (44–94)	.29	39	75.0 (44–93)	17	82.0 (72–94)	<.001
Lowest	42	72.0 (0–90)	56	67.5 (42–86)	.02	39	70.0 (42–80)	17	66 (61–86)	.39
Lymphocytes (%)										
Highest	42	18.0 (6–45)	56	21.0 (7–49)	.09	39	20.0 (7–49)	17	24.0 (12–30)	.70
Lowest	42	18.0 (5–34)	56	16.0 (0–33)	.21	39	17.0 (3–33)	17	11.0 (0–18)	<.001
Leukocytes										
Highest	61	10.8 (5.7–24.4)	67	8.8 (3.1–64.4)	<.001	44	8.3 (3.1–14.9)	17	10.4 (4.2–64.4)	.26
Lowest	61	9.3 (7.7–11.4)	67	6.1 (4.8– 8.3)	<.001	44	6.9 (2.9–16.1)	17	5.1 (3.5–8.3)	.004
Ferritin	27	16.5 (6.2–817.6)	40	44.3 (8.5–15,695.4)	.001	26	23.8 (8.5–175.6)	14	81.8 (17.9–15,695.4)	.003
ALT	50	12.0 (5–99)	53	18.0 (5–4997)	<.001	36	17.5 (5–670)	17	31.0 (10–4997)	.03
AST	50	21 (9–96)	53	27 (12–10,000)	.005	36	25 (12–327)	17	36 (17–10,000)	.01
hsCRP	30	11.0 (1.3–163.6)	42	37.1 (0.9–219.5)	.005	27	12.9 (0.9–219.5)	15	76.2 (36.4–203.6)	<.001
D-dimer	37	774 (242–6907)	47	613 (187–17,106)	.03	31	564 (187–3411)	16	689 (262–17,106)	.50
PCT	38	0.00 (0.0–3.5)	47	0.08 (0.0–19.0)	.02	32	0.05 (0.0–2.7)	15	0.25 (0.0–19.0)	<.001
LDH	47	224 (123–521)	47	221 (112–12,000)	.60	30	193 (112–10,851)	17	267 (151–12,000)	<.001

Data are presented as median (interquartile range), unless otherwise indicated. Reference range: neutrophils (55%–70%), lymphocytes (20%–40%), leukocytes (4.0–10.5 K/μL), ferritin (11–307 ng/mL), ALT (0–52 unit/L), AST (0–39 unit/L), hsCRP (0–10 mg/L), D-dimer (0–230 D-DU ng/mL), PCT (0.000–0.065 ng/mL), and LDH (0–271 unit/L).

ALT, alanine aminotransferase; *AST*, aspartate aminotransferase; *hsCRP*, high-sensitivity C-reactive protein; *LDH*, lactate dehydrogenase; *PCT*, procalcitonin.

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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)	Adjusted OR (95% CI)
Neutrophilia	42	28 (66.7)	56	45 (80.4)	.12	2.05 (0.82–5.13)	—
Neutropenia	42	1 (2.4)	56	3 (5.4)	.42	2.32 (0.23–23.14)	—
Lymphocytosis	42	1 (2.4)	56	2 (3.6)	.62	1.48 (0.13–16.91)	—
Lymphopenia	42	27 (64.3)	56	42 (75.0)	.25	1.67 (0.70–3.99)	—
Leukocytosis	61	34 (67.1)	67	18 (26.9)	.02	0.41 (0.20–0.84)	0.48 (0.19–1.18)
Leukopenia	61	0 (0)	67	7 (10.4)	.01	8.42 (1.01–70.6)	4.97 (0.37–66.65)
Elevated ferritin level	27	1 (3.7)	40	2 (5.0)	.65	1.37 (0.12–15.89)	—
Transaminitis	50	6 (11.8)	53	12 (21.8)	.16	2.15 (0.74–6.25)	—
Elevated hsCRP level	30	17 (56.7)	42	34 (81.0)	.03	3.25 (1.13–9.34)	4.51 (1.11–18.40)
Elevated D-dimer level	37	37 (100.0)	47	45 (95.7)	.20	0.63 (0.05–7.17)	—
Elevated PCT level	38	17 (44.7)	47	25 (53.2)	.44	1.40 (0.59–3.31)	—
Elevated LDH level	47	10 (21.3)	47	12 (25.5)	.63	1.27 (0.49–3.31)	—

Data are presented as number (percentage), unless otherwise indicated.

Adjusted ORs are adjusted for gestational age.

CI, confidence interval; *hsCRP*, high-sensitivity C-reactive protein; *LDH*, lactate dehydrogenase; *OR*, odds ratio; *PCT*, procalcitonin.

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

Variable	n	Mild to moderate	n	Severe to critical	*P* value	OR (95% CI)	Adjusted OR (95% CI)
Neutrophilia	39	28 (71.8)	17	17 (100.0)	.06	6.29 (0.74–53.28)	—
Neutropenia	39	3 (7.7)	17	0 (0)	.33	0.75 (0.07–7.77)	—
Lymphocytosis	39	2 (5.1)	17	0 (0)	.48	1.16 (0.10–13.68)	—
Lymphopenia	39	25 (64.1)	17	17 (100.0)	.003	8.96 (1.07–74.91)	7.08 (0.80–62.62)
Leukocytosis	44	11 (25.0)	17	7 (41.2)	.21	2.10 (0.64–6.85)	—
Leukopenia	44	4 (9.1)	17	3 (17.7)	.30	2.14 (0.43–10.78)	—
Elevated ferritin level	26	0 (0)	14	2 (14.3)	.12	4.17 (0.34–50.61)	—
Transaminitis	36	4 (11.1)	17	8 (47.1)	.006	7.11 (1.74–29.1)	5.67 (1.27–25.43)
Elevated hsCRP level	27	19 (70.4)	15	15 (100.0)	.09	5.89 (0.66–52.70)	—
Elevated D-dimer level	31	29 (93.6)	16	16 (100.0)	.43	1.03 (0.09–12.35)	—
Elevated PCT level	32	12 (62.5)	15	13 (86.7)	.002	10.83 (2.08–56.51)	16.60 (2.61–105.46)
Elevated LDH level	30	3 (10.0)	17	9 (52.9)	.002	10.13 (2.20–46.59)	17.55 (2.51–122.78)

Data are presented as number (percentage), unless otherwise indicated.

Adjusted ORs are adjusted for maternal age and obesity.

CI, confidence interval; *hsCRP*, high-sensitivity C-reactive protein; *LDH*, lactate dehydrogenase; *OR*, odds ratio; *PCT*, procalcitonin.

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leukopenia (OR, 2.73; 95% CI, 0.53–14.04) were not significant in bivariable analysis of biomarkers according to disease severity in pregnant patients with symptomatic SARS-CoV-2 infection. In additional sensitivity analysis among symptomatic patients, excluding those who had laboratory assessment done during labor or after delivery, only elevated PCT levels (adjusted OR, 10.85; 95% CI, 1.44–81.88) and elevated LDH levels (adjusted OR, 8.90; 95% CI, 1.06–75.10) were significantly associated with severe to critical disease; transaminitis was no longer significantly associated with disease severity (OR, 3.0; 95% CI, 0.57–15.87).

TABLE 5
Test characteristics of identified peak laboratory abnormalities in pregnant patients associated with clinical phenotype

Asymptomatic vs symptomatic infection	Sensitivity (95% CI)	Specificity (95% CI)
Elevated hsCRP level	81.0 (65.9–91.4)	43.3 (25.5–62.6)

Mild to moderate disease vs severe to critical disease	Sensitivity (95% CI)	Specificity (95% CI)
Transaminitis	47.1 (23.0–72.2)	88.9 (73.9–96.9)
Elevated PCT level	86.7 (59.5–98.3)	62.5 (43.7–78.9)
Elevated LDH level	52.9 (27.8–77.0)	90.0 (73.5–97.9)

CI, confidence interval; *hsCRP*, high-sensitivity C-reactive protein; *LDH*, lactate dehydrogenase; *PCT*, procalcitonin.

Sensitivity and specificity are reported in percentages (%).

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Comment

Principal findings

In our cohort of 175 pregnant patients with SARS-CoV-2 infection, we identified a relatively low but clinically important subset of patients with severe and critical diseases (17%). Among our analytical cohort of 128 patients with data on inflammatory biomarkers available, we observed a vast heterogeneity in measured biomarker levels among pregnant patients with SARS-CoV-2 infection even within cohorts (eg, among those who were asymptomatic or among those with mild to moderate disease). This pronounced heterogeneity decreases the discriminatory strength of any 1 specific inflammatory marker to differentiate the clinical phenotypes of the disease. Of all inflammatory markers analyzed, only hsCRP was independently associated with a symptomatic disease. However, 55% of patients with an asymptomatic disease had an abnormally elevated hsCRP level, making the specificity of this biomarker as a discriminatory test clinically not useful.

Among symptomatic pregnant patients, elevated liver enzymes and elevated PCT and LDH levels for peak laboratory values were all significantly associated with a severe or critical disease. Transaminitis and LDH both demonstrated poor performance as a

TABLE 6
Literature review of studies evaluating laboratory markers in pregnant patients

Study author, year	Number of subjects		Nonpregnant vs pregnant patients								
	Nonpregnant	Pregnant	Neutrophils	Lymphocytes	Leukocytes	D-dimer	ALT	AST	CRP	PCT	LDH
Liu et al,[18] 2020	14	16	↑	X	↑				X		
Wang et al,[17] 2020	42	30	↑	X	↑	↑	X	X	↑	↑	X

			Asymptomatic vs symptomatic pregnant patients								
	Asymptomatic	Symptomatic	Neutrophils	Lymphocytes	Leukocytes	D-Dimer	ALT	AST	CRP	PCT	LDH
Grechukhina et al,[21] 2020	12	7				X			X		
Fisher et al, 2021 (current study)	61	67	X	X	X	X	X	X	↑	X	X

			Pregnant patients stratified by severe vs critical disease								
	Severe	Critical	Neutrophils	Lymphocytes	Leukocytes	D-Dimer	ALT	AST	CRP	PCT	LDH
Pierce-Williams et al,[25] 2020	44	20				X	X	X	↑	↑	↑

			Pregnant patients stratified by mild to moderate disease vs severe disease								
	Mild to moderate	Severe	Neutrophils	Lymphocytes	Leukocytes	D-Dimer	ALT	AST	CRP	PCT	LDH
Pereira et al,[26] 2020	10	2	↑	X		↑	X	X	↑		X
Fisher et al, 2021 (current study)	39	17	X	X	X	X	↑	↑	X	↑	↑

The "X" indicates no significant difference identified between the groups, and the symbol "↑" indicates a significant increase in the laboratory values identified.

ALT, alanine aminotransferase; *AST*, aspartate aminotransferase; *CRP*, C-reactive protein; *LDH*, lactate dehydrogenase; *PCT*, procalcitonin.

Fisher. Laboratory analysis of SARS-CoV-2 in pregnant patients. Am J Obstet Gynecol MFM 2021.

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% to 90%. Elevated peak PCT demonstrated improved performance as a screening test but demonstrated poor performance as a diagnostic test for a 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 was poor and suggested that they have limited use in clinical practice.

Results

Although the obstetrical literature on inflammatory biomarkers associated with SARS-CoV-2 infection has demonstrated mixed results, several studies evaluating nonpregnant individuals with SARS-CoV-2 infection have noted that elevated D-dimer levels, neutrophil counts, ferritin levels, liver enzymes, LDH levels, and CRP levels and decreased lymphocyte counts have utility in differentiating morbidity and mortality risks resulting from widespread systemic inflammation.[11–15,20,24] However, we must consider that normal reference ranges for laboratory results may be altered by physiological changes in pregnancy.[24] In particular, D-dimer is typically elevated during pregnancy, but 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, whereas median CRP values in normal pregnancies seem to be higher than standardized values for nonpregnant individuals.[21,24–28] Pregnancy itself does not affect LDH levels or liver enzymes, although these can be elevated in the setting of preeclampsia or other liver diseases associated with pregnancy.[29–31] Moreover, leukocytosis, primarily related to increased circulation of neutrophils, without significant alteration in lymphocyte count is associated with the normal pregnancy state.[32–34] Finally, although elevated ferritin levels can be an indicator of infection in pregnancy, ferritin levels can be reduced as a result of hemodilution that is characteristic of pregnancy.[35] Therefore, it is possible that certain biomarker levels in our cohort may be labeled "normal" or "abnormal" merely because of pregnancy physiology and not solely because of 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 because of normal pregnancy physiology.

The previous evaluation of inflammatory biomarkers in pregnant patients with SARS-CoV-2 infection according to symptomatology and disease severity was limited and demonstrated mixed results (Table 6).[17,18,20,21,25,26]

Moreover, 2 studies compared the biomarkers between pregnant women and nonpregnant women with SARS-CoV-2 infection, although the studies did not include subgroups for symptomatic disease or disease severity.[17,18] Shi et al[20] published a meta-analysis of 173 people in 11 studies, evaluating biomarkers among pregnant women dichotomized as elevated vs normal and did not find elevated CRP or LDH levels to be associated with SARS-CoV-2 infection in pregnant women, although there was no attention to symptomatic disease or disease severity. Grechukhina et al[21] evaluated CRP and D-dimer levels in 19 asymptomatic and symptomatic pregnant women, with no significant difference identified between the groups. In contrast, we identified abnormally elevated hsCRP levels to be independently associated with a symptomatic disease.

Notably, 2 studies have evaluated biomarker abnormalities in pregnant women according to disease severity, the largest with 64 individuals; both studies identified elevated CRP levels to be associated with greater disease severity, but neither study identified a significant association between liver enzymes and disease severity.[25,26] Although we did not identify hsCRP to be independently associated with a more severe disease in pregnant patients, we identified liver enzymes to be significantly associated with disease severity. Furthermore, Pierce-Williams et al[25] identified elevated PCT and LDH levels to be associated with greater disease severity, whereas Pereira et al[26] did not find LDH to be associated with disease severity. Similar to Pierce-Williams et al,[25] we identified elevated PCT and LDH levels for peak laboratory values to be independently associated with a more severe disease. Previous 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 those studies.

Clinical and research implications

Although the inflammatory biomarkers evaluated in our cohort of pregnant patients did not seem to be clinically useful for discriminating between symptomatic and asymptomatic infection or particularly indicative of disease severity, other clinical applications of these biomarkers remain unclear. Previous studies have commented on the use of elevated D-dimer levels to guide prophylactic anticoagulation in patients with a more severe SARS-COV-2 infection either during inpatient admission or following delivery.[36–39] In addition, elevated PCT 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 was 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, considering pregnancy physiology.

Strengths and limitations

Our study was strengthened by the diverse patient population and comprehensive array of inflammatory biomarkers evaluated. Our results were likely generalizable to other pregnant individuals in the United States. In addition, 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.

To our knowledge, although this cohort is the largest cohort 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 introduce additional selection bias, limiting our ability to firmly conclude the frequency of abnormal laboratory results and the validity of comparisons between the groups. Moreover, changes in criteria for testing throughout the pandemic limited our ability to determine the proportion of pregnant individuals tested who will have a symptomatic infection. Changes in the care and management of patients with SARS-CoV-2 infection occurred throughout the study period with different treatments having the potential to affect peak biomarker levels; however, our study conclusions were 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 that this was 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 could not comment on biomarker trends over time throughout a patient's disease, and we could not fully capture laboratory data for pregnant patients managed primarily in the outpatient setting. Particularly in asymptomatic patients identified on admission and among symptomatic individuals, the actual timing of infection was unknown, and it was plausible that peak biomarker levels could have occurred before, or even after, admission.

Conclusions

Inflammatory biomarkers used to differentiate morbidity in nonpregnant patients with SARS-CoV-2 infection demonstrated 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 may be most useful for risk stratification and prognostication of pregnant patients with SARS-CoV-2

infection, considering the pregnancy physiology. ■

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ajogmf.2021.100458.

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The authors report no conflict of interest.

This project was supported by the Friends of Prentice Research Award (FY20-21). The funding source had no role in the study design; collection, analysis, and interpretation of data; or manuscript preparation.

Permission was obtained from the Northwestern University Feinberg School of Medicine Institutional Review Board (IRB number, STU00212232) for publication of this study.

All authors consent to the publication of these data.

All authors gave final approval of the version to be published and are responsible for the accuracy and integrity of this work.

This work was presented at the 41st annual meeting of the Society for Maternal-Fetal Medicine, held virtually, January 25—30, 2021.

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