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The Value of Lymphocyte to C-reactive Protein Ratio in Asymptomatic COVID-19 Cases in Pregnant Versus Non-Pregnant Women

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Asymptomatic cases
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LCR
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A B S T R A C T

Background: Asymptomatic COVID-19 cases (ACC) had a key role in the deleterious spread of infection. Breaking the transmission chain by detecting ACC is an integral part of reducing adverse fetomaternal outcomes. The aims: we aimed to screen for ACC in women irrespective of pregnancy. Moreover, we tested the superiority of lymphocyte to C-reactive protein ratio (LCR), which is an inflammatory biomarker in relation to COVID-19 infection, and in distinguishing ACC. Materials and methods: A retrospective study recruited a hundred confirmed COVID-19 cases by PCR at the University Hospital. Participants were subdivided into two groups; Gr.1 (50 pregnant women at 37-41 weeks gestational age) and Gr. 2 (50 non-pregnant women). They were age and body-mass index-matched. For all, we obtained demographics, clinical features, and lab tests including (hemoglobin(HB), White blood cells (WB) neutrophils, lymphocytes, platelets count, C-reactive (CRP), D-dimer, Alanine transaminase (ALT), Aspartate aminotransferase (AST), and renal function test. Additionally, LCR for both groups was assessed.

Results: ACC, LCR were significantly lower in pregnant versus non-pregnant (44.83% vs. 72.42%)P -value=0.0001, LCR (230.07 vs.337.22) respectively. HB, platelets, and LCR levels were significantly lower among Gr1 compared to group 2. While the WBC, NEU, LYM, CRP, Alanine transaminase counts, creatinine, and D-dimer were significantly higher in Gr 1. The two groups scored no meaningful differences in the aspartate aminotransferase and blood urea.

ROC calculated the LCR cutoff value in pregnant cases; at 232.8, with 53.9,90 % sensitivity and specificity. The area under the curve AUC was 0.69, P-value<0.005. However, LCR scored insignificant AUC 0.5, P=0.97 in determining ACC at a cutoff value of 291.14.

Conclusion: A significantly reduced LCR in pregnant women underlies the infection's severity compared to non-pregnant. However, the insignificant correlation of LCR to grammar symptoms in those affected makes LCR an unreliable marker in ACC detection; PCR is still the gold standard.

قيمة الخلايا الليمفاوية لنسبة البروتين التفاعلي C في حالات COVID-19 بدون أعراض في النساء الحوامل مقابل غير الحوامل

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الكلمات المفتاحية:
حالات بدون أعراض
كوفيد 19
حمل
LCR
تفاعل البوليميراز المتسلسل

الملخص

الخلفية: حالات كوفيد بدون أعراض كان لها دور رئيسي في الانتشار الضار للعدوى. يعد كسر سلسلة الانتقال عن طريق الكشف عن حالات كوفيد بدون أعراض جزءًا لا يتجزأ من تقليل النتائج السلبية للأجنة. الأهداف: استهدفنا فحص حالات الإصابة بفيروس كورونا عند النساء بغض النظر عن الحمل. علاوة على ذلك ، قمنا باختبار تفوق الخلايا الليمفاوية على نسبة البروتين التفاعلي C ، وهو مؤشر حيوي التهابي فيما يتعلق بعدوى كوفيد ، وفي التمييز بين حالات الإصابة بالفيروس عديمة الأعراض. المواد والطرق: قامت دراسة الحالات والشواهد بتجنيد مائة حالة إصابة مؤكدة بالفيروس عن طريق تفاعل البوليميراز المتسلسل في مستشفى الجامعة. تم تقسيم المشاركين إلى مجموعتين. المجموعة الأولى خمس عشرة امرأة حامل في عمر الحمل 37-41 أسبوعًا) والمجموعة الثانية خمسة عشر امرأة غير حامل

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كانوا متطابقين مع مؤشر كتلة الجسم والعمر. للجميع ، حصلنا على التركيبة السكانية والميزات السريرية والاختبارات المعملية بما في ذلك (الهيموغلوبين ، خلايا الدم البيضاء ، العدلات ، الخلايا الليمفاوية ، تعداد الصفائح الدموية ، المتفاعل سي، دي دايمر، الانين ترانس امنييس، اسبارتيت امانيوترانسفريس. واختبار وظائف الكلى. بالإضافة إلى ذلك ، تم تقييم نسبة الخلايا الليمفاوية إلى البروتين التفاعلي سي لكلا المجموعتين.

النتائج: في حالات كوفيد بدون أعراض ، كانت نسبة تفاعل الخلايا الليمفاوية ج أقل بشكل ملحوظ في الحوامل مقابل غير الحوامل (44.33% مقابل 72.24) القيمة الاحتمالية =00001 نسبة الخلايا الليمفاوية إلى البروتين التفاعلي سي .

230.07مقابل 337.22) على التوالي كانت مستويات الهيموجلوبين والصفائح الدموية واللمفاوية ج المتفاعلة أقل بشكل ملحوظ بين المجموعة الأولى مقارنة بالمجموعة الثانية. بينما تعداد الدم الأبيض ، العدلات ، الخلايا الليمفاوية ، البروتين التفاعلي ج. تعداد دي دايمر، الانين ترانس امنييس، الكيراتينين كانت أعلى بشكل ملحوظ في المجموعة الاولى لم تسجل المجموعتان أي فروق ذات مغزى في الأسبارتات واليوريا في الدم.

منحنى خاصية تشغيل جهاز الاستقبال والمنطقة الواقعة تحت المنحنى حسبت قيمة قطع نسبة البروتين التفاعلي في الخلايا الليمفاوية ج في الحالات الحامل ؛ عند232.8 مع حساسية وخصوصية عند 53.909%كانت المنطقة تحت المنحنى0.69 القيمة اقل من 0.005 مع ذالك سجل نسبة تفاعل الخلايا الليمفاوية ج قليلا من القيمة 0.97% ولمنطقة الواقعة تحت المنحي =0,5 ,

ي تحديد حالات كوفيد بدون اعراض عند قيمة قطع قدرها 219,14

الخلاصة: انخفاض حالات الإصابة بالفيروس عديمة الأعراض بشكل ملحوظ لدى النساء الحوامل هو السبب وراء شدة العدوى مقارنة بغير الحوامل. ومع ذلك ، فإن الارتباط الضئيل بين النسبة التفاعلية للخلايا الليمفاوية ج والأعراض النحوية لدى المصابين يجعل النسبة علامة غير موثوقة في اكتشاف حالات كوفيد بدون أعراض ؛ لا يزال تفاعل البلمرة المتسلسل هو المعيار الذهبي.

Introduction

Coronavirus 2 disease (COVID-19) is a new contagious respiratory disease related to the advanced strain of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), transmitted easily between people by respiratory droplets [1]. It is regarded as an emerging disease with an aggressive increase in death cases, however, there are limited data considering covid infection in pregnancy [2]. Infected persons may be asymptomatic; others exhibited heterogeneous symptoms of infection ranging from a mild flu-like illness to moderate presented as mild pneumonia or, in severe forms; hypoxia or dyspnea. Compared to symptomatic patients, asymptomatic COVID-19 cases (ACC) showed an equivalent transmission potential, making them extremely risky to healthcare providers, other patients, and their families [2]. The elderly and pregnant women are at risk of severe COVID-19 illness, although pregnancy does not increase the risk of infection as earlier studies claimed [3,4]. Altered cell-mediated immunity in pregnancy was accredited for harvesting more severe forms of infectious diseases, particularly respiratory pathogens, as in COVID-19 [5]. Therefore, we need to protect pregnant women from getting infected, owing to the risk of increased adverse pregnancy outcomes, including preterm birth, preeclampsia, miscarriage, and increased perinatal morbidity and mortality [6-8].

The prognosis of disease through pregnancy depends on the hyperinflammatory response and cytokine storm; therefore, several biomarkers were investigated to reflect the inflammatory status [9], and the gold standard test for the disease diagnosis is RT-PCR tests, unfortunately, it has a significant disadvantage such as; it takes time (72)hours and high false-negative testing, especially early in the illness [9,10]. As a result, there is a need for quick, easy-to-access, and alternative tests to assess the viral load, like hematological parameters and ratios [10].

lymphocyte-C-reactive protein ratio(LCR) found available and promising prediction biomarker during inflammation, tumor recurrence prognosis, and recently in COVID-19 cases [11-13]. the test was done as a severity and prognostic biomarker in admitted hospital cases [14-16]. It has been found that Pregnancy does not have a serious effect on clinical symptoms or the presentation time following the onset of these symptoms, however, adverse pregnancy outcomes were more common in pregnant women; as sepsis, DIC, renal failure, longer hospital stay, admission to intensive care unit [15].

However, the LCR role was not investigated in pregnant women or asymptomatic patients in previous studies, therefore. Our goal is to evaluate the effectiveness and superiority of LCR for predicting seropositive asymptomatic COVID-19 women, compared to non-pregnant.

Patient and methods

In a retrospective study conducted at the University Hospital Obstetrics Department, a total of 100 confirmed positive COVID-19 women, depending on a positive result for SARC-COVID-19 (nasopharyngeal swabs and real - time polymerase reaction test (PCR)), aged 20-40 years were enrolled between January and December 2021. Ethical approval was taken from the Medical Ethical Committee Department. In addition, the written consent form was taken owing to the study's retrospective nature. The study population was divided on whether the patients were pregnant; group 1 (50 pregnant women at 37-41 weeks gestational age) and group 2 (50 non-pregnant women), which age and body mass index (BMI) matched; for all recruited women we obtained the epidemiological features (age, gestational age and delivery mode for the pregnant group a), the gestational age of the pregnant women assessed by the last menstrual period and the early second-trimester ultrasound for confirmation, the clinical features (headache, fever, cough, dyspnea, difficult breathing, loss of smell and taste sensation).

at the time of enrollment in this study, 5 milliliters of blood sampling has been taken from each participant of both groups and sent to the laboratory to measure the following using Automated hematology analyzers; hemoglobin (Hb), White blood cell (WBC), neutrophil (NEU), lymphocyte (LYM), platelets counts, C-reactive (CRP), D-dimer, liver function test (LFT); Alanine transaminase U/L (ALT), Aspartate aminotransferase U/L (AST), Renal function test (Blood urea nitrogen mmol/L, and Creatinine μmol/L), and we assess the

lymphocyte to C-reactive protein ratio (LCR).
Exclusion criteria:
1. Patients had negative COVID-19 results repeated twice in two different laboratories.
2. Women with a history of hematological disease.
3. patients with medical co-morbidities, preeclampsia, diabetes, and those on steroids were excluded, and the flow chart of Figure 1 illustrated the protocol of patient collection.

In the present study, the management strategy followed the protocols announced by the National Health Commission of the People's Republic of China.

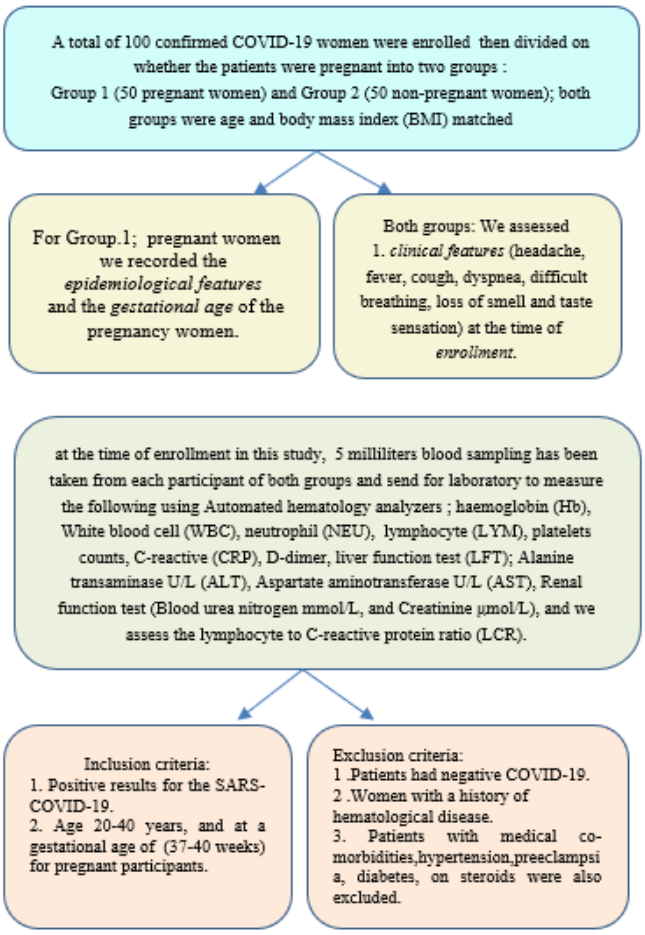

Figure 1 Flow chart of patient collection strategy in the study.

Statistics

The data normality was checked by the Shapiro-Wilkinson test. Continuous data were expressed as means and standard deviations. We compared the study versus the control group, basic demographic criteria by the Unpaired T-test. Correlation strength was assessed by the regression equation between SAA versus CRP. The ROC curve calculated the SAA cutoff value associated with the best sensitivity and specificity. Finally, we compared both ROC curves for both markers through AUC, SE a, and 95% CI b. The level of significance was set at P <0.05 for all tests.

Results

A total of 100 confirmed COVID-19 women, grouped into Gr.1(N=50)pregnant and Gr. 2(N=50) Nonpregnant; we conducted a retrospective study comparing the demographical, epidemiological, and inflammatory markers. The mean age of the study participant presented as means and SD was (31.1 ± 1 vs. 30.10 ± 1 years), P-value was 0.898 for Gr1, and Gr2, respectively. The BMI The gestational age for pregnant women was (38.70 ± 0.16 weeks). As for the delivery mode, 17(56.7%) were delivered by Caesarean section (CS), and 13(43.3%) were Vaginally delivered. We tested for asymptomatic cases in pregnant versus non-pregnant and compared their statistical differences in Table(1). Table (2) demonstrates the demographical, and hematological characteristics of the recruited cases; HB, platelets, and LCR levels were significantly lower among Gr1 compared to group 2. While the WBC, NEU, LYM, CRP, Alanine transaminase counts, creatinine, and D-dimer were significantly higher in Gr 1. The D-dimer relation to the mode of delivery was not studied. The two groups scored no meaningful differences in the aspartate aminotransferase and blood urea. Figure (2) shows the ROC Curve for LCR; the ratio scored significantly low levels among pregnant women vs. non pregants , at a cutoff value of 232.8, sensitivity and specificity were (53.3, 90) respectively. The AUC was 0.69, P-value < 0.005. Another ROC tested the correlation between the LCR ratio and symptomatic versus non-symptomatic women irrespective of pregnancy there were an insignificant association. AUC =0.50, P= 0.97. Implying that the ratio is not useful in discriminating asymptomatic carriers.

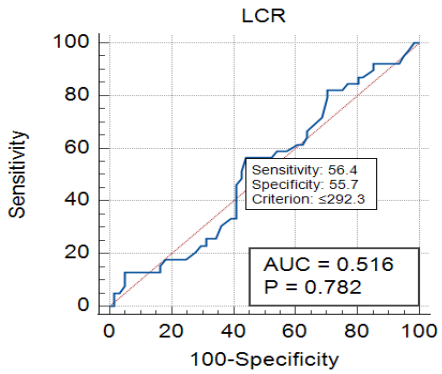

Fig. 2 shows the ROC Curve for LCR; the ratio scored significantly low levels among pregnant women vs. non pregants , at a cutoff value of 232.8, sensitivity and specificity were (53.3, 90) respectively

Discussion

This study showed that among confirmed COVID-19-infected women, ACC was significantly lower in pregnant women than in non-pregnant, and they were delivered by CS in 2/3 of the cases. In addition, the hematological indices showed a meaningfully low LCR in pregnant women.

Recent studies indicated that asymptomatic COVID-19 patients might have a similar transmission potential to ACC [17]. In addition, pregnant women are regarded as a high-risk group since they can get more severe forms of illness once they are infected. Thus multiple studies have evaluated Asymptomatic carriers [3-5].

Prabhu et al (2020) tested 675 pregnant women admitted to the labor ward; 78.7% of seropositive cases were asymptomatic. The authors described a higher rate of CS among symptomatic versus ACC (47.71 vs. 45.56), P=0.04, respectively. Moreover, the study confirmed that maternal problems are more frequent in the postnatal period [18]. Jenab *et al* (2020). examined the pregnancy outcome in 90 seropositive COVID-19 cases, divided into two groups, symptomatic and ACC. The study confirms a four-fold rise of CS among symptomatic cases; OR = 4.12, 95% CI (1.7- 10.05), P=0 .002. Furthermore, the odds ratio for delivering low birth weight infants was meaningfully higher in symptomatic women; OR = 2.1, 95% CI (1.2-6.29), P =0 .035 [19]. Sutton *et al* (2020). reported the benefit of universal testing; they confirmed that 13.7% of 211 seropositive cases were ACC upon admission to the delivery suites [20].

Traditionally, oropharynx swaps were the gold standard; nevertheless, Yokota *et al* (2020) recommended self-collected salivary secretion as a reliable universal screening for ACC; it showed the highest sensitivity and specificity (86% and 99%), respectively [21]. Similarly, Shivakumar BG *et al* (2021) used saliva to screen for ACC in1475 pregnant women Again, the author advised saliva testing to give pregnant women a sense of assurance. Saliva screening showed 0.014% of ACC with no false +ve or -ve test [22]. In line with Shivakumar BG et al (2022) results, Tanacan et al (2020) scored a low incidence(1.4 %) of ACC among 206 pregnant Turkish women; they screened based on demographic and medical co-morbidities. All asymptomatic carriers were high-risk pregnancies. The authors introduced an interesting concept: caution should be made in managing high-risk pregnancies since they communicate with health workers and other patients more frequently. Thus they are capable of spreading infection [23]. Lagunas - Rangel et al (2020); study

concentrated that the LCR was found to be a valuable and promising prediction biomarker for tumor recurrence, prognosis, and inflammatory disorders. It was studied as a severity biomarker in COVID-19 infections. The virus's respiratory insult causes widespread and fast inflammation. Thus, low LCR levels indicate accelerated inflammation. response and a worse clinical prognosis [24].

Moreover, the ratios can be used to distinguish severe from mild-moderate cases as well as their value can be examined among other inflammatory markers in predicting hospital mortality rates by COVID-19. They interpret LCR, platelet-to-lymphocyte ratio, neutrophil-to-lymphocyte ratio, and the systemic immune inflammation index [25-27]. COVID-19 is considered a multisystemic infection, including immunological and hematological systems; therefore, several changes could be observed in the blood tests and abnormal kidney and liver function test results. These changes happened due to hypoxia, hypoperfusion, and thrombosis caused by adult respiratory distress syndrome, shock, and disseminated intravascular coagulation, respectively [25,26]. Many agree that the viral load determines the duration and severity of COVID-19 infection in those affected. The greater the load, the greater the inflammatory reaction in the host. Many inflammatory indicators were evaluated; in the current study, LCR was found to be substantially lower in pregnant versus non-pregnant women, which is consistent with previous research linking LCR to a more severe disease course that pregnant women are known to experience once they are infected [27,28]. Still, the LCR ratio failed to discriminate asymptomatic from symptomatic cases irrespective of pregnancy, as ROC was statistically insignificant. Since asymptomatic seropositive women can be hazardous to hospital staff and other patients, thus universal testing by PCR can not be overestimated.

early reports about covid and other respiratory infections propose that pregnant women may get serious clinical symptoms which need information about the pregnancy status together with the fetal and maternal outcome, standard interventions required to control severe respiratory infection for pregnant women and this must be should be implemented vigorously in a base medical team [28].

The main study limitations are a retrospective design with small-sized and lacking analysis power. Study strength, no earlier study discussed the value of LCR in pregnant women nor evaluated its utility in distinguishing asymptomatic versus symptomatic cases.

Thus, even though LCR did not outstand PCR in detecting ACC, this study reinforces the current recommendation of universal PCR testing, especially on admission to labor wards, to all patients.

Conclusion

This study demonstrated that the incidence of ACC was lower among pregnant to non-pregnant. Thus, the LCR was an unreliable marker for predicting seropositive COVID-19 women.; however, it scored significantly low in pregnant, which underlies LCR relation to the severity of inflammation. Further studies are warranted to explore the implications of this ratio to the infection severity and prognosis in the fetomaternal outcome.

Abbreviations and Acronyms

Asymptomatic COVID -19 cases (ACC)
lymphocyte to C-reactive protein ratio (LCR)
C-reactive (CRP)
Alanine transaminase (ALT)
Aspartate aminotransferase (AST)

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Table 1: The statistical comparison between pregnant women versus non-pregnant women with regard to their clinical manifestation.

Parameter	Normal rang	Pregnant women with COVID-19 N=50	Non-pregnant women with COVID-19 N=50	P-value
Age	-	31.1 ± 1	30.10 ± 1	0.671
BMI	16-25	26.5± 3	26.1± 2	0.452
HB	9.5 -15 g/dL	12.47 ± 1.92050	13.97± 1.08252	0.0001*
WBC	5.6 - 16.9 10^9/L	13.48± 4.96	3.80± 1.03353	0.0001*
NEU Count	3.9 - 13.1 X 10^9/L	17.98± 3.42	3.48±0.62	0.0001*
LYM Count	1- 3.6 X 10^9/L	1.99±0.57	1.50± 0.41	0.0001*
PLATLET Count	150- 450 X 10^2 /mcL.	206.02 ± 43.63	351.20± 64.37	0.0001*
LCR (lymphocyte to CRP ratio)		297.97± 152.75	347.33± 109.45	0.067
CRP	<5-8 mg/dL	7.36 ± 2.55	4.56± 1.24	0.0001*
Alanine transaminase	7-35 u/l	9.41±1.72	2.36±. 075	0.0001*
Aspartate Aminotransferase	10-34 u/l	16.51±2.88	16.38±3.37	0.836
Blood urea nitrogen	2.5-7 mmol/l	2.70 ± 0.48	2.78± 0.64	0.472
Creatinine, µmol/L	0.7-1.3 mg/dL	1.84± 0.68	0.53± 0.07	0.0001*
D-dimer	<0.50	2.91± 1.05	0.93± 0.39	0.0001*

Table 2: The variables of laboratory tests for the two groups (A group of pregnant women with COVID-19, A group of non-pregnant women with COVID-19).

Variable	Pregnant (N=50)	Non-Pregnant(N=50)	P- value
Symptomatic	(26/50) 52 %	(13/50) 26%	0.01
Non-Symptomatic	(24/50) 46 %	(37/50) 74%	