

Neutrophil/lymphocyte ratio and Lymphopenia as a severity marker rather than diagnostic marker of Covid-19 in pregnant population, A retrospective case series.

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Abstract

Objective: Recommending using lymphopenia and neutrophil/lymphocyte ratio(NLR) as a severity marker rather than diagnostic marker for pregnant patients with COVID-19. **Design:** retrospective study. **Setting :**Birmingham city hospital, Birmingham, United Kingdom maternity unit admissions to delivery suite between 10 March 2020 and 31 May 2020. **Population:** We reviewed all patients who tested positive for COVID-19 and were pregnant. **Methods:** We looked at the white blood cell counts of all the patients and their outcomes. We specifically looked at lymphocyte count as well as neutrophil count and calculated the neutrophil lymphocyte ratio(NLR) for every case in our series. **Main Outcome Measures:** Only 15.3% of pregnant patients who tested positive for COVID-19 had lymphopenia and raised NLR in contrast with up to 90% in non-pregnant population. **Results:** Our results indicate that out of 13 patients who tested positive, for COVID-19, only 2 915.3% had lymphopenia and raised NLR more than 8. **Conclusions:** There are very conflicting results for normal values of white blood cells and lymphocytes in pregnancy. In our study Lymphopenia and raised NLR do not seem to be common findings in confirmed pregnant cases of COVID-19 but can help determine morbidity as patients that had lymphopenia and raised NLR displayed severe symptoms, were more unwell and needed high dependency unit admission.

Introduction:

Coronaviruses can infect humans and animals. A novel Coronavirus was identified in 2019, causing pneumonia in patients within China initially then spread globally, resulting in an epidemic. The virus that causes COVID-19 has been named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). (1), (3)

Full-genome analysis indicated that the coronavirus that causes COVID-19 is a beta coronavirus that resembles SARS Virus (severe acute respiratory syndrome virus). Similarly, the structure of the receptor-binding gene region is very similar to that of the SARS virus, and the virus has been shown to use the same receptor, the angiotensin-converting enzyme 2 (ACE2), for cell entry (2)

The cases of COVID-19 vary from asymptomatic or pauci symptomatic forms to clinical conditions characterized by respiratory failure , to multi-organ and systemic manifestations as well as sepsis, septic shock, and multiple organ dysfunction syndromes (MODS). (19)

One of the common laboratory findings among patients infected with COVID-19 is lymphopenia (5). We wanted to look at the presence of leucopenia in patients who tested positive for COVID -19 and delivered in our unit at Sandwell and West Birmingham hospital as many reports have been using it as a diagnostic marker but in our experience it seemed to be uncommon for CCOVID positive cases to have lymphopenia so we examined our results which confirmed our observations are true.

Material and Methods: We reviewed all patients who tested positive for COVID-19 and were pregnant in our unit between 10 March 2020 and 31 May 2020. We looked at the white blood cell counts of all the

patients and their outcomes. We specifically looked at lymphocyte count as well as neutrophil count and calculated the neutrophil lymphocyte ratio for every case in our series.

Results:

As per table 1 , out of 13 patients who tested positive, for COVID 19, only 2 (15.3%) had lymphopenia and raised NLR more than 8. Thus it is imperative not to use lymphopenia as a diagnostic marker but our case series shows that lymphopenia and NLR ratio was highly correlated to severity of cases. The 2 cases that had NLR of 8 and 12 and associated lymphopenia less than 1 were associated with increased morbidity and admission to high dependency unit.

Discussion:

Due to the semi-allograft nature of the fetus in utero, the immune response requires both stimulatory and suppressive functions for a successful pregnancy outcome. Lymphocytes are a contributor in the maternal immunological response to pregnancy. The normal lymphocyte count changes in pregnancy, and there is no consensus in the literature about how it changes. Some older papers suggest that there was no change overall in lymphocyte count during pregnancy (13,14). Results from more recent studies suggest that there is a decrease in lymphocyte count (15,16), with the biggest decrease occurring in the first and second trimesters (5). The bulk of available literature agrees with the findings of a reduction in overall lymphocyte count; however, a recent study in 2013 found a significant increase in the lymphocyte count of 200 pregnant women (17,18), further complicating the discussion.

Some papers suggested lymphopenia is associated with worse outcomes in COVID patients. (4) Another study observed that, progressive decline in the lymphocyte count and rise in the D-dimer over time were observed in non survivors compared with higher levels in survivors after COVID-19 infections (5). The same authors observed that common laboratory findings among hospitalized patients with COVID-19 include lymphopenia, elevated aminotransaminase levels, elevated lactate dehydrogenase levels, and elevated inflammatory markers (e.g., ferritin, C-reactive protein, and erythrocyte sedimentation rate) (5)

In a series of 393 adult patients hospitalized with COVID-19 in New York , 90 % had a lymphocyte count <1500/microL; leukocytosis (>10,000/microL) and leukopenia (<4000/microL) in 15% of cases(6)

Another study showed that high D-dimer levels and marked lymphopenia, are associated with higher mortality rate. (7) A retrospective analysis of eight pregnant cases of SARS-CoV-2 showed that 50% were asymptomatic before delivery but became symptomatic post-partum. This was associated with ,raised white blood cell counts , and reduced lymphocyte counts. C-reactive protein levels increased (8).

In another contradicting cohort study of 55 patients who gave birth with suspected COVID -19 disease of which 13 later turned out positive to COVID-19, there was no difference in the WBC, the ratio of the neutrophils and lymphocytes, CRP between both suspected and confirmed cases groups.(9)

Another study observed that in COVID-19 positive cases there was abnormalities on chest imaging, lymphopenia, leukopenia, and thrombocytopenia. (10)

A meta-analysis of 33 studies reporting 385 pregnant women with COVID-19 infection: noted 0.8% critical, 3.6% severe infection, 95.6% with mild symptoms. There were 6 women admitted to intensive care and one maternal mortality. Laboratory findings included elevated D-dimer in (22.3%), elevated C-reactive protein in (18.7%), lymphopenia in (14.0%), and thrombocytopenia in (1.0%) women. (11)

In another meta-analysis, lymphopenia was found in 79.8% (40/48) of cases. Also, it was reported that radiological features suggestive for pneumonia could be found in almost all of the hospitalized pregnant women, usually presenting with fever, cough and lymphopenia similar to the non-pregnant population. (12)

A recent meta-analysis with 828 patients, where 407 patients had severe disease (49.15%) concluded that the NLR values were found to increase significantly in patients with COVID-19 with severe disease (SMD =

2.404, 95% CI = 0.98-3.82) Increased NLR levels reflect an enhanced inflammatory process and may suggest a poor prognosis. (20).

Coronavirus mainly act on lymphocytes, especially T lymphocytes. Surveillance of NLR and lymphocyte subsets helps in screening for critical cases of COVID-19. A trial with 452 patients with COVID-19 , 286 were diagnosed with severe infection. Severe cases tend to have lower lymphocyte counts, and neutrophil-lymphocyte ratio (NLR). The number of T cells was significantly reduced in severe cases. Both helper and suppressor T cells in patients with COVID-19 were below normal levels, with lower levels of Th cells in the severe group. Patients with COVID-19 also have lower levels of regulatory T cells, which are more reduced in severe cases. (21)

Neutrophil to lymphocyte ratio (NLR), have been recognized as systemic inflammatory response (SIR) marker for many years. (22). Research revealed that NLR offer effective indication of severity of diseases as pre-eclampsia. NLR, with a cutoff value of 5.6, predicted severe pre-eclampsia with sensitivity 93.3% and specificity 86.6% . (23)

Another meta-analysis with 1371 patients showed significantly higher NLR in non-survivors than in survivors. They also looked at 10,685 patients evaluating the value of NLR for sepsis prognosis; results showed that higher NLR was associated with poor prognosis in patients with sepsis . (24)

Another study looked at NLR as a predictor of mortality and treatment response in sepsis patients in the intensive care unit (ICU). They looked at NLR on the 1st, 3rd, and last day in the ICU. If the NLR was ≥ 15 on the 3rd day, the mortality odds ratio was 6.96 (25)

Conclusion:

There are very conflicting results for normal values of white blood cells and lymphocytes in pregnancy. In our study Lymphopenia and raised NLR do not seem to be common findings in confirmed pregnant cases of COVID-19 but can help determine morbidity as patients that had lymphopenia and raised NLR displayed severe symptoms, were more unwell and needed high dependency unit admission. The limitation of our study is its small number but we recommend lymphopenia and raised NLR as an important parameter for escalation of care.

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Contribution to authorship: H.Elhossamy came up with the idea, planned roles, helped in data collection, data analysis, discussion and conclusion. N.Korrapati helped in data collection, analysis and contributed to discussion. F.Cole helped in data collection, analysis and contributed to discussion. M.Srinivasan oversaw the whole project supervision, helped in discussion and abstract writing.

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Table 1:

case	Lymphocyte count/microL	Neutrophil count/microL	NLR
1	1.26	4.04	3
2	0.88	7.25	8
3	1.65	9.66	6
4	1.87	13.15	7
5	2.1	4.16	2
6	1.63	8.27	5
7	3.08	14.74	5
8	2.12	6.58	3
9	1.13	7.66	7
10	0.6	7.3	12
11	4.56	1.21	4
12	2.24	11.22	5
13	1.4	6.13	4