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ORIGINAL ARTICLE

Peripheral Blood Smear Findings and Clinical Significance in Pregnant Women with COVID-19

COVID-19'lu Gebe Kadıinlarda Periferik Yayma Bulguları ve Klinik Önemi

[1]Defne Ay Tuncel, [2]Raziye Narin, [3]Türkan Muhlis, [4]Ayşe Yiğit Sönmez

[1] University of Health Sciences, Adana Faculty of Medicine, Department of Pediatric Hematology Oncology, Adana, Türkiye
[2] University of Health Sciences, Adana Faculty of Medicine, Department of Obstetric and Gynecology, Adana, Türkiye
[2] Adana State Hospital, Department of Obstetric and Gynecology, Adana, Türkiye
[3] Adana Yüreğir State Hospital, Gynecology and Obstetrics Clinic, Adana, Türkiye

Correspondence

Defne Ay Tuncel
University of Health Sciences, Adana Faculty of Medicine, Department of Pediatric Hematology Oncology, Adana, Türkiye

E-Mail: defneaytuncel@hotmail.com

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ABSTRACT

Aim: Peripheral blood smear analysis is a cornerstone diagnostic tool in hematology. For pregnant women with coronavirus disease 2019 (COVID-19), this diagnostic technique assumes heightened significance. Our study aims to elucidate the peripheral smear findings in pregnant women with COVID-19.
Method: Our study participants comprise 50 pregnant women diagnosed with COVID-19 and 50 controls. Clinical findings, medications, peripheral blood smear, and complete blood count parameters are some of the variables examined here. The chi-square tests were employed to compare categorical measurements. Samples t-test was used for numerical measurements. The groups were compared in terms of complete blood count parameters. Significant differences were identified between the groups.
Results: The values of ferritin, C-reactive protein, procalcitonin, D-dimer, activated partial thromboplastin time (aPTT), and fibrinogen exhibited significant differences among the groups. The lymphocyte ratio in the COVID-19 group is lower, compared to the control group. The proportions of band cells, lymphocytes, monocytes, neutrophils, vacuolated monocytes, and hypersegmented neutrophils exhibit statistically significant differences between the groups. Peripheral blood abnormalities are prevalent in microbial infections, particularly in viral infections.
Conclusions: These abnormalities can provide insights into the underlying pathophysiological changes. In patients with COVID-19, no abnormalities have been observed in platelets and erythrocytes. However, compared to the controls, atypical monocytes and neutrophil hypersegmentation are significantly elevated in COVID-19 patients.

Keywords: Complete blood count, COVID-19, lymphocyte ratio, peripheral blood smear, pregnant women

ÖZ

Amaç: Periferik kan yayma analizi hematolojide temel bir tanı aracıdır. COVID-19'lu gebe kadınlarda, bu tanı tekniği daha da önem kazanmaktadır. Çalışmamız COVID-19'lu gebe kadınlarda periferik yayma bulgularını açıklamayı amaçlamaktadır.
Materyal ve Yöntemler: Çalışmamızın katılımcıları COVID-19 tanısı almış 50 gebe kadın ve 50 kontrolden oluşmaktadır. Klinik bulgular, ilaçlar, periferik kan yayması ve tam kan sayımı parametreleri incelenen değişkenlerden bazılarıdır. Kategorik ölçümleri karşılaştırmak için Ki-Kare testleri kullanıldı. Sayısal ölçümler için Örnek T-Testi kullanıldı. Gruplar tam kan sayımı parametreleri açısından karşılaştırıldı. Gruplar arasında anlamlı farklılıklar belirlendi.
Bulgular: Ferritin, CRP, prokalsitonin, D-dimer, aPTT ve fibrinojen değerleri gruplar arasında anlamlı farklılıklar gösterdi. COVID-19 grubunda lenfosit oranı kontrol grubuna göre daha düşüktür. Bant hücreleri, lenfositler, monositler, nötrofiller, vakuollü monositler ve hipersegmente nötrofillerin oranları gruplar arasında istatistiksel olarak anlamlı farklılıklar göstermektedir. Periferik kan anormallikleri mikrobiyal enfeksiyonlarda, özellikle viral enfeksiyonlarda yaygındır.
Sonuçlar: Bu anormallikler altta yatan patofizyolojik değişikliklere dair içgörüler sağlayabilir. COVID-19 hastalarında trombositlerde ve eritrositlerde anormallik gözlenmemiştir. Ancak kontrollerle karşılaştırıldığında atipik monositler ve nötrofil hipersegmentasyonu COVID-19 hastalarında önemli ölçüde yüksektir.

Anahtar Kelimeler: COVID-19, gebe kadınlar. lenfosit oranı, periferik kan yayması, tam kan sayımı

Introduction

Peripheral blood smear analysis is a cornerstone diagnostic tool in hematology, providing critical insights into the morphology and composition of blood cells (1). In the context of pregnant women with coronavirus disease 2019 (COVID-19), this diagnostic technique assumes heightened significance, given the unique hematologic changes during pregnancy and the additional impact of the viral infection on maternal and fetal health (2).

Pregnancy induces physiological alterations in the hematologic system, including increased plasma volume, dilutional anemia, and leukocytosis, complicating the interpretation of blood smears (3). The advent of COVID-19 introduces further complexities. SARS-CoV-2 infection has been associated with hematologic abnormalities, including lymphopenia, neutrophilia, thrombocytopenia, and atypical lymphocytes (4). These aberrations reflect the body's

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Complaints: geneltip@selcuk.edu.tr

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immune response to the virus and are pivotal in prognostication and therapeutic decision-making (4).

In pregnant women with COVID-19, a peripheral blood smear can reveal crucial data informing both maternal and fetal prognosis (5). For instance, severe lymphopenia might indicate a more aggressive disease course (6), necessitating closer monitoring and potentially more intensive therapeutic interventions. Moreover, detecting thrombocytopenia, especially in conjunction with elevated D-dimer levels (7), may suggest a predisposition to thromboembolic events, a recognized complication of COVID-19. This is particularly concerning in pregnancy, where hypercoagulability is already a physiological state, thus amplifying the risk of adverse outcomes such as venous thromboembolism (8).

Furthermore, the presence of fragmented red blood cells or schistocytes (9) on a blood smear could be indicative of microangiopathic hemolytic processes, which, in the setting of COVID-19, may suggest severe complications like disseminated intravascular coagulation or preeclampsia superimposed by viral infection (10). The differentiation of these conditions is crucial, as they have distinct management protocols and implications for maternal and fetal health (8-10).

The clinical significance of peripheral blood smear findings extends beyond immediate therapeutic implications (1). They can also provide prognostic information, guiding the need for intensive care and informing decisions regarding the timing and mode of delivery to optimize maternal and neonatal outcomes (11). In addition, serial blood smear examinations can help monitor the progression of the disease and the effectiveness of interventions, thereby enabling a dynamic and responsive approach to management (11).

In summary, peripheral blood smear analysis in pregnant women with COVID-19 is an invaluable diagnostic modality, offering profound insights into hematologic changes with significant clinical and prognostic implications. Its role in the comprehensive management of these patients underscores the importance of meticulous hematologic evaluation in the context of this complex interplay between pregnancy and viral infection. As the pandemic evolves, continued research into the hematologic manifestations of COVID-19 in pregnancy will be essential to refine diagnostic criteria and therapeutic strategies, ultimately enhancing maternal and fetal health outcomes. Our study aims to elucidate the peripheral smear findings in pregnant women with COVID-19 infection and determine their clinical significance.

Materials And Methods

Study Population

Our study's participants comprised 50 pregnant women diagnosed with COVID-19 presenting to a tertiary healthcare center in Adana, Türkiye, and 50 healthy pregnant women consenting to participate. The control group consists of healthy pregnant participants.

Power Analysis

A power analysis was employed to determine the sample size. The effect size was set at d=0.75, the power (1-β) at 0.90, and the allocation ratio at 1. Consequently, the minimum required sample size was 40 individuals per group.

Study Design and Participants

This is a prospective, controlled study. It included 100 participants diagnosed with COVID-19 between November 2021 and January 2022 at a tertiary facility in Adana in Türkiye. The researchers collected and analyzed the data about all participants.

Exclusion Criteria

Participants refusing to participate in the study,

Individuals outside the 18-45 age range.

Those using acetylsalicylic acid (ASA).

Groups

Group 1: Pregnant women diagnosed with COVID-19.

Group 2: Control group.

Examined Variables

Age, height, weight

Obstetric history (gravidity, parity, abortions, number of living children)

Previous surgeries

Comorbidities

Clinical findings (cough, dyspnea, fever, oxygen saturation)

Medications used

Gestational age

Week of delivery

Mode of delivery

APGAR score of newborns

Neonatal or maternal intensive care requirement

Duration of hospital stay

Peripheral blood smear

Complete blood count parameters

Ethics

Approval was obtained from the local ethics committee (Date and number: 11/11/2021-1623). Participation in the study was voluntary. Informed consent was obtained, stating that the participants' identities would remain confidential. The principles of the Declaration of Helsinki were adhered to throughout all stages of the research.

Statistical Analysis

In descriptive statistics, categorical measurements are presented as counts and percentages, while numerical measurements are expressed as means and standard deviations (and medians where necessary). The Chi-Square tests were employed to compare categorical measurements between groups. The Shapiro-Wilk test was utilized to analyze the normality of the distribution of numerical measurements. If the data conformed to a normal distribution, the Independent Samples T-Test was used for numerical measurements; otherwise, the Mann-Whitney U test was applied. The Statistical Package for Social Sciences for the Windows, version 20.0 software was employed for the statistical analysis of the data (SPSS, IBM Corp., Armonk, NY, USA). A statistical significance level of 0.05 was considered for all tests.

Results

The groups were compared in terms of age, pregnancy week, cough, dyspnea, fever, and oxygen saturation. Significant differences were identified between the groups concerning the data on pregnancy week, cough, dyspnea, and fever. The other variables were similar in both groups. In the control group, none of the participants exhibited cough, dyspnea, or fever symptoms.

The groups were compared in terms of complete blood count parameters. Significant differences were identified between the groups. The values of ferritin, C-reactive protein (CRP), procalcitonin, D-dimer, activated partial thromboplastin time (aPTT), and fibrinogen exhibited significant differences among the groups. These differences were statistically significant. The other parameters, however, were at similar levels across the groups. The CRP, procalcitonin, D-dimer, aPTT, and fibrinogen values were elevated in the COVID-19 group compared to the control group. Conversely, the ferritin level is lower (Tables 1 and 2) (Figure 1).

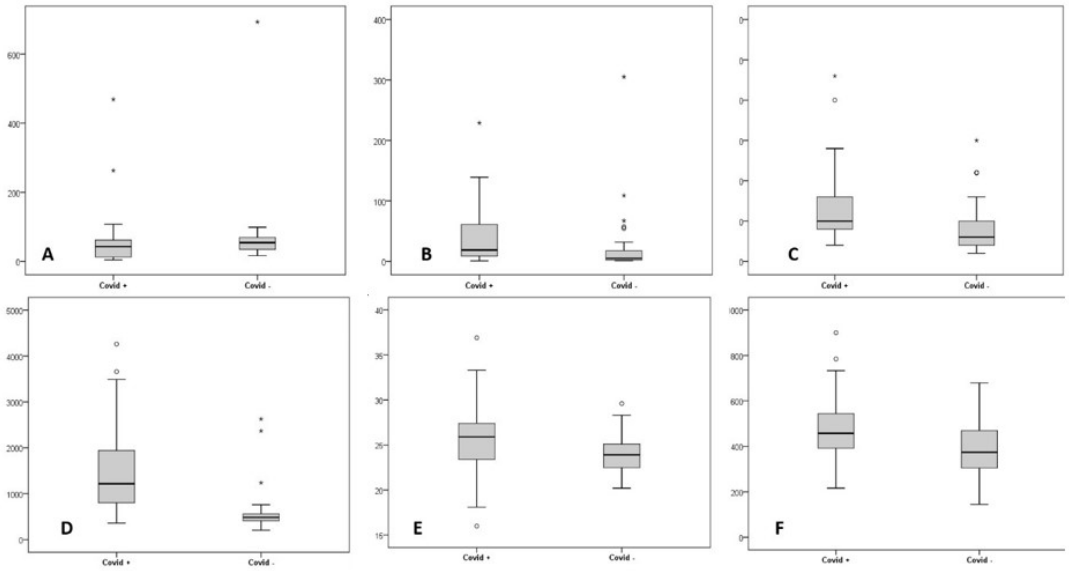

Figure 1. The values of ferritin, CRP, procalcitonin, D-dimer, aPTT, and fibrinogen. A. Ferritin, B. CRP, C. Procalcitonin, D. D-Dimer, E. aPTT, F. Fibrinogen

Table 1. Comparison of gestational weeks, cough, dyspnea, and fever between groups

Groups (Mean±SD)	COVID-19 Patients	Controls	p
Gestational Weeks	30.4±6.9	36.7±4	<0.001
Cough			<0.001
Yes	39 (78%)	0 (0%)	
No	11 (22%)	50 (100%)	
Dyspnea			<0.001
Yes	19 (38%)	0 (0%)	
No	31 (62%)	50 (100%)	
Fever			0.006
Yes	8 (16%)	0 (0%)	
No	42 (84%)	50 (100%)	
O_2 saturation	96.96±2.46	96.96±0.97	1

Table 2. Comparison of complete blood count between groups

	Groups		p
	COVID-19 Patients	Controls	
WBC*	8.8±2.9	9.8±4	0.150
RBC*	3.9±0.6	3.9±0.4	0.938
HGB*	10.9±1.4	10.7±1.6	0.502
PLT*	221.8±84.3	213.1±75.1	0.586
Ferritin**	42.6 (49.3)	54.5 (35.9)	0.025
CRP**	18.7 (53.9)	4.8 (15.8)	<0.001
Procalcitonin**	0.05 (0.04)	0.03 (0.03)	<0.001
Troponin*	4±2.4	3.8±2.4	0.739
D-Dimer**	1215 (1152)	483.5 (153)	<0.001
Prothrombin Time *	11.5±0.7	11.7±0.9	0.264
INR*	0.93±0.06	0.95±0.08	0.172
aPTT*	25.6±3.9	24.1±2.2	0.018
Fibrinogen*	483.2±136.9	392.9±108.5	<0.001

*Mean±SD, **Median. WBC: White blood cell, RBC: Red blood cell, HGB: Hemoglobin; PLT: Platelets; CRP: C-Reactive Protein; INR: International normalized ratio, aPTT: Activated partial thromboplastin time.

Peripheral blood smear results in our study indicate that the lymphocyte ratio in the COVID-19 group is lower compared to the control group, while other values are elevated. The proportions of band cells, lymphocytes, monocytes, neutrophils, vacuolated monocytes, and hypersegmented neutrophils exhibit statistically significant differences between the groups. The groups are similar in terms of Platelet Structure and Erythrocyte Structure. Vacuolated monocyte and hypersegmented neutrophil forms were observed exclusively in the COVID-19 group. The control group did not detect these forms (Table 3) (Figure 2).

Table 3. Findings of peripheral blood smear

	Groups		p
	COVID-19 Patients	Controls	
Band Cells (%)	20.5±4.3	5.7±2.1	<0.001
Lymphocytes (%)	12.7±4.5	37.7±6.9	<0.001
Monocytes (%)	7.3±2.6	5.4±2.1	<0.001
Neutrophils (%)	60±5.8	56.3±7.2	0.006
Platelet Structure			
Normal	36 (72%)	38 (76%)	0.245
Large	1 (2%)	4 (8%)	
Small	13 (26%)	8 (16%)	
Erythrocyte Structure			
Normochromic Normocytic	46 (92%)	47 (94%)	0.999
Hypochromic Microcytic	4 (8%)	3 (6%)	
Monocyte Structure			
Vacuolated	32 (64%)	0 (0%)	<0.001
Normal	18 (36%)	50 (100%)	
Neutrophil Structure			
Hypersegmentation	17 (34%)	0 (0%)	<0.001
Normal	33 (66%)	50 (100%)	

Discussion

In our study, the groups were compared based on complaints of cough, shortness of breath, fever, and oxygen saturation measurements. Significant differences were detected between the groups concerning the cough, shortness of breath, and fever data. Cough, shortness of breath, and fever are among the most common complaints of COVID-19. According to the analysis of studies, fever is observed in 81.2%, cough in 58.5%, and dyspnea in 26.1% of COVID-19 patients (12).

None of the participants in the control group exhibited symptoms of cough, shortness of breath, or fever. Oxygen saturation was similar in both groups, with values in the COVID-19 and control groups being relatively close to each other. This finding contradicts the information available in the literature (13-15).

Respiratory involvement is joint in COVID-19 (16). Different levels of low oxygen saturation can be detected, including clinical, subclinical, or asymptomatic presentations (17). The pathophysiological mechanisms of low oxygen saturation are multifactorial. The development of localized inflammatory damage progressing to interstitial lung edema and microvascular thrombosis are among the most critical mechanisms. Low oxygen saturation tends to be accompanied by impaired vasoregulation, dysregulated lung perfusion, and hypercoagulability. It is considered responsible for rapid clinical deterioration and mortality (18).

Some studies have found that the oxygen saturation values of COVID-19 patients correlate with their short-term outcomes and the severity of the disease (14). The situation detected in our study may be related to the severity of the diseases in our participants. The high oxygen saturation is correlated with the severity of the disease. The number of participants experiencing severe infection might be low, which could result in similar oxygen saturation values across the groups.

Significant differences in complete blood count

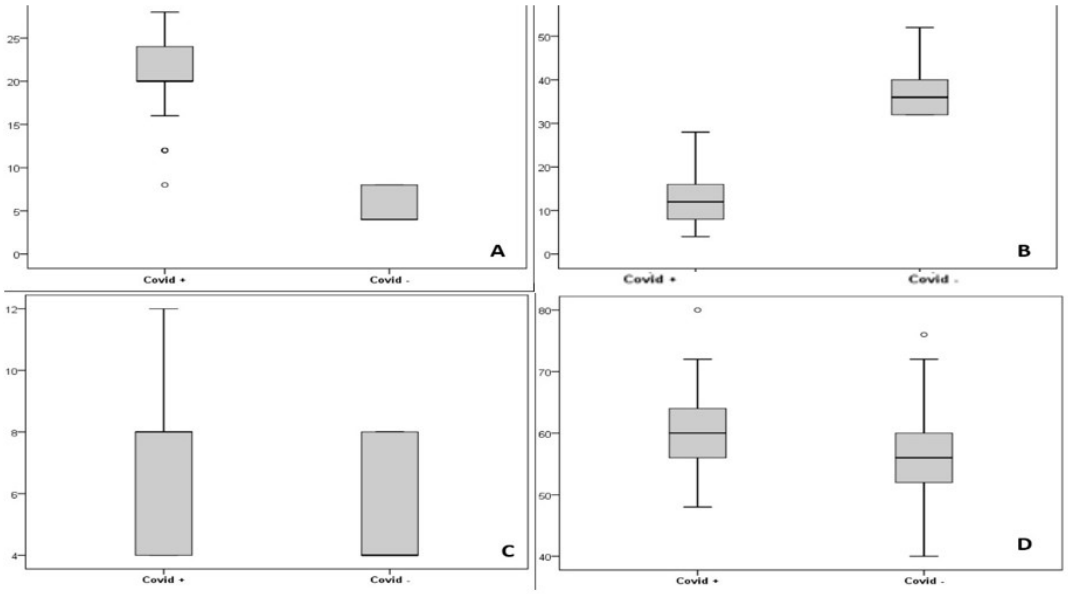

Figure 2. A. Band cells, B. Lymphocytes, C. Monocytes, D. Neutrophils

parameters were identified between the groups. Ferritin, CRP, procalcitonin, D-Dimer, aPTT, and fibrinogen levels demonstrated statistically significant variations among the groups. However, other parameters remained at similar levels across the groups. In the COVID-19 group, CRP, procalcitonin, D-dimer, aPTT, and fibrinogen levels were elevated compared to the control group, while ferritin levels were lower.

Laboratory abnormalities identified in COVID-19 include lymphopenia in approximately 50% of patients, leukopenia, eosinopenia, neutrophilia, and monocytosis (19-21). In the literature, lymphopenia is reported as the most significant hematological finding associated with COVID-19, known to indicate the severity of the disease (22). Various hypotheses have been proposed regarding the mechanism of lymphopenia. These include viral toxicity due to ACE-2 (Angiotensin-converting enzyme) receptor expression, lymphocyte apoptosis, and metabolic products causing lymphocyte inhibition (23).

In one study reporting absolute lymphopenia in 15% of participants, a decrease in absolute T cell count was detected in 90% of participants using flow cytometry analysis, and all participants with decreased T cell counts required mechanical ventilation (24). Disease activity is associated with changes in lymphocyte subpopulations in COVID-19 patients. Flow cytometry is often used as a sensitive method to detect these changes. A similar study reported that no specific complete blood count abnormalities were detected in COVID-19 cases compared with controls (25).

Significant differences were identified among the groups concerning complete blood count parameters.

In one study, ferritin levels were significantly higher in moderate and severe COVID-19 infections compared to mild infections. In the same study, ferritin levels were higher in those with complications, compared to those without. In addition, median ferritin levels were increased in those treated in intensive care units (26). In our study, ferritin levels of COVID-19-positive patients were lower than those of negative patients. This seemingly contradictory situation is due to the analysis of different data in the two studies.

The pathogenesis of COVID-19 is complex (27). The virus's entry into the body triggers the release of various cytokines and chemokines, initiating an adaptive immune response characterized by lymphopenia and neutrophilia (28). The increase in cytokines exacerbates the body's systemic inflammation (29). During this process, inflammatory biomarkers such as Interleukin-6, Lactate dehydrogenase, CRP, D-Dimer, and Ferritin rise; these biomarkers predict disease severity and response to treatment (30-32). Aside from

Ferritin, the data obtained from our study support these findings.

Only a limited number of studies in the literature investigating peripheral smear findings in COVID-19. One study on this subject reported the presence of monolobed neutrophils, neutrophilic granulation, abnormal platelet morphology, and apoptotic cells (33). The results of this study indicated that the abnormalities in neutrophils resolved following antiviral treatment (33).

The results of our study indicate the presence of hypersegmentation in neutrophils in 34% of COVID-19 cases. In this respect, our findings are consistent with the study above. Neutrophil hypersegmentation can be observed in anemic conditions such as vitamin B12 and iron deficiency, chemotherapy toxicity, and uremia (34-36). In our study, no other condition in the COVID-19 group could cause neutrophil hypersegmentation. In a study examining the peripheral smears of COVID-19 cases, hypersegmented neutrophils were detected in 84% (37). The same study reported the presence of giant platelets and atypical lymphocytes in all cases. The frequency of hypersegmented neutrophils in the control group was 25%, and no atypical lymphocytes or giant platelets were observed (37). In contrast to this study, the frequency of neutrophil hypersegmentation identified in our study was lower. Additionally, none of the controls exhibited hypersegmentation.

Peripheral blood abnormalities are prevalent in microbial infections, particularly in viral infections. These abnormalities can provide insights into the underlying pathophysiological changes. In patients with COVID-19, no abnormalities have been observed in platelets and erythrocytes. However, compared to controls, atypical monocytes and neutrophil hypersegmentation are significantly elevated in COVID-19 patients.

Our study has certain limitations. It is essential to evaluate our findings and their applicability critically. Firstly, although the sample size represents the population under investigation, ethnic groups underrepresented or populations with various comorbidities have not been considered. COVID-19 symptoms may manifest differently in these populations, potentially influencing the results. Additionally, our study focused on hospitalized patients, which may lead to inaccuracies when generalizing the findings to individuals with mild or asymptomatic disease courses. Another limitation lies in the rapidly evolving nature of COVID-19. The emergence of new variants and changes in public health interventions may affect the progression of the disease and the efficacy of treatments. Consequently, some of the study's outcomes may become less applicable to future outbreaks.

Data availability statement

The data are available upon reasonable request from the corresponding author.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

None.

Ethics Committee Approval

Ethical approvals were obtained from the ethics committees of the researchers' institutions. Participation in the study was voluntary. Informed consent was obtained, stating that the participants' identities would remain confidential. The principles of the Declaration of Helsinki were adhered to throughout all stages of the research.

Peer-review

Externally peer-reviewed.

Declaration of Interests

The authors have no conflicts of interest to declare.

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