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Is it Possible to Differentiate Community-Acquired Pneumonia from COVID-19 Pneumonia?

Toplum Kökenli Pnömoniyi COVID-19 Pnömonisinden Ayırmak Mümkün Mü?

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Abstract

Objectives: Coronavirus disease-2019 (COVID-19) caused a pandemic, which has been going on for about 1 year. How long the pandemic will continue remains uncertain. Determining the etiology of pneumonia is the most important point for the treatment approach. In this study, it was aimed to determine the parameters that might be useful in the differentiation of community-acquired pneumonia (CAP) from COVID-19 pneumonia.

Materials and Methods: CAP group consisted of 53 people who applied to the infectious diseases polyclinic and chest diseases polyclinic between 01.12.2019 and 30.01.2020 in our country, including the periods when the incidence of CAP increased and influenza peaked, and were hospitalized after being diagnosed with pneumonia. For the COVID-19 pneumonia group, 37 patients with Severe Acute Respiratory Syndrome-Coronavirus-2 detected by polymerase chain reaction from the combined nasal throat swab and with computed tomography showing lesions consistent with COVID-19 were included.

Results: Age, leukocyte count, neutrophil count, monocyte count and C-reactive protein (CRP) were significantly higher in pneumonia patients in the CAP group. In receiver operating characteristic analysis, positive predictive value of age CRP monocyte count formula was 0.83 and negative predictive value was 0.75.

Conclusion: The age difference between the groups was used in different studies on the etiology of pneumonia. It has been thought that the detection of monocytes in the tissues in postmortem studies in COVID-19 pneumonia may be due to consumption. Higher CRP detection in CAP compared to covid pneumonia was found to be similar to the literature. Our study has shown that the formulation containing monocytes, CRP and age factors, which were found to be statistically significantly different, is suitable for use in diagnostic differentiation.

Key Words: Community-Acquired Pneumonia, COVID-19, Monocyte

Öz

Amaç: Koronavirüs hastalığı-2019 (COVID-19), yaklaşık 1 yıldır devam eden bir salgına neden oldu. Salgının ne kadar süreceği belirsizliğini korumaktadır. Pnömoni etiyolojisinin belirlenmesi tedavi yaklaşımı için en önemli noktadır. Bu çalışmada toplum kökenli pnömoninin (TKP) COVID-19 pnömonisinden ayrımında faydalı olabilecek parametrelerin belirlenmesi amaçlanmıştır.

Gereç ve Yöntem: Ülkemizde 01.12.2019-30.01.2020 tarihleri arasında, TKP'nin insidansının arttığı ve influenzanın pik yaptığı dönemlerde enfeksiyon hastalıkları polikliniği ve göğüs hastalıkları polikliniğine başvuran ve pnömoni tanısı aldıktan sonra hastaneye yatırılan 53 kişi TKP grubunu oluşturdu. COVID-19 pnömoni grubuna, kombine nazal boğaz sürüntüsünden polimeraz zincir reaksiyonu ile pozitiflik saptanan ve bilgisayarlı tomografide COVID-19'a uyumlu lezyonları olan 37 hasta dahil edildi.

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Bulgular: TKP grubundaki hastalarda yaş, lökosit sayısı, nötrofil sayısı, monosit sayısı ve C-reaktif protein (CRP) anlamlı olarak daha yüksekti. İşlem Karakteristik Eğrisi analizinde, yaş CRP monosit sayısı formülünün pozitif prediktif değeri 0,83 ve negatif prediktif değeri 0,75 idi.

Sonuç: Gruplar arası yaş farkı, pnömoni etiyolojisine yönelik farklı çalışmalarda kullanılmıştır. COVID-19 pnömonisinde postmortem çalışmalarda dokularda monosit tespit edilmesinin tüketime bağlı olabileceği düşünüldü. TKP'de COVID pnömonisine kıyasla daha yüksek CRP tespiti literatüre benzer bulunmuştur. Çalışmamız, istatistiksel olarak anlamlı derecede farklı olduğu tespit edilen monosit, CRP ve yaş faktörlerini içeren formülasyonun tanısal ayrımda kullanılmasının uygun olduğunu göstermiştir.

Anahtar Kelimeler: Toplum Kökenli Pnömoni, COVID-19, Monosit

Introduction

The factor that started in Wuhan city of China and caused the pandemic was defined as severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) and the pneumonia caused by it was named Coronavirus disease-2019 (COVID-19) (1). There are no specific antivirals for patients and it seems impossible to predict how the pandemic will progress in the future (2,3). Community-acquired pneumonia (CAP) is often caused by *Streptococcus pneumoniae, Staphylococcus aureus, Mycoplasma pneumoniae, Chlamydophila pneumoniae,* rhinovirus, influenza, respiratory syncytial virus, continues to be a persistent global public health problem (4,5). It can be more difficult to determine the empirical treatment to be applied in periods of pandemic, especially when the incidence of CAP is increasing (5). The mortality of COVID-19 pneumonia is up to 14.4 times higher than CAP, and timely delivery of medical treatments for SARS-CoV-2 is required to reduce mortality (6,7). Distinguishing covid-pneumonia patients from CAP subjects will limit unnecessary antibiotic use. A biomarker that differentiates COVID-19 pneumonia from CAP could be important for an early and appropriate empirical treatment algorithm. In our study we evaluated features of two different pneumonia groups in order to discover a readly available and favourable marker that differs etiologies.

Materials and Methods

Patients

Two groups of patients were included in study. First group (CoV) comprising patients >18 years old, diagnosed with COVID-19 pneumonia according to a positive nasal swap sample for SARS-CoV-2 virus in polymerase chain reaction and a thorax computed tomography imaging suitable for COVID-19 pneumonia, and hospitalized from date 15 April 2020 to 30 April 2020. Hospitalization was decided according to guideline provided by Turkish Republic Health Ministry which suggest hospitalization of patients >50 years, having additional comorbidity, with a pulse saturation of ≤94, and one laboratory criteria of poor prognosis. Second group (CAP) including patients >18 years old, diagnosed with CAP according to clinical examination and imaging data, and hospitalized from date 1 December 2019 to 30 January 2020, the time gap in which Influenza used to make a peak in our country and any COVID-19 pneumonia has not been detected yet. Hospitalization was assessed according to CURB-65 criteria which contains a score of five items, one point for each of: Confusion, urea >7 mmol/L, respiratory rate >/=30/min, low systolic (<90 mm Hg) or diastolic (</=60 mm Hg) blood pressure, age >/=65 years (8). Those who scored two points or more were admitted to the hospital. Outpatients were excluded.

All data regarding socio-demographics, admissional laboratory [hemoglobin, platelet, white blood cell (WBC), lymphocyte, neutrophil, monocyte, D-dimer, ferritin, lactatedehydegenesis, C-reactive protein (CRP), alanine amino transferase, aspartate amino transferase, gamma glutamyl transferase, alkaline phosphatase, sodium, potassium, creatine, blood urea nitrogen, troponine], comorbid diseases, admissional physiological values (fever, oxygen saturation, blood pressure, pulse), supplemental oxygen (O_2) requirement, transfering to intensive care unit on follow-up, lenght of stay, and outcome was gathered retrospectively from hospital's electronical records. Our study has been approved by local ethical commission with a registiration number of 2020/150. Patient consent was not obtained for our retrospective study.

Statistical Analysis

All values were represented as mean ± standard deviation, 95% confidence intervals (95% CI), percentages, medians with interquartile ranges as appropriate. Suitable analyzes including Mann-Whitney U/Student's t, paired t and chi-square/exact tests were appropriately used. A sample analysis to detect a group difference regarding monocyte count was calculated with a power of 0.8 and an alpha of 0.05 that showed 36 patients a group was required. A ROC analysis using area under curve (AUC), has been performed by parameters considered to provide clinical meaning, while evaluating a favourable biomarker able to distinguish patients with COVID-19 pneumonia from others, then sensitivity and specificity analysis were appropriately calculated. A p-value of <0.05 was accepted as significant. All analyzes were calculated with SPSS 23 IBM® statistics program provided by Hacettepe University Faculty of Medicine, Ankara, Turkey.

Results

A total of 90 patients were evaluated. Mean age was 52±15 years [Female (F): 21 (57%)] in CoV group while it was 73±15 in [F: 24 (45%)] CAP group (p<0.001 for age, p=0.248 for gender). Comorbidities other than congestive heart failure, chronic lung and neurologic diseases did not differ between groups (Table 1). Cough as an onset symptom was much more common in group CoV than in group CAP (Table 1). When compared to group CoV, laboratory parameters related with WBCs and CRP level were higher in group CAP. Only median pulse saturation and mean heart rate (beat/min), unlike other admissonal physiologic parameters, differed between groups [96 (94-98) vs. 91 (86-96), p<0.001); 92±13 vs 103±21, p=0.006]. No mortality difference was detected between groups.

ROC analysis, with combined parameters in order to achieve a more extended AUC, revealed that an admissional neutrophil x CRP ratio to have an AUC of 0.91 (p<0.001) while a formula gathered age x CRP x monocyte (count) to have a that of 0.92 (p<0.001) (Figure 1) with a sensitivity and specificity of 0.83 (0.70-0.91) and 0.84 (0.67-0.93), respectively. The latter formula had a positive predictive value of 0.88 (0.75-0.95) and a negative predictive value of 0.75 (0.61-0.89) (Table 2). Only age x CRP x monocyte count with a cut-off value of 167.662 and having chronic obstructive lung disease were found to be an independent factor for predicting non-COVID-19 pneumonia while adjusted for age (>65 years), gender, and comorbidities [OR (95% CI): 18.5 (4.6-74.4), p<0.001; OR: 24.1 (2.4-246), p=0.007, respectively] (Data not shown).

Discussion

We have been getting involved in a period in which CAP is increasing while there is not a certain knowledge about how COVID-19 will evolve. In this study, we found that age x CRP x monocyte formula could be a reliable marker to distinguish COVID-19 pneumonia from CAP.

People in CoV group were detected to be younger than CAP group and found as statistically significant in our study which was similar to literature (9). When COVID-19 pandemic had been realized for the first time in our country, a curfew order for people older than 65 years was administered by the goverment. The restriction has to be taken into account, also. Especially old age condition and comorbid diseases, which were also known to be risk factors for CAP, were detected higher in CAP group (10-12). In addition to the fact that old age poses a risk for CAP, the younger age group is more likely to be in crowded environments due to working life and social life and is excluded from restrictions. For these reasons, the age difference made us think of it as a predictor, not a constraint. It is also stated in the literature that old age can be considered as diagnostic for COVID (13). Being elderly is a parameter in the PES score which is used to predict the etiology of pneumonia in the literature, and there are age-related studies in the prediction of etiology (14,15). One of the dynamics in the transmission of SARS-CoV-2 is age, and serological studies in England, Brazil, Japan and Germany estimate that the seroprevalence is highest in adults under 35 years of age (16,17).

Among the presentation symptoms, in our study, cough, fatigue, fever and myalgia were significantly common in

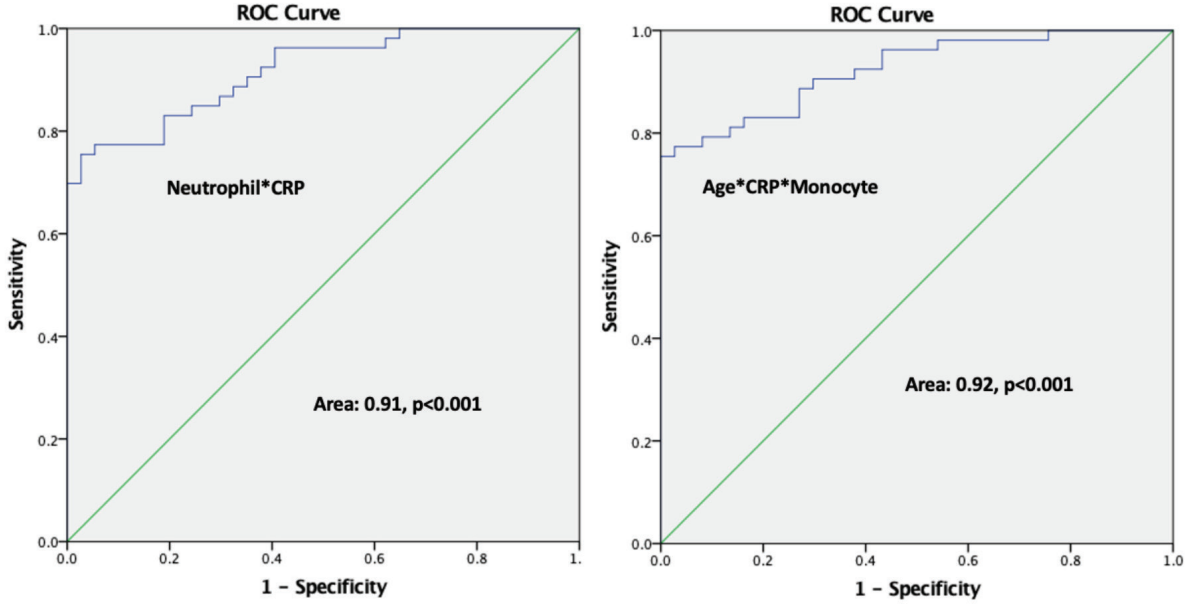

Figure 1: ROC/AUC analyzes of neutrophil x CRP (left) and age x CRP x monocyte (right) parameters, respectively

AUC: Area under curve, CRP: C-reactive protein, ROC: Receiver operating characteristic

Table 1: Comparison between COVID-19 and CAP

	COVID pneumonia (n=37)	CAP pneumonia (n=53)	p
Age* (year)	**52±15**	**73±15**	**<0.001**
Gender (F), n (%)	21 (57)	24 (45)	0.284
Symptom inteval** (day)	**3 (2-5)**	**1 (1-2)**	**<0.001**
Hb 1st day* (g/dL)	12.9±2	12.9±2	0.885
Plt 1st day* (x10³/mm³)	**229±62**	289±128	0.005
WBC 1st day* (x10³/mm³)	**5.4±1.5**	**14.8±7**	**<0.001**
Lmyphocyte 1st day** (x10³/mm³)	1.2 (0.9-1.7)	1.2 (0.8-1.9)	0.980
Neutrophil* (x10³/mm³)	**3.5±1.1**	**11.5±6.3**	**<0.001**
Monocyte* (x10³/mm³)	**0.5±0.2**	**1.5±1.2**	**<0.001**
Lmyphocyte %	**24 (19-30)**	9 (5-14)	<0.001
Neutrophil %	**62 (58-72)**	**78 (71-83)**	**<0.001**
Monocyte %	**9 (7-11)**	**9 (6-12)**	**0.771**
Dimer 1st day** (ng/mL)	430 (330-953)	2.572 (1.239-2.572)	0.065
Ferritine** (ng/mL)	105 (56-409)	-	-
LDH* (U/)	275±111	665±111	0.567
CRP 1st day** (mg/L)	**1.8 (1-6.6)**	**14.7 (8-23)**	**<0.001**
AST** (U/L)	**25 (21-39)**	**19 (15-27)**	**0.003**
ALT** (U/L)	**25 (17-37)**	**14 (10-20)**	**<0.001**
GGT 1st day** (U/L)	30 (18-62)	24 (24-24)	0.678
ALP* (U/L)	74±19	139±21	0.765
Na** (mEq/L)	139 (136-140)	139 (135-141)	0.801
K* (mEq/L)	4.3±0.4	4.3±0.6	0.557
Cre** (mg/dL)	0.8 (0.7-1)	0.9 (0.7-1.3)	0.169
BUN** (mg/dL)	**25 (21-34)**	**39 (29-62)**	**<0.001**
Troponine** (ng/mL)	**2 (1-5)**	16 (7-48)	<0.001
Fever** (°C)	36.6 (36.5-37.1)	36.7 (36.5-36.9)	0.907
Pulse* (beat/min)	**92±13**	**103±21**	**0.006**
SBP 1st day** (mm-Hg)	120 (110-130)	125 (100-130)	0.749
DBP** (mm-Hg)	70 (70-80)	70 (60-80)	0.971
MAP* (mm-Hg)	83±22	73±36	0.107
SpO_2** (%)	**96 (94-98)**	**91 (86-96)**	**<0.001**
LOS** (day)	7 (6-10)	7 (4-10)	0.451
Mortality, n (%)	1 (3)	7 (13)	0.134
HT, n (%)	12 (32)	26 (49)	0.116
DM, n (%)	8 (22)	11 (21)	0.921
CAD, n (%)	7 (19)	11 (21)	0.830
CHF, n (%)	**0 (0)**	**9 (17)**	**0.008**
CRF, (%)	0 (0)	2 (4)	0.510
COPD, n (%)	**1 (3)**	**23 (43)**	**<0.001**
Malignity, n (%)	1 (3)	5 (9)	0.394
Astma, n (%)	**0 (0)**	**5 (9)**	**0.075**
HL, n (%)	0 (0)	2 (4)	0.510
Dementia, n (%)	**1 (3)**	**11 (21)**	**0.013**

Table 1: Continued

	COVID pneumonia (n=37)	CAP pneumonia (n=53)	p
Stroke, n (%)	0 (0)	8 (15)	**0.019**
Cough, n (%)	**25 (68)**	22 (42)	**0.015**
Fever, n (%)	15 (41)	5 (9)	**<0.001**
Fatigue, n (%)	**12 (35)**	**4 (8)**	**0.001**
Dyspnea, n (%)	**6 (16)**	**48 (91)**	**<0.001**
Myalgia, n (%)	**4 (11)**	**0 (0)**	**0.014**
Agousia, anosmia, n (%)	2 (5)	0 (0)	0.087

AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, BUN: Blood urea nitrogen, CAD: Coronary artery disease, CAP: Community acquired pneumonia, CHF: Congestive hearth failure, COPD: Chronic obstructive lung disease, CRP: C-reactive protein, CT: Computed tomography, COVID: Coronavirus, COVID-19: Coronavirus disease-2019, DM: Diabetes mellitus, F: Female, GGT: Gamma glutamyl trasferase, Hb: Hemoglobin, HL: Hyperlipidemia, HT: Hypertension, LDH: Lactate dehydrogenese, LOS: Lenght of stay, MAP: Mean arterial pressure, NS: Not significant, PCR: Polymerase chain reaction, SBP: Systolic blood pressure, WBC: White blood cell, ALP: Alkaline phosphatase, CRP: Chronic renal failure, DBP: Diastolic blood pressure, *mean ± SD **median (IQR), SD: Standard deviation, IQR: Interquartile range, a Student t-test was used for parameters signed by*, a Mann-Whitney U test was used for parameteres signed by**

Table 2: Age CRP monocyte analysis with a cut-off of "167.262" for predicting CAP*

	Estimated value	95% CI
Sensitivity	0.83	0.70-0.91
Specificity	0.84	0.67-0.93
PPV	0.88	0.75-0.95
NPV	0.75	0.61-0.89

NPV: Negative predictive value, PPV: Positive predictive value, CI: Confidence interval, CAP: Community acquired pneumonia
*A given value equal or greater than 167.262 predicts a diagnosis of CAP

COVID pneumonia, while dyspnea was more common in CAP patients. There are significant differences in the comparison of presentation symptoms of COVID and non-COVID pneumonias in the literature, and symptoms other than dry cough do not appear as appropriate data for the prediction of the causative agent of respiratory system infection (18,19). Among the vital signs of the patients at admission, tachycardia and relative hypoxia are more common in the CAP group and may be associated with an excess of comorbid diseases in the same group.

Hitherto, laboratory parameters especially lymphocyte and monocyte count have been investigated already in detail and those revealed findings similar to our study had revealed (19-22). In these studies, the leukocyte and neutrophil counts were relatively lower in COVID pneumonia than in non-COVID pneumonia including other viral pneumonia (18-21). Our study showed monocyte count to be an essential parameter to distinguish patients with COVID-19 and others. Migration and redistrubition of monocytes from blood to both lung and non-respiratory tissue, thus consumption might be the explanation of significantly reduced monocyte count in COVID-19 patients, while compared to patients those are not (18,22-25). It has been shown in most studies that the number of monocytes is decreased in COVID patients, and in addition, the correlation between severe alterations of monocyte subtypes and severe clinical findings shows the importance of monocyte in the pathogenesis of COVID and it should be clarified with ongoing studies (26,27).

CRP is an acute phase reactant that is released dependant on inflammation of the body and is also used in differential diagnosis between viral infections and bacterial infections (25,28). In our study, the CRP value in the CAP group was found to be statistically significantly higher than the CoV group. In the literature, there are studies in which the CRP value in non-COVID diseases including other viral diseases was found to be higher than COVID pneumonia (29).

As a consequence, we are hopeful of the vaccination programs implemented for the pandemic that caused serious losses all over the world for 1 year. The fact that RNA viruses can mutate frequently is the biggest obstacle to the success of vaccinations and the possibility of COVID-19 getting out of our lives. For this reason, studies for the development of early diagnosis methods and the discovery of direct-acting antivirals should continue in the fight against SARS-CoV-2.

Study Limitations

Our study has some limitations. First one is the retrospective nature of the study that might have caused data loss. Second is the possible selection bias due to the prohibition for elderly to be outside by goverment provision in Turkey that might be a protective factor for them which results in lower mean age in CoV group. Third, limited number of patients, eventhough our study is not underpowered, restrained subgroup analysis.

Conclusion

We aimed to establish a suitable marker to distinguish patients with COVID-19 pneumonia from those with CAP and found age CRP monocyte formula to be reliable. Validation of

our result in larger studies will provide an easily accessed and readily available parameter for health workers.

Ethics

Ethics Committee Approval: Our study has been approved by Düzce University Local Ethical Commission with a registiration number of 2020/150.

Informed Consent: Patient consent was not obtained for our retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: A.D.H., C.Ç., Design: A.D.H., S.D., Data Collection or Processing: Ö.A., F.M.S., Analysis or Interpretation: F.M.S., M.Y.P., Literature Search: S.D., Ö.A., Writing: A.D.H., M.Y.P.

Conflict of Interest: No conflict of interest was declared by the authors.

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References

1. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395:1054-1062.
2. He R, Lu Z, Zhang L, et al. The clinical course and its correlated immune status in COVID-19 pneumonia. J Clin Virol. 2020;127:104361.
3. Fontanarosa PB, Bauchner H. COVID-19-Looking Beyond Tomorrow for Health Care and Society. JAMA. 2020;323:1907-1908.
4. Wunderink RG. Community Acquired Pneumonia. Evidence-Based Critical Care. 2019:155-160. https://link.springer.com/chapter/10.1007/978-3-030-26710-0_20
5. Murdoch KM, Mitra B, Lambert S, et al. What is the seasonal distribution of community acquired pneumonia over time? A systematic review. Australas Emerg Nurs J. 2014;17:30-42.
6. Faust JS, Del Rio C. Assessment of Deaths From COVID-19 and From Seasonal Influenza. JAMA Intern Med. 2020;180:1045-1046.
7. Şimşek Yavuz S, Ünal S. Antiviral treatment of COVID-19. Turk J Med Sci. 2020:611-619.
8. Lim WS, van der Eerden MM, Laing R, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. Thorax. 2003;58:377-382.
9. Kuluöztürk M, İn E, Telo S, et al. Efficacy of copeptin in distinguishing COVID-19 pneumonia from community-acquired pneumonia. J Med Virol. 2021;93:3113-3121.
10. Almirall J, Rofes L, Serra-Prat M, et al. Oropharyngeal dysphagia is a risk factor for community-acquired pneumonia in the elderly. Eur Respir J. 2013;41:923-928.
11. Vinogradova Y, Coupland C, Hippisley-Cox J. Risk of pneumonia in patients taking statins: population-based nested case-control study. Br J Gen Pract. 2011;61:e742-e748.
12. Müllerova H, Chigbo C, Hagan GW, et al. The natural history of community-acquired pneumonia in COPD patients: a population database analysis. Respir Med. 2012;106:1124-1133.
13. Liu KC, Xu P, Lv WF, et al. Differential diagnosis of coronavirus disease 2019 from community-acquired-pneumonia by computed tomography scan and follow-up. Infect Dis Poverty. 2020;9:118.
14. Cillóniz C, Cardozo C, García-Vidal C. Epidemiology, pathophysiology, and microbiology of community acquired pneumonia. Ann Res Hosp. 2018;2:1-11.
15. Sahuquillo-Arce JM, Menéndez R, Méndez R, et al. Age-related risk factors for bacterial aetiology in community-acquired pneumonia. Respirology. 2016;21:1472-1479.
16. Goldstein E, Lipsitch M, Cevik M. On the Effect of Age on the Transmission of SARS-CoV-2 in Households, Schools, and the Community. J Infect Dis. 2021;223:362-369.
17. Oster AM, Caruso E, DeVies J, Hartnett KP, et al. Transmission Dynamics by Age Group in COVID-19 Hotspot Counties - United States, April-September 2020. MMWR Morb Mortal Wkly Rep. 2020;69:1494-1496.
18. Zhou Y, Guo S, He Y, et al. COVID-19 Is Distinct From SARS-CoV-2-Negative Community-Acquired Pneumonia. Front Cell Infect Microbiol. 2020;10:322.
19. Tang X, Du RH, Wang R, et al. Comparison of Hospitalized Patients With ARDS Caused by COVID-19 and H1N1. Chest. 2020;158:195-205.
20. Shen C, Tan M, Song X, et al. Comparative Analysis of Early-Stage Clinical Features Between COVID-19 and Influenza A H1N1 Virus Pneumonia. Front Public Health. 2020;8:206.
21. Sun Y, Koh V, Marimuthu K, et al. Epidemiological and Clinical Predictors of COVID-19. Clin Infect Dis. 2020;71:786-792.
22. Merad M, Martin JC. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. Nat Rev Immunol. 2020;20:355-362.
23. Gómez-Rial J, Rivero-Calle I, Salas A, et al. Role of Monocytes/Macrophages in Covid-19 Pathogenesis: Implications for Therapy. Infect Drug Resist. 2020;13:2485-2493.
24. Pence BD. Severe COVID-19 and aging: are monocytes the key? Geroscience. 2020;42:1051-1061.
25. Martinez FO, Combes TW, Orsenigo F, et al. Monocyte activation in systemic Covid-19 infection: Assay and rationale. EBioMedicine. 2020;59:102964.
26. Kvedaraite E, Hertwig L, Sinha I, et al. Major alterations in the mononuclear phagocyte landscape associated with COVID-19 severity. Proc Natl Acad Sci U S A. 2021;118:e2018587118.
27. Meidaninikjeh S, Sabouni N, Marzouni HZ, et al. Monocytes and macrophages in COVID-19: Friends and foes. Life Sci. 2021;269:119010.
28. https://www.cdc.gov/nchs/data/nhanes/nhanes_01_02/l11_b_met_c_reactive_protein.pdf
29. Li Y, Wang H, Wang F, et al. Comparison of hospitalized patients with pneumonia caused by COVID-19 and influenza A in children under 5 years. Int J Infect Dis. 2020;98:80-83.