Effects of age and comorbidities on inflammatory markers in community-acquired pneumonia

Diego Viasus (dviasus@uninorte.edu.co)
Universidad del Norte Division Ciencias de la Salud https://orcid.org/0000-0001-8408-3947
Antonella F Simonetti
Consorci Sanitari del Garraf
Andres Estupiñan-Bohorquez
Universidad del Norte Division Ciencias de la Salud
Jordi Carratalà
Hospital Universitari de Bellvitge

Research

Keywords: age, comorbidities, multimorbidity, immune response, community-acquired pneumonia

Posted Date: August 11th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-56322/v1

Abstract

Background: Studies have suggested that an inappropriate inflammatory response is a major cause of treatment failure and mortality in patients with community-acquired pneumonia (CAP). We aimed to determine the effect of comorbidities and age on serum inflammatory markers in CAP.

Methods: We performed a prospective cohort study of adults hospitalized with CAP. For the purposes of this study, we compared patients according to comorbidities and age. Inflammatory markers were measured at hospital admission, focusing on acute phase proteins, cytokines, and monocyte human leukocyte antigen DR (mHLA-DR) expression.

Results: In patients with chronic pulmonary disease (COPD), serum cytokines had significantly decreased levels of tumor necrosis factor (TNF)-α, interleukin (IL)-6, and mHLA-DR expression, as well as the C-reactive protein (CRP), compared with patients who had no comorbidities. Similarly, patients with chronic heart disease had a significantly reduced CRP levels and mHLA-DR expression, whereas patients with chronic kidney disease had significantly higher serum levels of procalcitonin and TNF-α. Lower procalcitonin, IL-6, and IL-10 levels, as well as mHLA-DR expression, were documented in older patients, but with no significant differences compared to younger patients. Multimorbidity in older patients was associated with significant lower levels of CRP and mHLA-DR expression.

Conclusions: The circulating inflammatory markers to CAP have profiles that differ with age and underlying comorbidities. Multimorbidity in the elderly is also associated with lower serum levels of some inflammatory markers. These findings suggest that age and comorbidities have much more of an impact than to simply reduce physiological reserve and can cause variations in the inflammatory response in CAP.

Background

Community-acquired pneumonia (CAP) is a major public health problem worldwide, representing a major cause of death and the leading cause among infectious diseases [1, 2]. Studies have also documented that the incidence has increased significantly over recent years, and time trend analyses have shown significant increases in the number of comorbidities, need for non-invasive mechanical ventilation, and readmission rates [3, 4]. Although the overall mortality rates are 8%–15%, mortality can be higher in patients with CAP who require intensive care unit admission [1, 2, 5].

Studies have suggested that an inappropriate inflammatory response is a major cause of treatment failure and mortality in patients with CAP [1, 6], and this has led to growing interest in identifying drugs that can modulate the inflammatory response. To date, however, the results have been unsatisfactory [7, 8]. Most studies of immunomodulatory treatments have presumably failed as a result of the following: a) incomplete understanding of the mechanisms of immune response during CAP; b) heterogeneity of the study population in terms of age, comorbidities, disease severity, and the causative pathogen; and c) assuming that all patients with CAP have a similar immune response (proinflammatory or anti-

inflammatory). Indeed, research has now shown that previous interpretations of the inflammatory response in CAP and/or sepsis may be incorrect [6, 9]. It is therefore necessary to increase our knowledge of the host response and pattern of inflammatory marker response in CAP, but information about levels of some biomarkers by sociodemographic features in the host are scarce [10, 11]. More information is necessary given that variation in the inflammatory pattern by different variables may impact prognosis and patient selection for future studies of biomarker-guided therapy, which may improve outcomes in patients with CAP [12]. Adequate classification is critical to the clinical applicability of personalized medicine in diagnostics and prognostics for CAP and sepsis.

We aimed to determine the effect of comorbidities and age on the serum levels of inflammatory markers at hospital admission for non-immunosuppressed adult patients with CAP. Our hypothesis was that patients with comorbid conditions and older age would have characteristic inflammatory signatures in response to CAP. Identifying these patterns may improve our understanding of the host response to CAP.

Methods

This prospective cohort study was conducted at Hospital Universitari de Bellvitge, a 700-bed hospital in Barcelona, Spain. All non-immunosuppressed adults admitted to hospital with CAP via the emergency department from January 2013 to June 2016 were prospectively followed-up. Patients with immunosuppression were excluded from the study (e.g., chemotherapy, HIV infection, bone marrow or solid-organ transplantation, and systemic corticosteroid therapy).

For the purposes of this study, patients were split into sub-groups by age and the presence of comorbidity for comparison. For the age cut off, younger and older patients were classified as those aged <85 and ≥85 years old, respectively. The following individual comorbid conditions were considered: chronic cardiac disease, chronic obstructive pulmonary disease (COPD), diabetes mellitus, chronic kidney disease (CKD), and liver cirrhosis. Multimorbidity was defined as the presence of two or more of these chronic conditions.

Levels of the following inflammatory markers were measured at hospital admission: acute phase proteins (C-reactive protein [CRP] and procalcitonin [PCT]), cytokines (tumor necrosis factor-alpha [TNF-α], interleukin [IL]-6, and IL-10), and monocyte human leukocyte antigen DR (mHLA-DR) expression. The primary outcomes were the serum levels of inflammatory markers at hospital admission in each of the study groups.

Definitions and follow-up

CAP was defined as an acute illness with fever or hypothermia, cough with or without sputum production, dyspnea, altered breath sounds, pleuritic chest pain, and leukocytosis or leukopenia associated with a new infiltrate on a chest radiograph. At hospital admission, patients underwent a comprehensive clinical history and physical examination. If indicated by the attending physician, microbiological studies were performed, including two sets of blood cultures, including sputum Gram stain and culture when available,

and urinary antigen detection for *Legionella pneumophila* and *Streptococcus pneumoniae*. Patients were stratified into risk class according to the Pneumonia Severity Index (PSI) [13] and were seen daily during admission by one or more of the investigators, who recorded clinical, laboratory and microbiological information. Empirical antibiotic treatment was applied according to hospital recommendations, typically using a β-lactam (ceftriaxone or amoxicillin/clavulanate) with or without a macrolide or a fluoroquinolone.

Regarding comorbid conditions, chronic heart disease was defined if there was evidence in clinical records or if the patient was receiving treatment for coronary artery disease, congestive heart failure, or arrhythmia, or if they had valvular heart disease [14]. COPD was defined as the coexistence of chronic and progressive symptoms such as dyspnea, cough, sputum, and airflow obstruction (diagnosed by spirometry), as described elsewhere [15]. A diagnosis of diabetes mellitus was made when the fasting plasma glucose concentration was ≥126 mg/dL on two or more separate occasions, or when a random plasma glucose ≥200 mg/dL was found in a patient with classic symptoms of hyperglycemia. Alternatively, the diagnosis was based on prior treatment with oral antidiabetic agents or insulin and/or clinical and/or a biochemical diagnosis of DM [16]. A patient was considered to have CKD if they had chronic renal disease and a glomerular filtration rate <60 mL/min/1.73 m^2 or the need for chronic dialysis [17]. Finally, diagnosis of liver cirrhosis was made by histology and/or by clinical, laboratory, and imaging criteria, as described elsewhere [18].

Determination of biomarkers

Blood samples were taken from patients in the first 24 hours of hospital admission, centrifuged, and frozen at -80°C for later analysis. PCT, TNFα, IL-6, IL-10, and CRP levels were determined by using an enzyme immunoassay according to the manufacturer's instructions. Monocyte HLA-DR expression was investigated on the same day, using a double-immunofluorescent whole-blood technique. At least 10,000 cells from each sample were analyzed on the flow cytometer.

Statistical analysis

Analysis of study variables was performed by SPSS Statistics for Windows, Version 17.0 (SPSS Inc., Chicago, USA). Continuous variables are described as median and interquartile range (IQR) and categorical variables are described as counts and percentages. To detect significant differences between study groups, we used the χ^2 test or Fisher's exact test for categorical variables and the Student *t*-test or the Mann–Whitney *U*-test for continuous variables, as appropriate. All statistical analyses were specified before the data were seen. Statistical significance was accepted for two-tailed P-values of 0.05.

Results

Baseline characteristics

Over the study period, 375 non-immunosuppressed adult patients were admitted to our hospital with CAP. The main demographic, clinical, and outcome data are shown in Table 1. Older patients (≥85 years old) and those with comorbidities accounted for 79 (21%) and 262 (69.8%) cases, respectively. The most common comorbidities were chronic heart disease (n = 130; 49.6%), COPD (n = 107; 40.8%), diabetes mellitus (n = 99; 37.7%), CKD (n = 42; 16%), and liver cirrhosis (n = 15; 5.7%). Multimorbidity was present in 147 (39.2%) patients, and compared with younger patients, multimorbidity was more frequent in older patients (≥85 years old) (18.8% vs 58.2%, P-value < 0.001). Regarding illness severity, almost 60% were classified into high-risk PSI groups (classes IV and V). The principal etiology was *Streptococcus pneumoniae*, followed by aspiration pneumonia, *Haemophilus influenzae*, and *Legionella pneumophila*. Regarding outcomes, 6% required admission to intensive care and 4% died during hospitalization.

Table 1 Demographic and clinical features, plus outcomes, for all patients with CAP

Characteristics	(n = 375)
Age, median (IQR), years	75 (63–83)
≥85 years old	79 (21%)
Sex, male	217 (57.9)
Current smoker	56 (14.9)
Comorbidities	262 (69.8)
Chronic heart disease, all/individual	130 (34.6)/43 (11.4)
COPD, all/individual	107 (28.5)/47 (12.5)
Diabetes mellitus, all/individual	99 (26.4)/30 (8)
Chronic kidney disease, all/individual	42 (11.2)/6 (1.6)
Chronic liver disease, all/individual	15 (4)/4 (1.0)
Clinical features	
Altered consciousness	50 (13.3)
Hypotension	19 (5.1)
Tachypnoea	126 (33.6)
Multilobe pneumonia	125 (33.3)
Bacteremia	30 (8.0)
High-risk PSI (Groups IV-V)	216 (57.6)
Streptococcus pneumoniae pneumonia	99 (26.4)
Outcomes	
ICU admission	23 (6.1)
In-hospital mortality	15 (4.0)

Data are reported as n (%), unless otherwise stated. Abbreviations: CAP, community-acquired pneumonia; COPD, chronic obstructive pulmonary disease; PSI, Pneumonia Severity Index; ICU, intensive care unit.

Markers of inflammatory response in patients with comorbid conditions

Analysis of the inflammatory markers in patients with comorbid conditions are shown in Table 2. This analysis was performed in 43 patients who had chronic heart disease with no other comorbidity, 47 with only COPD, and 30 with only diabetes mellitus. Due to the small number of patients with chronic kidney and liver disease, patients with these comorbidities were pooled for this analysis. Comparing the groups with and without comorbid conditions, patients with CAP and COPD had decreased levels of serum cytokines TNF-α and IL-6, as well as low levels of CRP and mHLA-DR expression. Similarly, patients with chronic heart disease had low levels of CRP and mHLA-DR expression. In contrast to these findings, however, patients with CKD had higher serum levels of PCT and TNF-α and no significant differences in the serum levels of other biomarkers. No differences were documented for all serum levels of inflammatory markers in patients with diabetes mellitus and liver cirrhosis compared to patients without comorbidities.

Table 2 Inflammatory marker levels by the main comorbidities in patients with CAP

Marker	Chronic cardiac disease (n = 43)	COPD (n = 47)	Diabetes mellitus (n = 30)	Chronic kidney disease[a] (n = 42)	Liver cirrhosis[a] (n = 15)	No comorbid condition (n = 113)
PCT (ng/mL)	1.10 (0.24–3.62)	0.51 (0.11–3.25)	0.62 (0.15–3.05)	1.53 (0.41–5.47)[b]	0.59 (0.25–4.49)	0.62 (0.14–1.91)
TNF-α (pg/ml)	19.4 (16.1–24.7)	16.8 (13–20.6)[b]	20.2 (14.6–25)	24.8 (17.1–35)[b]	18 (16.4–32.6)	19.7 (15–27.8)
IL-6 (pg/ml)	143 (41.2–323)	52.6 (31–153)[b]	90 (32.9–273)	100 (27.2–387)	96 (43–577)	115 (46.1–234.7)
IL-10 (pg/ml)	1.14 (0.54–3.70)	1.07 (0.53–2.82)	1.49 (0.45–4.13)	1.39 (0.84–4.80)	2.33 (0.84–3.8)	1.19 (0.38–3.10)
CRP (mg/L)	143.8 (101–282.1)[b]	223.4 (118.3–323.8)	201.2 (63.9–283.9)	215 (118.7–292.8)	205.2 (92.5–247.4)	236.4 (131.7–343.6)
HLA-DR (fluorescence intensities)	96.6 (58–195.2)[b]	85.5 (54.1–177.6)[b]	99.6 (72.6–254.8)	123.6 (84.6–249)	127 (90.9–230.5)	160.1 (86.4–297.1)

Data are reported as median (interquartile range). Abbreviations: CAP, community-acquired pneumonia; COPD, chronic obstructive pulmonary disease; PCT, procalcitonin; TNF, tumor necrosis factor; IL, interleukin; CRP, C-reactive protein; HLA-DR, expression of monocyte human leukocyte antigen DR. [a]Include patients with other comorbidities. [b]P-value ≤0.05 compared with patients without comorbid conditions.

Markers of inflammatory response in older patients

Patients were divided into three age groups: ≥85 years, 66–84 years, and ≤65 years. The analysis of patients by age group, without comorbid conditions, is presented in Table 3. Lower levels of PCT, IL-6, IL-10, and monocyte HLA-DR expression were seen in older patients (≥85 years old), but without significant differences compared with younger patients (≤65 years). However, compared to younger patients with no

underlying diseases, the immune response pattern in older patients with multimorbidity showed lower CRP levels (median, 246.1 vs 205.0 mg/L; P = 0.03) and mHLA-DR expression (median, 144.4 vs 108.4 fluorescence intensities; P = 0.04).

Table 3 Inflammatory marker levels by age group in patients with CAP and no comorbid conditions

Marker	Aged ≤65 years old (n = 64)	Aged 66–84 years old (n = 37)	Aged ≥85 years old (n = 12)
PCT (ng/mL)	1.0 (0.1–3.1)	0.5 (0.2–1.8)	0.2 (0.1–0.5)
TNF-α (pg/ml)	19.2 (14.4–30.0)	19.6 (15.0–26.8)	22.3 (16.9–25.8)
IL-6 (pg/ml)	103.0 (44.4–242.0)	121.0 (56.0–255.5)	64.5 (22.7–195.0)
IL-10 (pg/ml)	1.3 (0.3–3.9)	1.2 (0.5–1.6)	0.9 (0.5–1.66)
CRP (mg/L)	253.8 (126.5–345.6)	210.7 (165.1–304.5)	251.0 (178.2–311.9)
HLA-DR (fluorescence intensities)	169.8 (90.3–302.3)	153.7 (70.6–285.1)	145.8 (80.4–274.2)

Data are reported as median (interquartile range). Abbreviations: CAP, community-acquired pneumonia; PCT, procalcitonin; TNF, tumor necrosis factor; IL, interleukin; CRP, C-reactive protein; HLA-DR, expression of monocyte human leukocyte antigen DR. All P-values > 0.05

Discussion

In this prospective cohort study of non-immunocompromised patients hospitalized for CAP, the circulating inflammatory markers showed a different profile in patients with comorbidities, notably in COPD. In addition, multimorbidity in elderly patients was associated with lower serum levels of some immune response markers. These findings suggest that comorbidities have much more of an impact than to simply reduce physiological reserve and can cause variations in the inflammatory response in CAP.

Recent studies have suggested the importance of host features in the prognosis of CAP, including their inflammatory response, susceptibility to specific pathogens, genome, and metabolic condition [1, 19]. In this regard, distinguishing the factors that modify inflammatory biomarkers offers additional evidence that may broaden our understanding of the host inflammatory response in CAP. However, there is only limited data on the pattern of inflammatory markers by comorbidity in CAP. Crisafulli et al. [10] has performed the only available study to investigate the specific inflammatory pattern of patients with CAP and comorbidity. They found that patients with CAP and COPD had lower serum levels of TNF-α, IL-1, and IL-6 compared with those who had no COPD. They documented no differences in PCT, IL-10, or CRP between the study groups. Thus, we found similar results in the present study, but additionally showed that patients with CAP and COPD had lower mHLA-DR expression.

Although biomarker measurement may be influenced by renal function, most investigations have failed to address this issue. Recent evidence has indicated that renal function is a confounder when evaluating both copeptin levels in healthy subjects [20] and mid-regional pro-atrial natriuretic peptide levels in patients with chronic hypertensive disease [21]. In light of these findings, we evaluated inflammatory marker levels in patients with CAP and CKD, revealing that serum PCT and TNF-α levels were significantly

higher than in patients with CAP and no comorbidities. However, no differences were documented in other biomarkers (i.e., IL-6, IL-10, and CRP) or in monocyte HLA-DR expression. These findings concur with those of previous studies indicating that TNF-α levels were significantly elevated in patients with CKD and that TNF-α was significantly and positively related to the severity of CKD [22]. Other studies have also shown that baseline PCT levels in patients with CKD are negatively associated with renal function[23], with the authors concluding that the predictive value of PCT for infection is not good and requires adjustment to avoid inappropriate PCT use in this population. Thus, some biomarkers in CAP may need to be interpreted in the context of the renal function.

In the present study, having comorbid conditions was associated with lower serum levels of monocyte HLA-DR expression in patients with COPD or chronic heart disease. To the best of our knowledge, no previous clinical studies have measured mHLA-DR expression in relation to comorbid conditions in CAP. This is a notable gap in the literature because HLA-DR expression on antigen presenting cells is a central pathway in antigen-dependent lymphocyte activation. Loss of mHLA-DR expression on monocytes is considered a diagnostic and prognostic indicator of sepsis-related immunosuppression [24]. Consequently, it has been proposed that this biomarker be used as a guide to starting immunostimulant treatment in sepsis [25]. However, there is no appropriate cut-off value for mHLA-DR expression when estimating adverse outcomes because of variations between patients, as experienced in the present study. It was also notable that we found lower levels of mHLA-DR expression in elderly patients, albeit without being significantly different compared with younger patients, probably due to the low number of patients without comorbidities. These changes in HLA-DR expression have previously been described with aging and may contribute to the decreased immunologic responsiveness observed in older patients known as “inflamm-aging” [26, 27].

Multimorbidity in elderly patients also affected biomarker levels, with CRP and mHLA-DR levels being lower in this group of patients. The effect of pre-existing chronic conditions therefore seems to go much further than simply reducing the physiological reserve. Interestingly, multimorbidity has been independently associated with death, hospitalization, or return to the emergency department within 90 days of discharge in CAP patients [28].

The study benefited from the prospective collection of comprehensive clinical data that allowed us to identify and analyze patients with only one of comorbid condition. In addition, we evaluated different inflammatory markers (i.e., cytokines, acute phase response proteins, and HLA-DR expression). However, several limitations should be acknowledged. First, our study was conducted at a single centre and we included few patients with CKD and chronic liver disease, as well as older patients without comorbidities; thus, our findings need to be validated in larger cohorts. Second, we did no evaluate other less common underlying diseases. Third, we measured biomarkers at only one point of the disease and did not evaluate the effect of comorbidities on the immune response during admission

Conclusion

Circulating inflammatory markers to CAP differ by comorbidity, and this is notable among patients with COPD who have different cytokine profiles. Multimorbidity in the elderly is also associated with lower serum levels of some inflammatory markers. Overall, our findings suggest that inflammatory markers in CAP should be interpreted after considering comorbid conditions and age.

Declarations

Ethics approval

The research was conducted ethically in accordance with the latest World Medical Association Declaration of Helsinki. The study protocol was approved by the institutional ethics committee (CEIC 2013/0048). Patients were included after having obtained informed consent.

Competing interests

The authors declare that they have no competing interests.

Availability of data and materials

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Funding

This work is funded by the Ministerio de Economia y Competitividad, Instituto de Salud Carlos III (PI11/01106).

Author Contributions

DV and JC had the idea for and designed the study, had full access to all data, and take responsibility for the integrity of the data and the accuracy of the data analysis. DV and AE conducted the statistical analysis. DV, AS and AE contributed to data acquisition, data analysis or data interpretation. DV and JC contributed to drafting the manuscript. AS and AE contributed to critical revision of the manuscript for valuable intellectual content. The final version had been reviewed and approved by all authors.

References

1. Ferreira-Coimbra J, Sarda C, Rello J. Burden of Community-Acquired Pneumonia and Unmet Clinical Needs. Adv Ther. 2020;37(4):1302-18.
2. José RJ, Periselneris JN, Brown JS. Community-acquired pneumonia. Curr Opin Pulm Med. 2015;21(3):212-8.
3. de-Miguel-Díez J, Jiménez-García R, Hernández-Barrera V, Zamorano-Leon JJ, Villanueva-Orbaiz R, et al. Trends in hospitalizations for community-acquired pneumonia in Spain: 2004 to 2013. Eur J

Intern Med. 2017;40:64-71.

4. Ruhnke GW, Coca-Perraillon M, Kitch BT, Cutler DM. Trends in Mortality and Medical Spending in Patients Hospitalized for Community-Acquired Pneumonia: 1993-2005. Med Care. 2010;48(12):1111-6.
5. Garnacho-Montero J, Barrero-García I, Gómez-Prieto MG, Martín-Loeches I. Severe Community-Acquired Pneumonia: Current Management and Future Therapeutic Alternatives. Expert Rev Anti Infect Ther. 2018;16(9):667-77.
6. Kellum JA, Kong L, Fink MP, Weissfeld LA, Yealy DM, Pinsky MR, et al; GenIMS Investigators. Understanding the inflammatory cytokine response in pneumonia and sepsis. Arch Intern Med. 2007;167(15):1655-63.
7. Cheng AC, Stephens DP, Currie BJ. Granulocyte-colony stimulating factor (G-CSF) as an adjunct to antibiotics in the treatment of pneumonia in adults. Cochrane Database Syst Rev. 2007; (2):CD004400.
8. Briel M, Spoorenberg SMC, Snijders D, Torres A, Fernandez-Serrano S, Meduri GU, et al; Ovidius Study Group; Capisce Study Group; STEP Study Group. Corticosteroids in Patients Hospitalized With Community-Acquired Pneumonia: Systematic Review and Individual Patient Data Metaanalysis. Clin Infect Dis. 2018;66(3):346-54.
9. Gogos C, Kotsaki A, Pelekanou A, Giannikopoulos G, Vaki I, Maravitsa P, et al. Early alterations of the innate and adaptive immune statuses in sepsis according to the type of underlying infection. Crit Care. 2010;14(3):R96.
10. Crisafulli E, Menéndez R, Huerta A, Martinez R, Montull B, Clini E, et al. Systemic inflammatory pattern of patients with community-acquired pneumonia with and without COPD. Chest. 2013;143(4):1009-17
11. Kim JH, Seo JW, Mok JH, Kim MH, Cho WH, Lee K, et al. Usefulness of plasma procalcitonin to predict severity in elderly patients with community-acquired pneumonia. Tuberc Respir Dis (Seoul). 2013;74(5):207-14.
12. Urwyler SA, Blum CA, Coslovsky M, Mueller B, Schuetz P, Christ-Crain M. Cytokines and Cortisol - predictors of treatment response to corticosteroids in community-acquired pneumonia? J Intern Med. 2019;286(1):75-87.
13. Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. N Engl J Med. 1997;336(4):243-50.
14. Viasus D, Garcia-Vidal C, Manresa F, Dorca J, Gudiol F, Carratalà J. Risk stratification and prognosis of acute cardiac events in hospitalized adults with community-acquired pneumonia. J Infect. 2013;66(1):27-33.
15. Gómez-Junyent J, Garcia-Vidal C, Viasus D, Millat-Martínez P, Simonetti A, Santos MS, et al. Clinical features, etiology and outcomes of community-acquired pneumonia in patients with chronic obstructive pulmonary disease. PLoS One. 2014;9(8):e105854.

16. Di Yacovo S, Garcia-Vidal C, Viasus D, Adamuz J, Oriol I, Gili F, et al. Clinical features, etiology, and outcomes of community-acquired pneumonia in patients with diabetes mellitus. Medicine (Baltimore). 2013;92(1):42-50.
17. Viasus D, Garcia-Vidal C, Cruzado JM, Adamuz J, Verdaguer R, Manresa F, et al. Epidemiology, clinical features and outcomes of pneumonia in patients with chronic kidney disease. Nephrol Dial Transplant. 2011;26(9):2899-906.
18. Viasus D, Garcia-Vidal C, Castellote J, Adamuz J, Verdaguer R, Dorca J, et al. Community-acquired pneumonia in patients with liver cirrhosis: clinical features, outcomes, and usefulness of severity scores. Medicine (Baltimore). 2011;90(2):110-8.
19. Leoni D, Rello J. Severe community-acquired pneumonia: optimal management. Curr Opin Infect Dis. 2017;30(2):240-47.
20. Ettema EM, Heida J, Casteleijn NF, Boesten L, Westerhuis R, Gaillard CAJM, et al. The Effect of Renal Function and Hemodialysis Treatment on Plasma Vasopressin and Copeptin Levels. Kidney Int Rep. 2017;2(3):410-19.
21. Theilade S, Hansen TW, Goetze JP, Rossing P. Increased plasma concentrations of midregional proatrial natriuretic Peptide is associated with risk of cardiorenal dysfunction in type 1 diabetes. Am J Hypertens. 2015;28(6):772-9.
22. Lee BT, Ahmed FA, Hamm LL, Teran FJ, Chen CS, Liu Y, et al. Association of C-reactive protein, tumor necrosis factor-alpha, and interleukin-6 with chronic kidney disease. BMC Nephrol. 2015;16:77.
23. Grace E, Turner RM. Use of procalcitonin in patients with various degrees of chronic kidney disease including renal replacement therapy. Clin Infect Dis. 2014;59(12):1761-7.
24. Zhuang Y, Peng H, Chen Y, Zhou S, Chen Y. Dynamic monitoring of monocyte HLA-DR expression for the diagnosis, prognosis, and prediction of sepsis. Front Biosci (Landmark Ed). 2017;22:1344-1354.
25. Meisel C, Schefold JC, Pschowski R, Baumann T, Hetzger K, Gregor J, et al. Granulocyte-macrophage colony-stimulating factor to reverse sepsis-associated immunosuppression: a double-blind, randomized, placebo-controlled multicenter trial. Am J Respir Crit Care Med. 2009;180(7):640-8.
26. Murray MA, Chotirmall SH. The Impact of Immunosenescence on Pulmonary Disease. Mediators Inflamm. 2015;2015:692546.
27. Le Morvan C, Cogné M, Troutaud D, Charmes JP, Sauvage P, Drouet M. Modification of HLA expression on peripheral lymphocytes and monocytes during aging. Mech Ageing Dev. 1998;105(3):209-20.
28. Weir DL, Majumdar SR, McAlister FA, Marrie TJ, Eurich DT. The impact of multimorbidity on short-term events in patients with community-acquired pneumonia: prospective cohort study. Clin Microbiol Infect. 2015;21(3):264.e7-264.e13.