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Immune and inflammatory predictors of survival in patients with severe community-acquired pneumonia

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Questions of survival predicting in patients with severe community-acquired pneumonia (CAP) remain relevant and poorly understood.

The aim of this work was to determine the significance of cellular immunity markers CD_4, CD_8 and markers of systemic inflammation procalcitonin (PCT) and C-reactive protein (CRP) as a predictor of survival in these patients using of cluster analyze.

According the research revealed that more than half of patients with severe community-acquired pneumonia have violations of cellular immunity of varying severity, the feature of survival predicting of patients with severe CAP is the account of the pathogenetic mechanisms, namely a complex set of immune factors interact with inflammatory markers. The most significant laboratory predictors of the outcome are the individual dynamics of the cell immunity marker CD_4 and inflammatory marker PCT.

At a significant reduction of the serum PCT level and an increase of CD_4 count during the adequate ABT a favorable outcome of pneumonia can be expected, while the PCT increase and CD_4 decrease, on the contrary, are unfavorable for the survival.

Keyword: severe community acquired pneumonia, prognosis, predictors, Outcome.

1. Introduction

The problem of management of patients with community-acquired pneumonia (CAP) has not lost its relevance in the world. Despite the emergence of new antibacterial drugs (AB) and other therapeutic measures, there is an increase in deaths from CAP, especially during its severe course [1]. The mortality rate for severe CAP reaches 25–40% [2].

Today the question remains: what are the greatest determines of the mortality of patients with severe CAP and is it possible to affect the most significant predictors of survival [3].

It is necessary to look for objective predictors of survival in patients with severe CAP based on pathogenetic features of this disease. According to the modern concept, peculiarities of severe CAP due to the complex interaction mechanism

of pro-and antiinflamatory factors with immune ones. With the generalization of the inflammatory response in severe CAP, a state of immunosuppression, manifested lymphopenia and loss of immune function, which determines not only the severity of patients, but also their refractory to antimicrobial therapy (ABT) [4, 5, 6].

The most studied and most accessible to research inflammatory markers are procalcitonin (PCT) and C-reactive protein (CRP). In modern literature, there are studies that have examined the diagnostic role of these factors in patients with severe CAP. Whereas their predictive role is described in a few studies. It is believed that high levels of PCT and CRP for admission is a poor prognostic factor in these patients [7, 8, 9].

The role of cellular immunity markers as prognostic criteria for pneumonia has been studied only in HIV-infected patients [10]. In these cases, the usual to count the number of T-helper cells (CD_4), T-suppressor (CD_8) (from the clusters of differentiation). However, the role of these factors in assessing the prognosis of patients with severe CAP without HIV did not studied yet.

That is why **the aim of our work** was to determine the significance of cellular immunity markers CD_4, CD_8, and markers of systemic inflammation PCT and CRP as a predictor of survival in patients with sCAP.

2. Materials and methods.

We examined 51 patients with verified severe CAP, which included to a basic group (age–57, 50±4, 31 years, men–37 (72, 5%), women–14 (27, 5%). The wording of the clinical diagnosis was performed according to the Ukrainian national guidelines [11]. Exclusion criteria was the presence of HIV infection.

Except general clinical research methods the determination of serum PCT levels by immunochemical electrochemiluminescence and CRP by immunoturbodimetric method [12, 13], the calculation of lymphocyte subsets CD_4, CD_8 by flow cytometry laser [14] were done.

Evaluation of clinical and laboratory data function was performed on the first day of hospitalization prior to the appointment of ABT (visit 1), on 3–5 day of ABT (visit 2), on 8–10 day of ABT (visit 3).

Statistical processing of the results of research carried out using the methods of biometric analysis, implemented in software packages EXCEL-2003 (№ 74017-641-9475201-57075) and STATISTICA 6.0 (№ 31415926535897) [15, 16]. In order to find the most significant predictors of survival in patients with sCAP we conducted cluster analysis.

The given study proves by the local ethics committee, used research methods did not offend and did not cause harm to the health and lives of patients. All patients agreed to conduct all research methodologies and processing and publication of the given data.

3. Results and discussion.

On admission (visit 1) the status of all patients of the group was reported as serious. Furthermore, data analysis of immunograms found that more than half (30 or 58, 8%) of patients experienced immunodeficiency, which manifests itself in the reduction of CD_4 and CD_8 least 500 mcg^{-1}. In this case a sharp increase in serum PCT and CRP levels were determined, which amounted 18, 7±3, 62 ng/ml and 268, 3±16, 72 mg/l respectively.

After verification of severe CAP and the initial survey all patients were assigned to the adequate combined ABT according to national guidelines, which included a "protected" aminopenicillins (amoxicillin/clavulanic acid or ampicillin/sulbactam) or cephalosporins of III generation (ceftriaxone) in combination with macrolides, as an alternative therapy used combination of fluoroquinolones of III or IV generation and "protected" aminopenicillin or cephalosporin of III generation [11].

In 6 (11, 7%) patients with severe CAP, despite ongoing adequate ABT, the lethal end of the disease was determined after 2–7 day of hospital treatment. Comparative evaluation of initial and final clinical and laboratory data of survivors and deceased patients with severe CAP (table 1) found that at baseline all patients were characterized by pronounced inflammatory response and impaired cellular immunity, regardless of the outcome of treatment.

While the final data obtained that levels of CD_4, the PCT and CRP were significantly different among the dead and the survivors patients. In this case, there was a clear pattern: the patients who survived, even in the presence of a certain decline in CD_4 early in the disease, there was a gradual increase and/or restore to normal, which is accompanied by a decrease in the level of inflammatory markers, and those who died–on the contrary, the dynamic reduction in the number of CD_4 and increase in PCT and CRP determined. It is therefore the particular interest is the study of the difference of the results of the investigated parameters of immunity and inflammation at the final visit (visit 3 or visit 2 for dead patients) relative to the primary data (visit 1) –delta (Δ).

The analysis confirmed the importance of immune and general inflammatory markers in terms of dynamic monitoring and prognosis for survival of patients with severe CAP. However, is it necessary to systematize and generalize the data with the help of cluster analysis. It is bringing together the figures of the patients not in isolation, but going into each other.

As a result of the cluster analysis the dividing of the main group of 51 patients on certain groups (classes) was observed, while within one class of patients is characterized by a set of parameters of ΔPCT and ΔCD_4 which are not significantly differ from each other, and within the various clusters–significantly different. For the formation of classes hierarchical classification was selected, as an association rules–a single method of communication, as a measure of proximity–Euclidean distance. The resulting dendrogramm (fig. 1) shows a sequential mechanism of association of two clusters of patients in the next one and the distance between them. The red line denotes the threshold distance–the distance above which will unite two distant figures.

Table 1: Dynamics of general inflammatory and immunological parameters in patients with severe CAP depending on the outcome of the disease.

parameter	Initial data (visit 1)		Final data (visit 2 or visit 3)	
	survivors (n=45)	died (n=6)	survivors (n=45)	died (n=6)
CD_4, mcg^{-1}	447,2±47,2^	313,7±126,2	802,3±62,1*^	185,8±79,3*^
PCT, ng/ml	17,9±3,9^	23,7±8,4	0,08±0,01*^	36,5±11,6*
CRP, mg/l	262,8±18,2^	309,3±38,9	39,9±4,7*^	579,1±74,3*^

N o t e s:

1. * – $p_{s\text{-}d}<0,05$ by the Mann-Whitney;
2. ^ – $p_{v1\text{-}v2,3}<0,05$ by Wilcoxon;
3. s – survivors;
4. d – died;
5. $v_{1,\ 2,\ 3}$ – visit 1, 2, 3

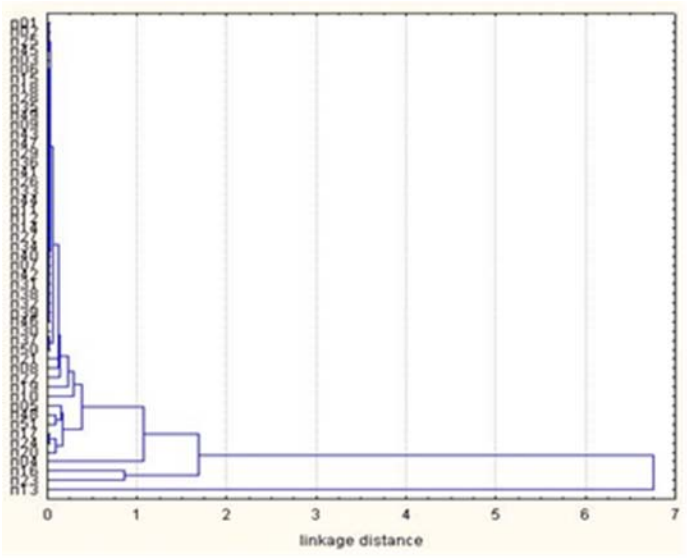

Fig. 1: Horizontal clustering dendrogram of patients with severe CAP.

To determine the threshold distance the schedule of a combination circuit used (fig. 2), which shows that the point of refraction has a 46 step of clustering, i.e. linkage distance is 0,5.

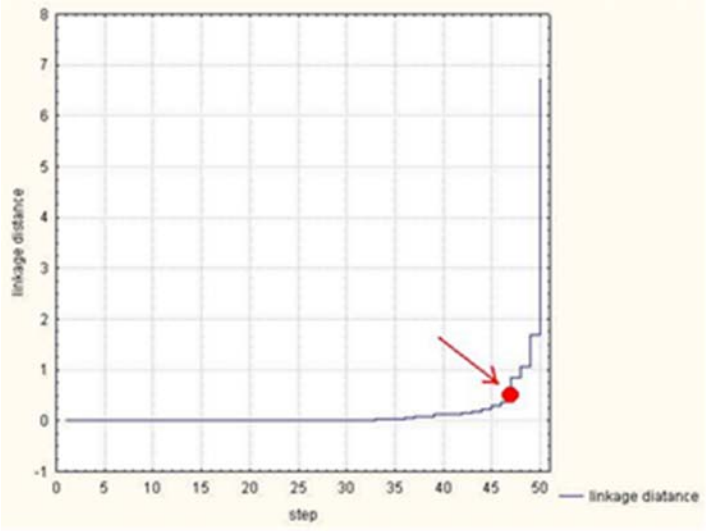

Fig. 2: Diagram of combining distance by steps.

The number of classes that are convenient to divide all patients, determined by the formula: (n-m), where n–the total number of observations, m –step of refraction, that is, in our case, the number of classes: 51-46=5. Confirmation of the chosen number of classes is an analysis of the dendrogramm where we see that at the threshold distance of 0, 5 (which is the point of refraction) is 5 perpendicular intersections with "branches" of the dendrogramm (fig. 1). The number of determined intersections is the number of classes, and the objects, which turned to the left of the severed branches, are the composition of the cluster. Thus, patients of the main group to

modify the initial and final data of PCT and CD_4 can be divided into five classes. When checking the difference in means of each cluster $p<0,005$.

In class 1 there are 2 patients whose serum PCT at visit 3 was decreased by more than on 98, 2% compared with the data of the visit 1 and CD_4 increased very significantly (by more than 1455, 6%). When analyzing the results of treatment of these patients was determined that they had a quick, positive trend without pulmonary complications, and the normalization of the majority of clinical and functional parameters was held on 3–5 day of ABT.

To class 2 7 patients refers whose serum PCT at visit 3 decreased by more than on 95, 6% compared with the data on the visit 1 and CD_4 increased significantly (by more than 335,7%). However, when analyzing the results of treatment of these patients it was found that 6 of them recovered and it was resolution of pneumonia, and 1 (p24) dead. When detailing the cause of sudden death of 1 patient was a massive pulmonary embolism, which was not directly related to intoxication and multiple organ failure, which are the cause of death at severe CAP, and was associated with concomitant varicose veins of the lower extremities.

Class 3 combines the greatest number of cases (37 patients), in which the serum PCT at visit 3 decreased by more than 95, 3% compared with the data of the visit 1 and CD_4 increased significantly (by more than 4, 7%). Despite the fact that this class of patients had episodes of pulmonary complications, the need to replace of the ABT and long term therapy, they had a positive treatment outcome.

Classes 4 and 5 include patients who died from sCAP. In this cases, serum PCT at visit 2 or 3 decreased very slightly (by 1%) or significantly increased (by more than 11, 460% in comparison with the data of the visit 1) and CD_4, which was originally a small, unchanged or decreased by more than 50%.

4. Conclusions:

More than half of patients with severe CAP have violations of the cellular immunity of varying severity.

Features of survival predicting in patients with severe CAP is the account of the pathogenetic mechanisms, namely a complex set of interactions inflammatory markers with immune factors. The most significant laboratory predictors of outcome in patients with severe CAP is individual dynamics of marker CD_4 and inflammatory marker PCT. With a substantial reduction of the serum PCT level and increase of CD_4 counts during the adequate ABT a favorable outcome of severe CAP can expect, whereas the increasing of PCT and decreasing of CD_4, on the contrary, the survival is unfavorable.

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