Studying the prognostic value of the CRP level dynamics in 30 patients with ventilator-associated pneumonia in ICU

[1]Radev Vl, Radev R, Bogdanov Sl, [2]Tsankov L, [3]Tonchev P

[1]Department of ICU, [2]Department of Image diagnostic, [3]Department of Burns and plastic surgery
[1,2,3] Hospital Dr.Georgi Stranski, Medical University of Pleven Pleven, Bulgaria
[1]lyubomirtsankov@yahoo.com

Abstract— **BACKGROUND: Any tissue injury results in an inflammatory response by the body. During this inflammatory process, different changes in the body (called acute-phase response) occur in different organs and systems remote from the inflammatory focus. This response is associated with a change in the concentration of a large number of plasma proteins called acute-phase proteins – CRP, albumin, prealbumin, transferring, etc.**
METHODS: A prospective study on the CRP levels was carried out in the Clinic of Anesthesiology and Intensive Treatment monitoring the CRP levels dynamics in 30 VAP patients from the 1st to the 20th day in order to assess the severity and the possible prognosis on the outcome of the disease. 30 patients aged 57.3 years on average were monitored and assessed by means of the APACHE II scoring system >20.We review the dynamics of the CRP levels in surviving patients and the CRP levels of patients who died.
RESULTS: The CRP levels of the patients studied are significantly increased (from 20 to 100 times higher than normal). There is a tendency to stabilize the CRP levels around the 5th-7th day of the treatment. After the 10th day the CRP levels increase in patients who died later and decrease in surviving patients.
CONCLUSIONS: These features of the dynamics of the CRP levels in patients with VAP can be used as an element for assessing the effect of the therapy and a prognosis of the treatment outcome.

Index terms- **acute phase response, CRP, albumin, prealbumin, transfferin, VAP, APACHE II.**

I. INTRODUCTION

Any tissue injury results in an inflammatory response by the body. During inflammationdifferent changes in the body – called acute-phase response –occur in different organs and systems remote from the inflammatory focus. This reactionis associated with a change in the concentration of a vast number of plasma proteins called acute-phase proteins. They are divided into two groups(1,2,3,4):

1. The first group – those are increasing their plasma concentrations (positive acute-phase proteins) like CRP (C-reactive protein), fibrinogen, etc.
2. Second group – those are decreasing their plasma levels (negative acute-phase proteins). These include albumin, prealbumin, transferrin, etc.).

The CRP belongs to the α2-globulinfraction. Due to its low serum concentrationof below 5 mg/l, it is practically not detected in the proteinogram. It is an extremely sensitive, but nonspecific indicator of an inflammatory damage.

CRP isprimarily synthesizedby hepatocytes; the synthesis is stimulated byantigens, immune complexes, bacteria and fungi, traumas (4-6 hours after the injuries incurred to the body), and inflammatory response. It activates the phagocytosisand the classical complement pathwayand affects the lymphocyte response to mitogens.

The CRP response starts within the first hours, whereas the remaining proteins of the acute phase of inflammation respond after 1-2 days. The progress of inflammation can be estimated by the dynamics of the values of the acute-phase protein (CRP). It should be borne in mind that the normalization of its values, though more often associated with suppression of the inflammatory process, can also be observed in the depletion of the body'sdefensive reservesor in the severe dystrophic damage and impaired liver synthetic function (1,3,4,6,7).

Methods:

To determine whether CRP can be used as anoutcomemarker forthe of patients with VAP. The prospectivestudy was conducted from March 2014 to January 2015 in the ICU of University Hospital "Dr. Georgi Stranski", Pleven. The CPR levels dynamics was observed in 30 patients with VAP from the 1stto the 20thday to assess the severity and the possible prognosis on the outcome of the disease. 30 patients with mean age 57.3 yearswere monitored and evaluatedusingthe APACHE II scoring system > 20.

CPR levels were analysedthrough different statistic methods as a variation and dynamic of average levels, analysis of the relationship between the days of the therapy and the average CRP levels, Fisher's exact test.

Results:

II. IN SURVIVING PATIENTS THE CRP DYNAMICS IS AS FOLLOWS:

A. Analysis of the variation of average CRP levels

The mean value of the CRP indicator for the first day is 83.7mg/l, but the variation in the CRP levels for the individual patients is significant – the spread of the variation calculated as the difference between the highest and the lowest value of the indicator is 376 mg/l (8). The standard deviation is 73, and the coefficient of variation is 87.19%. By the fifth day of the treatment, significant differences are found in the values of the indicator, andin the majority of patients there is an increase in the CRPlevels–the meanvalue for the third day of 106.5 mg/l; and for the 5th day – 106.9 mg/l.Although the average CRP levels for the 7th day are not significantly different from the values for the 3rd and the 5th days, the lower value of the standard deviation 65.06 and of the coefficient of variation 62.18% supports that there is a convergence of the outcomes and a decrease in the differences in the indicators.The standard deviation measures the variation of thevariablecompared to the center of thedistribution, it is influenced by the change of all cases and, therefore it is widely used in assessing the variation/dispersion in the sample(8).

On the 9th day of the therapy /treatment/ there is a visible decrease in the average value of the indicator by 17.8 mg/l, and this process continues on the 10th day – a reduction in the mean value of the indicator by 18.5 mg/l.

The dynamics of the average CRP levels is presentedin Fig.1 and it clearly shows that after the 7th day the CRP levels decrease, between the 10th and 12th days the average levels are almost similar, but after the 12th day the average CRP levels begin to decrease significantly– from 65.6mg/l to 18.9mg/l and begin to converge towards the upper permissible limit for this indicator – CRP <5.
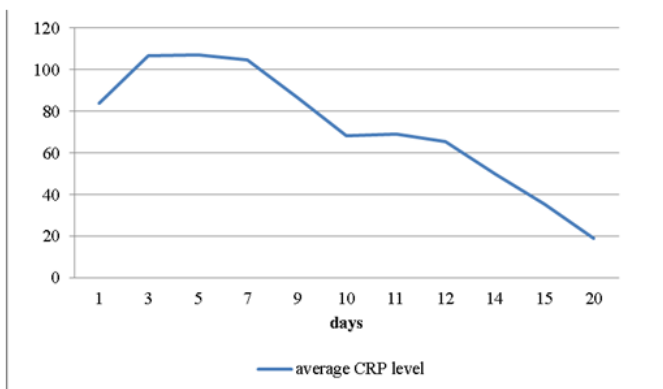

Fig. 1. Dynamics of the average CRP levelsby days

B. Analysis of the dynamics of the mean CRP level by days

The analysis of the dynamics of the mean CRP level is carried out based on the descriptors for time series and by subsequent modelling of the trend in the change of indicators using the method of least squares and the choice of an appropriate trend model based on the competing models. The data on the mean CRP levels is used to calculatethe absolute growth of the indicator compared to its previous value. The

results show that for the 20-day period of treatment of patients, the indicator increases compared to its value for the previous day untilthe 5th day of the treatment (Table 1).

Table I.Dynamics of the average CRP level by days

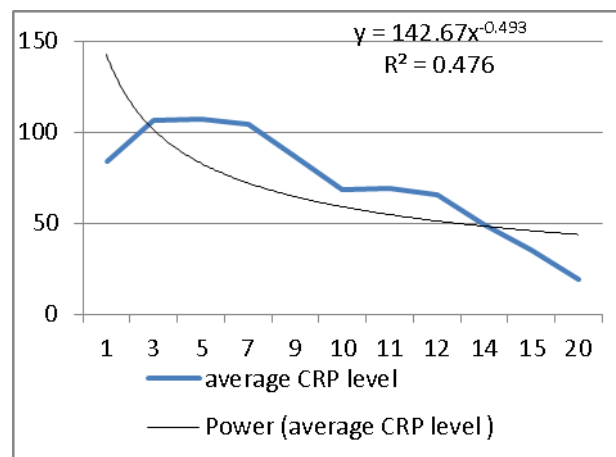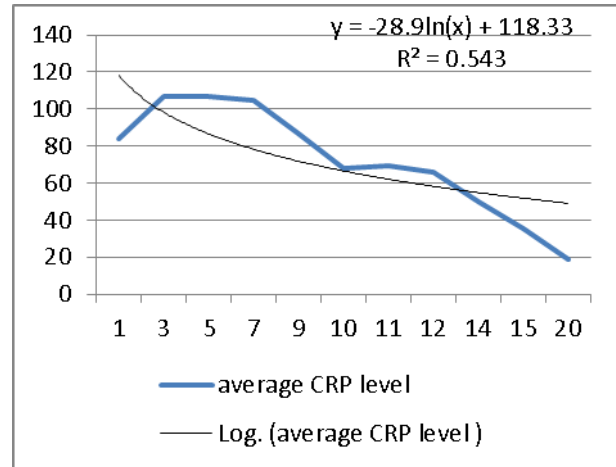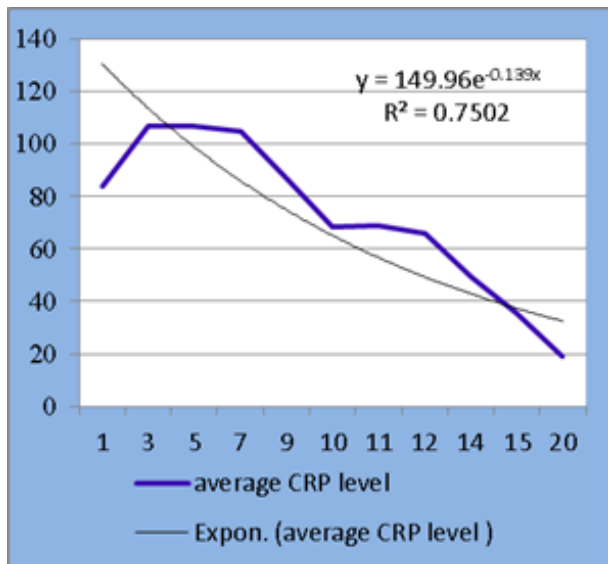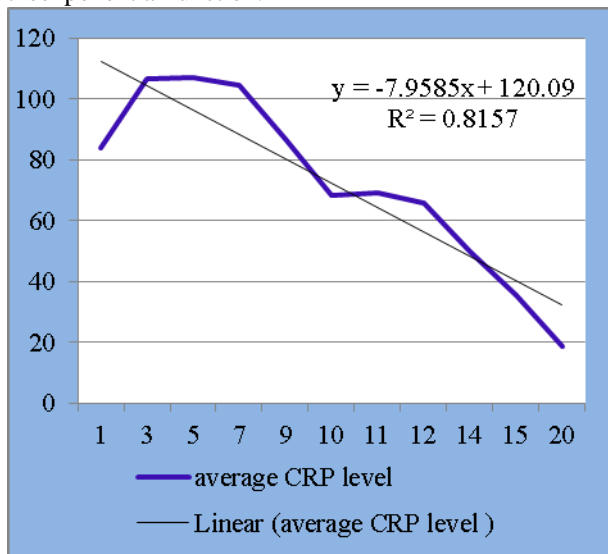| Days	Average CRP level by days	Absolute growth in CRP levels compared to the previous average level	Rate of development of the mean CRP levels compared to the previous averagelevel	Growth rateof the meanCRP levels compared to the previous mean value(%)
1	83.72	-	-	-
3	106.56	22.84	1.272814	27.28141
5	106.92	0.36	1.003378	0.337838
7	104.64	-2.28	0.978676	-2.13244
9	86.8	-17.84	0.829511	-17.0489
10	68.24	-18.56	0.786175	-21.3825
11	69.08	0.84	1.012309	1.23095
12	65.64	-3.44	0.950203	-4.97973
14	49.68	-15.96	0.756856	-24.3144
15	35.56	-14.12	0.715781	-28.4219
20	18.92	-16.64	0.532058	-46.7942

The table shows that there is a process of decreasing the average CRP levelon the 7th day of the treatmentcompared to the value on the 5th day. Between the 7th and the 9th day of the treatment there is a significant drop in the mean CRP level. This is a period of a positive response of the body to the treatment carried out, which isevidenced by the negative growth. The decrease in the average CRP level on the 9th day compared to the 7th day is 17.8 mg/l, and on the 10th day compared to the 9thday –18.5 mg/l. The onset of secondary response,with an increaseof the mean CRP levels on the 11th day,can be considered a critical moment of the treatment.The average CRP levels tend to decrease from 69.1 mg/l on the 11th day, to 49.7 mg/l on the 14th day to reach 18.9 mg/l on the 20th dayreflecting an adequatechange ofantibiotic treatment.Conclusions can be drawn by the values between the 7th and the 11th days about the expected outcome and treatment carried out.

C. Modelling the trend of change of the average CRP levels by days in surviving patients

Modelling the trend of change of themean CRP daily level for the studied period requires testing different models and choosing the most relevant one. The hypothesis of a presence of trend is confirmed by the value of the first-order

autocorrelation coefficient r1=0.912. The theoretical values of the coefficient in degrees of freedom α=0.05have a left-handlimit-0.564 and a right-handlimit 0.360,and the resulting autocorrelation coefficient is outside these limits. Therefore the time series containing data on the average CRP levels by days hada trend (9).

Linear functions are the most commonly used in modelling the trend as they meet the requirements for applying the least squares method. Non-linear models need further transformation, whereby the modelis converted to linear on parameters (10). From a theoretical point of view, the following models can be tested: linear, logarithmic, second-degree polynomial, third-degree polynomial, power and theexponential function.

$$y = -28.9\ln(x) + 118.33$$
$$R^2 = 0.543$$

$$y = -7.9585x + 120.09$$
$$R^2 = 0.8157$$

$$y = 142.67x^{-0.493}$$
$$R^2 = 0.476$$

$$y = 149.96e^{-0.139x}$$
$$R^2 = 0.7502$$

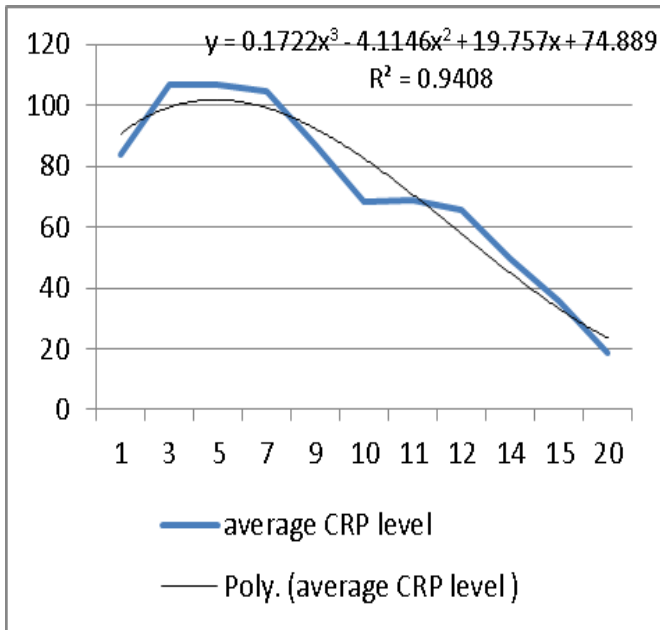$$y = -1.0155x^2 + 4.2272x + 93.691$$
$$R^2 = 0.9193$$
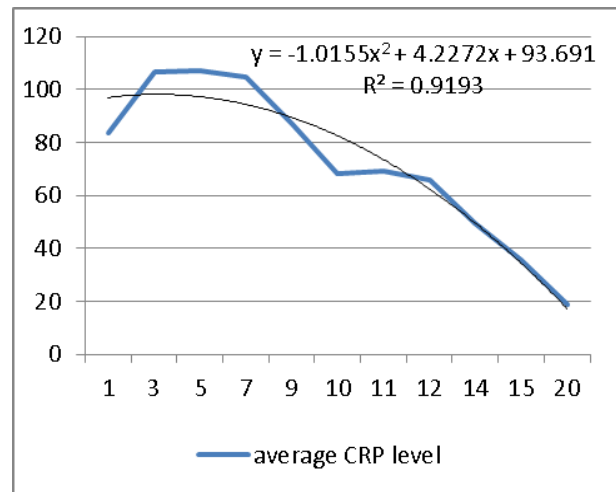
Fig. 2. Presents 6 models of trend containing a graphic image, an equation and a coefficient of determination.

The linear model and the exponential function model are adequate, i.e. they are appropriate for describing the trend of development and show that as the number of days of the therapy increases, the average CRP level decreases. The straight line model hasthehighest coefficient of determination and F-test, but the standard error of the model wassignificant. Themodel with the lowest standard error was selected as the most appropriate.The exponential function hasa smaller standard error as compared to the linear model. Since both models are adequate and describe the trend well enough, we assume that the prognoses derived based on the equation of the exponential function $\hat{y}=149.96e-0.139t$are more accurate due to the smaller standard error of the model.

D. Analysis of the relationship between the days of the
    therapy and the average CRP levels

The regression and correlation analyses are methodologies for studying the relationships between the phenomena, and they measure and quantify the strength of the relationship between them. The power of the relationship between the studied phenomena is measuredusing different methods – coefficients of correlation,determination, and indetermination. The nature of the relationship determines the limits of changeof the correlation coefficient (r)   The correlation coefficients varywithin the range of -1 to +1 (11,12). The relationship between the duration of treatment expressed in a consecutive day and mean CRP levels by days wastested.

The regression equation of the relationship between the day of treatment of the patient and the mean CRPlevels (Fig.3) is as follow $\hat{y}=117.86-4.6799\chi$. The regression coefficient is negative and indicates that the relationship is inverse, namely that as the number of days of treatment increases the average CRP level   decreases. The interpretation of the resulting regression coefficient is that the mean CRP level by days decreases by 4.6799 for one day (12). The calculated correlation coefficient r=0,891847indicates a strong inverse

(negative) relationship between the duration of the treatment and the average CRPlevelfor the respective day of therapy. The regression coefficient is statistically significant (p=0.000225<0.05) (13).
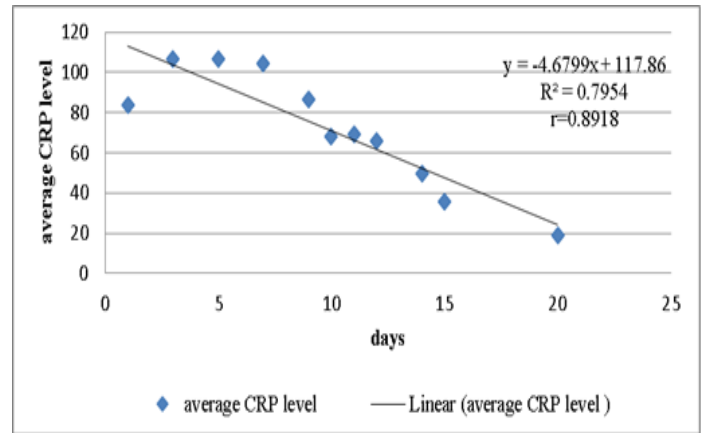

Fig.3. Linear regression model of the relationship between the day of treatment of the patient and the average CRP levels

The resulting regression model is adequate, andFisher's F-test for testing hypotheses – Fem=39.84538>Fsign=0.000139confirms that(12). The predicted and observed values of the CRP levels are very close. This regression model is appropriate for describing the studied relationship and for predicting the expected CRP levels.

III. ANALYSIS OF THE CRP LEVELS OF PATIENTS WHO DIED

A. . Analysis of the variation of the average CRP levels

The mean CRP level for the first day is 120mg/l, but the variation in the CRP levels for the individual patients is significant –215mg/l. The standard deviation is 229.5,and the coefficient of variation is 191.25%. On the third day of the therapy, the average CRP level is increased to 136mg/l. By the 9th day of the treatment, the mean CRP levels by days decrease, but this decline is minimal – the difference in the average values for the ninth and the first day of therapy is only 6.3mg/l. This minimal difference and the maintaining of high CRP levels over the days suggest that the initial therapy is not efficient. From the 10thto the 14th daythe average CRP level begins to increase from 115mg/l to 190mg/l.Chronologically, the loss of patients is as follows: 1 patient dies on the 9thday of the treatment, 1 patient dies on the 10thday, 1 patient dies on the 14th day, and the remaining 2 patients die on the 15thday. The insufficient decrease in the CRP levelsat the 7thday predictsthe loss of patients, and that can clearlybe seen in the average CRP level variation by days.The decrease in the variation in the sample also shows that the values are close to the average, and they were as high as the average for patients who have survived after treatment. The dynamics of the average CRP levels is shown in Fig. 4.It clearly indicates that there is no significant decrease in the CRP values after the 7thday of the treatment, and they remain relatively constant. Fromthe 10th day a process of increasing the average CRP levels begins, and becomes irreversible resulting in a loss of patients.
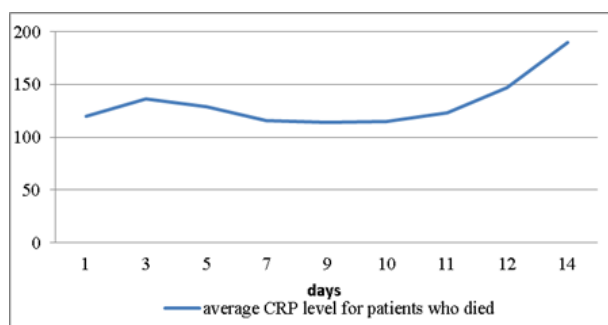
Fig. 4. Dynamics of the mean CRPlevel for patients who died

Fig. 5 shows the dynamics of the average CRP levels for both groups –the surviving patients and the patients who died, which indicates that the average CRP levels and the trend in their variation, betweenthe7th and the 10th days are crucial for the outcome of the treatment.
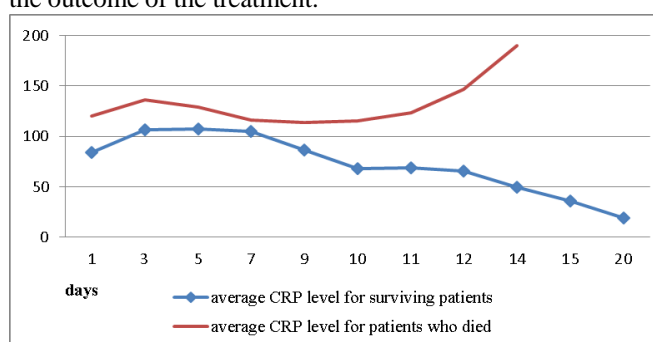

Fig. 5. Dynamics of the average CRP level for the totality of surviving patients and the totality of patients who died

The same conclusions are validated by analyzing the growth rate of the mean CRP levels by days compared to the previous levels.
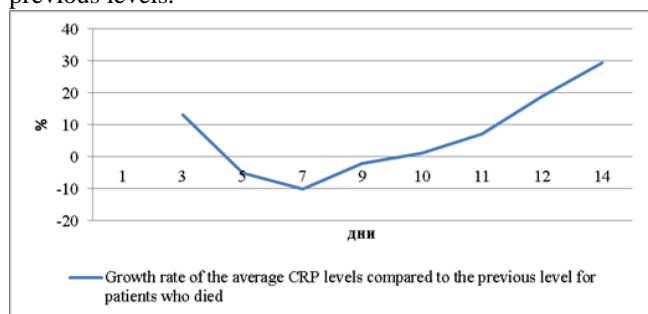

Fig.6. Growth rate of the average CRP levels by dayscompared to the average levels for the previous day regarding the totality of patients who died

The data presented in Fig. 6 shows that if there were no significant improvements by the7th day and between the 7thand 9thday, in the following days,the average CRP begin to rise. The presented dynamics of indicators inFig.7, accurately shows the moment of intersection of the two curves and confirms that the trend of change inthe CRP levels between the 7th and the 11th days is decisive for the outcome of the treatment – if thevalues decrease, the therapy is successful and if the values increase, the therapy is unsuccessful,and the patient dies.
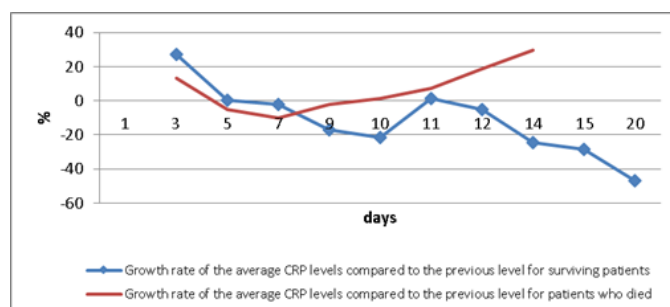

Fig. 7. Dynamics of the growth rate of the average CRP levels compared to the previous levels for the totality of surviving patients andthe totality of patients who died

Discussio:

The CRP levels of the patients studied are significantly increased (from 20 to 100 times higher than normal), which is an expression of the manifested inflammatory response syndrome or the sepsis developed.There is a tendency to stabilize the CRP levels around the 5th-7th day of the treatment.After the 10thday the CRP levels increased in patients who died later and decreased in surviving patients, which demonstrates deterioration of condition or lack of response to therapy.The CRP levels in surviving patients decrease by 4.7 per day on average, and this dependency is particularly indicative after the 10th day.

CONCLUSIONS

These features of the dynamics of the CRP levels in patients with Ventilator Associated Pneumonia can be used as an element for assessing the effect of the therapy and a prognosis of the treatment outcome.

References

[1] Friedman R.B., Anderson R.E., Entius S.M., Hirshberg S.B., Effects of diseases on clinical laboratory tests, Clin. Chem., 1980, 26, (4), (supplementary issue).

[2] Henry J.B., (ED), Todd-Sanford-Davidnohn. Clinical Diagnosis and Management by Laboratory Methods, 16thed., Philadelphia W.B., Saunders Co., 1979.

[3] Krastev Z., Shishikov T., Clinical laboratory and medicine., Sofia, 2005

[4] Shishkov T., Krastev Z., Clinical results in diagnosis process., Medicine, Sofia, 2007.

[5] Pepys M.B., Hirschfield G.M., C-reaktive pro tein: a critical update, The Journal of Clinical Ivestigation, June, 2003, volume 111, № 12, p. 1805-1812.

[6] Povoa P., Coelho L., Almedia E., Fernandes A., et al., C-reactive protein as a marker of ventilator-associated pneumonia resolution: a pilot study, European Respiratory Journal, vol. 25, № 25, p. 804-812, 2005.

[7] Angelova P.,Statistic, Svishtov, Library"Science and education", 2013

[8] Velichkova N., Statistical methods for research and prognosis of social and economical development, Science and education, Sofia, 1981

[9] Ivanov L., Statistical research and prognosis of development,"D.A. Cenov", Svishtov, 2008.

[10] Petrov V., Angelova P., Slaveva K., Statistical methods for research in social area, Library Bisness world №78, "D.A.Cenov", Svishtov, 2006

[11] Съйкова, И., А. Стойкова-Къналиева, С. Съйкова. Статистическо изследване на зависимости. С., УИ "Стопанство", 2002.

[12] Saikova I, Stoikova-Kanalieva A., Stoikova S., Research of statistical dependence, Bisnes, 2002