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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Significance of fibrinogen, interleukin-6, and C-reactive protein as predictors of pleural complications after rib fractures in blunt chest trauma

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SUMMARY

Introduction/Objective Rib fractures are common in blunt chest trauma (BCT), and when they are associated with pleural complications (PC) – pneumothorax, hemothorax and hemopneumothorax – the treatment of these patients is prolonged and difficult. Without the ability to predict PC after rib fractures in BCT, most doctors are forced to initially treat these patients through observation and conservative treatment.

The goal of this research is to determine which of the investigated biomarkers of inflammation – fibrinogen, interleukin-6 (IL-6), and C-reactive protein (CRP) – are significantly associated with the occurrence of PC after rib fracture in BCT, and whether they can be used in stratifying patients for hospitalization and further treatment.

Methods The prospective study included 90 patients with rib fractures caused by BCT. The test group comprised 45 patients with rib fractures and the presence of PC, and the control group consisted of 45 patients with rib fractures without PC. Blood sampling was performed on admission, on the second, third, and fifth day after the injury, and PC were monitored until the seventh day after the injury.

Results Serum values of IL-6 on the second day and fibrinogen and CRP on the second and third day after injury were statistically significantly higher in patients with PC, and IL-6 showed a good discriminative ability in assessing the occurrence of PC on the second day after a rib fracture in BCT.

Conclusion The investigated biomarkers of inflammation – fibrinogen, IL-6, and CRP – can be used as predictors of PC after rib fracture in BCT, and their application can significantly replace clinical observation.

Keywords: blunt chest trauma; rib fractures; pleural complications; fibrinogen; IL-6; CRP

INTRODUCTION

Chest trauma is one of the leading causes of morbidity and mortality in all age groups. Chest injuries are the most frequent injuries followed by head and limb injuries [1]. Mortality in patients with chest injury is 4–60% [1]. Chest injuries are divided into two entities – blunt and penetrating, where blunt chest trauma (BCT) is characterized by injury to structures of the chest without open communication between the pleural space and the external environment [2]. BCT accounts for 10–15% of all trauma cases [3]. BCT is more common than penetrating injury and accounts for more than 90% of chest injuries [1]. Such a high frequency of BCT poses a major social and medical problem [4]. The most common causes of BCT are traffic trauma (in 70% of the injured), injuries at home (very often due to falls from a height or downstairs), and workplace accidents [1, 2, 3].

Rib fractures are common in BCT [1]. Some patients with rib fractures develop pleural complications (PC) – pneumothorax (presence of air in the pleural space), hemothorax (blood in the pleural space), hemopneumothorax (combination of the aforementioned conditions) – which largely affect the outcome of treatment [5]. In patients without rib fractures after BCT, pneumothorax and/or hemothorax occur in 6.7% of cases, while in patients with rib fractures these complications occur in 24.9% (with one or two rib fractures) up to 81.4% (with fracture of more than two ribs) of cases [6].

In cases of BCT with rib fractures special care must be taken since PC can occur within 24–72 hours after the initial injury and examination of the patient, and in elderly patients even within one week of the injury [7]. If PC are not recognized in time, death is also possible [8]. Prompt and accurate diagnosis of

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injuries and PC in BCT is very important since it enhances further medical treatment of these patients.

Without the ability to predict PC after rib fractures in BCT, most doctors are forced to initially treat these patients through observation and conservative treatment, even in the absence of visible injuries, which significantly burdens a country's health care system financially.

Little data can be found on predicting the occurrence of PC after BCT. Also, there is still no clear evidence that inflammatory biomarkers (and particularly which ones) can be used as predictors of PC in rib fractures in BCT.

Immediately after injury, the body's immune system is activated, releasing inflammatory mediators, which are also biomarkers of inflammation [9]. According to the definition of the World Health Organization, biomarkers represent "any substance, structure, or process that is measurable in the body, or its products and effects are measurable, or that predict the incidence of an outcome or disease." Chest trauma does not have "its own" biomarkers, since the role of cytokines and inflammatory biomarkers in BCT has not yet been fully explored [10].

Fibrinogen, interleukin-6 (IL-6), and C-reactive protein (CRP) are among the most significant and frequently used markers of inflammation in clinical practice.

Fibrinogen as an acute phase protein is synthesized in the liver and released into the circulation, and as a damage-associated molecular patterns (DAMP) molecule it is found in the extracellular matrix and is released after trauma-induced tissue damage (especially after blunt trauma) [11]. Fibrinogen participates in blood coagulation, inflammation, mediates interactions between cells and the extracellular matrix, wound healing and neoplastic processes [12]. Rib fractures are accompanied by significant accumulation of fibrin deposits that promote inflammation at the fracture site and in the surrounding tissue [13].

DAMP molecules are endogenous nuclear, mitochondrial, or cytoplasmic molecules that have their physiological role inside the cell, which are released from the damaged or dying cell and/or the extracellular matrix after injury and as mediators indirectly stimulate a "sterile" inflammatory response [14]. As a DAMP molecule, fibrinogen is found in the extracellular matrix and indirectly stimulates a "sterile" inflammatory response after injury [14].

IL-6 is a pro-inflammatory cytokine released by activated monocytes and macrophages and plays a role in amplifying inflammatory signals, thereby activating leukocytes that in turn produce other inflammatory mediators [15]. Also, IL-6 participates in the activation of the complement cascade and coagulation, enhances hematopoiesis and increases vascular permeability [16]. IL-6, after being released from activated macrophages, induces the synthesis and release of acute phase proteins, especially CRP. IL-6 is one of the key pro-inflammatory cytokines in trauma due to its significant association with injury severity and clinical complications [15]. The level of IL-6 in the serum is significantly increasing during the first two hours after the injury and continuing to increase over the next 24 hours, dropping significantly afterwards, reaching its peak four to six hours after the injury, which is significant earlier than the increase in the level of other reactants of the acute phase [17]. Some of the authors state that IL-6 as a reactant of the acute phase is elevated in a patient with BCT and that determining the level of IL-6 can be used to determine the severity of the injury in the first 24 hours after the injury [18].

CRP is an acute-phase protein primarily synthesized in the liver, but also in smooth muscle cells, macrophages, endothelium, lymphocytes, and adipocytes and is released in the plasma [19]. In addition to the fact that CRP is a traditional marker of cardiovascular events, it has been proven that it participates in the process of inflammation and the host's response to infection, in the complement pathway, apoptosis, phagocytosis, the release of nitrogen monoxide and the production of cytokines, especially IL-6 and tumor necrosis factor α [19]. Plasma concentrations of CRP can increase a thousandfold within 24–48 hours, especially in conditions of local and systemic infection and/or after tissue damage [20]. A persistently high level or a secondary increase in CRP indicates the presence of complications and is widely used to diagnose postoperative wound infections and other complications [21]. A sudden increase in CRP levels in traumatized patients with a peak concentration in the period over 48–72 hours is followed by a rapid decrease in CRP concentration and a return to the initial levels before trauma and surgery within two to three weeks [21]. A similar increase in peak CRP concentration on the third and the fifth day after the injury also exists in abdominal surgery [22]. Certain authors determined the initial level of CRP in traumatized persons upon admission to treatment in order to verify the possible later occurrence of infection, whereby they noted that an increase in CRP level was not always associated with infection [19]. CRP is a simple, inexpensive, and sensitive test widely used in medical institutions. The main disadvantage of CRP as a diagnostic tool is its low specificity in determining the cause of inflammation. In addition to its sensitivity, due to its low specificity, CRP does not have a high predictive value in the detection of postoperative complications [22]. Despite the fact that the positive predictive value of CRP is limited, a low CRP level can be used to exclude the existence of complications.

The main hypothesis of this research is that there is a statistically significant relationship between the change in the level of inflammation biomarkers – fibrinogen, IL-6, and CRP – in the plasma and the occurrence of PC in patients with rib fractures caused by BCT, which can be used to stratify patients for hospitalization and further treatment.

The aim of this study is to determine which of the investigated biomarkers of inflammation – fibrinogen, IL-6, and CRP – are statistically significantly associated with the occurrence of PC – pneumothorax, hemothorax and hemopneumothorax – in rib fractures after BCT.

METHODS

This research was conducted in the Clinic for Thoracic Surgery, Emergency Center and Anesthesia Clinic of the University Clinical Center in Niš, Serbia, in the period

from November 2020 to January 2022, and was approved by the Ethics Committee of the Faculty of Medicine in Niš (N⁰. 12-3094/4). Examinations of the patients' biological material were performed at the Center for Medical Biochemistry and at the Immunology Laboratory of the University Clinical Center in Niš. Radiological examinations were performed at the Radiology Center of the University Clinical Center in Niš.

The prospective study included 90 patients with rib fractures caused by BCT. The patients were divided into two groups: the test group and the control group; 1) the test group included 45 patients with rib fractures and PC, and 2) the control group consisted of 45 patients with rib fracture, without PC. Blood sampling was performed on admission, on the second, third, and fifth day after the injury, and complications were monitored until the seventh day after the injury.

Inclusion criteria were as follows: persons of both sexes over 18 years of age, with isolated blunt chest injury and rib fracture who were observed and treated in the aforementioned institutions. Exclusion criteria were the following: persons under 18 years of age, patients with penetrating chest trauma, patients with BCT as part of polytrauma, and pregnant women.

Biomarkers of inflammation examined in the research were: fibrinogen, IL-6, and CRP. The level of fibrinogen in the serum was determined on the coagulometer BE Trombostat, (Behnk Elektronik, Norderstedt, Germany). Reference values for fibrinogen were 2–4 g/l. The level of IL-6 in the serum was determined by the immunochemical electrochemiluminescence immunoassay method on the immunochemical analyzer Cobas e411 (Roche, Basel, Switzerland). IL-6 reference values were 0.0–40.0 pg/ml. Serum CRP values were determined by standard International Federation of Clinical Chemistry methods on a Beckman Coulter/Olympus AU680 biochemical analyzer. Reference values for CRP were 0.0–5.0 mg/l.

PC are marked as: pneumothorax, hemothorax and hemopneumothorax. The diagnosis of PC was made through anamnestic, clinical examination and radiological examinations – standard radiography and multislice spiral computed tomography of the chest. All patients with PC underwent therapeutic chest drainage.

Statistical analysis was performed in the R software package (R Core Team, Vienna, Austria) [23]. Data are presented as mean ± standard deviation, or frequency and percentage. Comparison of continuous variables was performed by t-test and Mann–Whitney test. Comparison of categorical characteristics was performed using the χ^2 test. The discriminative ability of the tested biomarkers was assessed by receiver operating characteristic curve analysis. The null hypothesis was tested with a significance level of $p < 0.05$.

RESULTS

The study included 90 subjects (74 male and 16 female subjects). The demographic, clinical and biochemical characteristics are provided in Table 1. The mean age of the enrolled patients was 61.97 ± 13.87 (min 25 years, max 92 years). At the first measurement, there was no statistically significant difference in the investigated clinical parameters (Table 1).

Table 1. Demographic and clinical characteristics in groups

Group	Complications		Other		p
Age†	62.91 ± 14.32		61.05 ± 13.51		0.535[1]
Sex‡					
Male	37	(82.2%)	37	(82.2%)	1.000[2]
Female	8	(17.8%)	8	(17.8%)	
Number of ribs‡					
1	4	(8.9%)	9	(20%)	
2	8	(17.8%)	3	(6.7%)	
3	8	(17.8%)	5	(11.1%)	
4	6	(13.3%)	4	(8.9%)	
5	4	(8.9%)	6	(13.3%)	
6	3	(6.7%)	7	(15.6%)	
7	7	(15.6%)	1	(2.2%)	
8	1	(2.2%)	0	(0%)	
10	2	(4.4%)	0	(0%)	
11	1	(2.2%)	0	(0%)	
Multiple	1	(2.2%)	10	(22.2%)	
Glycemia†	7.18 ± 2.29		9.44 ± 11.05		0.812[3]
Fibrinogen†	5.45 ± 1.81		5.05 ± 1.28		0.453[3]
D-dimer†	1824.24 ± 1882.86		1917.93 ± 2925.19		0.245
CRP†	33.5 ± 37.63		24.45 ± 31.46		0.188[3]
PCT†	0.23 ± 0.39		0.24 ± 0.37		0.616[3]
Se†	19.49 ± 16.11		20.56 ± 18.93		0.716[3]
Uric acid†	292.69 ± 111.35		279.45 ± 100.99		0.704[3]

CRP – C-reactive protein; PCT – procalcitonin; Se – sedimentation;
[1]t-test;
[2]the χ^2 test;
[3]Mann–Whitney test;
†data are presented as mean ± standard deviation;
‡data are presented as count (%)

The values of fibrinogen, IL-6 and CRP on the second day were significantly higher in patients with PC after rib fractures in BCT ($p = 0.029$, $p = 0.017$, and $p = 0.025$, respectively). The values of fibrinogen and CRP on the third day were significantly higher in patients with PC after rib fractures in BCT ($p = 0.008$, $p = 0.008$) (Table 2).

The value of IL-6 on the second day was shown to have a good discriminative ability in assessing PC after rib fracture in BCT (AUC 0.782, $p = 0.029$). The cutoff value was estimated at 21.33 pg/mL (Table 3) (Figure 1).

DISCUSSION

This is the first prospective study in which the association between PC after rib fracture in BCT and serum levels of fibrinogen, CRP and IL-6 is statistically linked and revealed.

Recognizing which of the patients with rib fractures in BCT will develop PC is important for preventing them, and our research follows that line of thinking.

Table 2. Levels of inflammation biomarkers in pleural complication and non-complication groups after ribs fracture in blunt chest trauma as a function of time data are presented as mean ± SD

	IL-6	Fibrinogen	CRP
Day I			
Complications	53.13 ± 35.9	5.45 ± 1.81	33.5 ± 37.63
Others	49.49 ± 83.5	5.05 ± 1.28	24.45 ± 31.46
p-value[1]	0.181	0.453[3]	0.188[3]
Day II			
Complications	**29.57 ± 22.52**	**6.26 ± 1.65**	**57.8 ± 44.8**
Others	**12.63 ± 7.83**	**5.46 ± 1.33**	**41.37 ± 49.51**
p-value[1]	**0.029**	**0.017**	**0.025**
Day III			
Complications	21.39 ± 14.38	**6.86 ± 1.69**	**59.16 ± 42.69**
Others	13.78 ± 10.14	**5.95 ± 1.47**	**39.19 ± 38.71**
p-value[1]	0.105	**0.008**	**0.008**
Day V			
Complications	15.48 ± 9.73	6.5 ± 1.69	39.99 ± 39.2
Others	13.16 ± 10.87	6,00 ± 1.4	31.01 ± 42.35
p-value[1]	0.439	0.065	0.094

CRP – C-reactive protein;
[1]Mann–Whitney test

Table 3. The area under receiver operating characteristic curve, cut-off value, sensitivity and specificity in pleural complications assessment

	AUC	95% CI	Cut off value	Sensitivity (%)	Specificity (%)
IL-6	0.782	0.582–0.982	21.33	60	90.9
Fibrinogen	0.627	0.379–0.875	5.68	60	63.6
CRP	0.645	0.401–0.890	17.90	70	54.5

CRP – C-reactive protein; AUC – the area under the receiver operating characteristic curve; CI – confidence interval

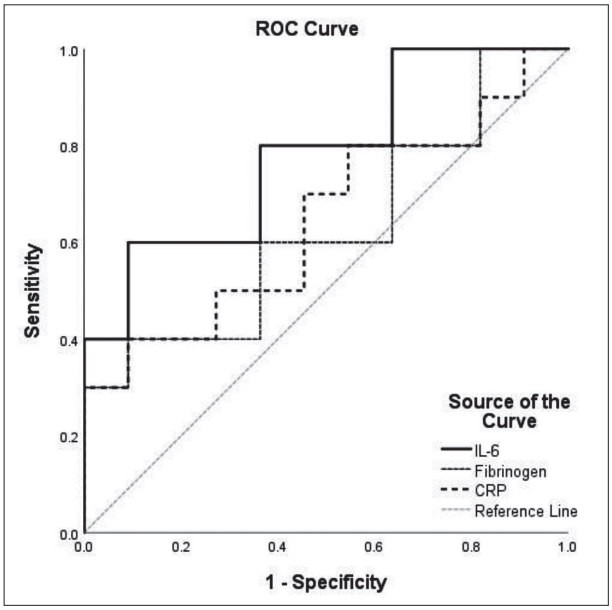

Figure 1. The receiver operating characteristic (ROC) curve of IL-6, fibrinogen, and C-reactive protein (CRP) on the second day in pleural complication assessment

Serum values of IL-6 on the second day and fibrinogen and CRP on the second and third day after injury in BCT were statistically significantly higher in patients with PC. This indicates that, as frequently used clinical markers of inflammation, fibrinogen, CRP and IL-6 can be used to predict the occurrence of PC after rib fractures in BCT, their timely repair, and that they can significantly replace clinical observation in these patients.

During our research we found out that there was an increase in blood fibrinogen values on the second and third day after injury in patients with PC in BCT with rib fracture, and not in the later period, which is in agreement with the results of the paper [24]. We believe that the role of fibrinogen as a DAMP molecule in this case is dominant in promoting the inflammatory reaction and in the process of coagulation in inflammation.

Our research has also shown that IL-6 levels were statistically significantly higher on the second day after injury in patients with PC after rib fractures in BCT. Moreover, our research has shown that there is a correlation between elevated levels of IL-6 in the early stages of trauma and the severity of the injury, which is in agreement with the results in the paper [25]. Also, our results are consistent with the view that IL-6 correlates with the severity of the injury, and not with the elapsed time since the injury, which is in agreement with the results in the paper [26]. All our patients who were exposed to violent BCT and who developed PC had elevated IL-6 values, which is in agreement with the previous findings [17].

The results of our research indicate that IL-6 can be used to predict the occurrence of PC after BCT with rib fracture, since serum levels of IL-6 on the second day after the injury are statistically significantly higher in patients with PC. The hypothesis that the level of IL-6 can be used in the stratification of patients for therapeutic intervention is confirmed by our finding of a good discriminative ability of IL-6 in the assessment of the occurrence of PC on the second day after rib fracture in BCT. Also, our results show that IL-6 levels are increased after injury and that IL-6 can be used as a biomarker in BCT, which is in agreement with other papers [10, 25].

In our research, we have come to the conclusion that in patients with PC and rib fracture in BCT, CRP values are statistically significantly higher on the second and third day after the injury. It was stated in agreement with the results that CRP values are highest on the second and third postoperative day, after orthopedic and abdominal surgery operations due to trauma [22, 27].

In traumatized patients, special attention should be paid to the cause of the increase in CRP levels, which can also be applied in patients with BCT [19]. Trauma and surgical intervention (due to tissue damage) cause a strong inflammatory response. All our patients with PC after rib fracture in BCT underwent surgical intervention – drainage of the chest, and we believe that the finding of the elevated CRP values in them is in agreement with the findings that the difference in peak CRP levels is partly a consequence of trauma, and partly a consequence of the surgical procedure after trauma [27]. Since an increase in the level of CRP also occurs after surgical procedures, and patients with PC in a large number of cases undergo therapeutic drainage of the chest, caution is needed in declaring CRP as a "marker of the occurrence of PC in BCT".

Some authors believe that low levels of CRP can be used to exclude the existence of complications in orthopedic surgery [27]. Our results show that normal CRP values significantly exclude the existence of PC in BCT. Regardless of that, we believe that additional research is needed in order to confirm with even greater certainty that a low level of CRP, analogous to the previous one, can be used to rule out PC after a rib fracture in BCT.

The results of our research are in agreement with similar results that can be found in the available literature related to trauma in orthopedics and abdominal surgery.

CONCLUSION

The available literature offers scarce data on the possibility of using fibrinogen, IL-6 and CRP as predictors of possible PC after rib fractures in BCT.

Based on the results of our research, it can be concluded that biomarkers of inflammation, fibrinogen, IL-6 and CRP can be used as predictors of PC after rib fractures in BCT.

The combination of fibrinogen, IL-6 and CRP after rib fracture in BCT can significantly replace clinical observation in these patients.

In patients with PC after rib fractures in BCT, fibrinogen has the highest values on the second and third day after the injury and as such can be used as a predictor of PC.

In patients with PC after rib fractures in BCT, IL-6 has the highest values on the second day after the injury. Due to its good discriminative ability in assessing the occurrence of PC on the second day after rib fracture in BCT, IL-6 can be used in stratifying patients for therapeutic intervention.

CRP in the prediction of PC is significant on the second and third day after a rib fracture in BCT. CRP values within the normal range largely exclude the existence of PC after rib fractures in BCT. If there is an increase in the level of CRP, special attention should be paid to searching for the cause of this increase.

Further prospective studies are needed to fully reveal the role of other inflammatory biomarkers in patients with rib fracture complications in BCT.

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Значај фибриногена, интерлеукина-6 и Ц-реактивног протеина као предиктора плеуралних компликација после прелома ребара у тупој трауми грудног коша

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САЖЕТАК

Увод/Циљ Преломи ребара су чести у тупој трауми грудног коша (ТТГК), а када су удружени са плеуралним компликацијама (ПК) – пнеумотораксом, хематотораксом и хематопнеумотораксом, лечење ових пацијента је продужено и отежано. Без могућности да се предвиде ПК након прелома ребара у ТТГК, већина лекара је приморана да иницијално у лечењу ових пацијената примени опсервацију и конзервативни третман.

Циљ истраживања је утврђивање који су од истраживаних биомаркера инфламације – фибриноген, ИЛ-6 и ЦРП у статистички значајној мери повезани са настанком ПК након прелома ребара у ТТГК, што би се користило у стратификовању пацијената за хоспитализацију и даље лечење.

Метод Проспективним истраживањем било је обухваћено 90 пацијената са преломима ребара изазваних ТТГК. Групу испитаника чинило је 45 пацијената са преломом ребара и присутним ПК, а контролну групу чинило је 45 пацијената са преломом ребара без ПК. Узорковање крви је вршено при пријему, другог, трећег и петог дана од повређивања, а праћење појаве ПК је било до седмог дана од повређивања.

Резултати Серумске вредности ИЛ-6 другог дана и фибриногена и ЦРП другог и трећег дана по повређивању биле су статистички значајно веће код пацијента са ПК, а ИЛ-6 је показао добру дискриминативну способност у процени настанка ПК другог дана по прелому ребара у ТТГК.

Закључак Испитивани биомаркери инфламације – фибриноген, ИЛ-6 и ЦРП могу се користити као предиктори ПК након прелома ребара у ТТГК и њихова примена у значајној мери може заменити клиничку опсервацију.

Кључне речи: тупа траума грудног коша; преломи ребара; плеуралне компликације; фибриноген; ИЛ-6; ЦРП