Follow-up of inflammatory markers after initiation of antibiotic therapy in emergency department - comparison of clinical practice and guidelines

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“Follow-up of inflammatory markers after initiation of antibiotic therapy in emergency department - comparison of clinical practice and guidelines"

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Abbreviations

CRP: C reactive protein

PCh: Phosphocholine

PCT: Procalcitonin

APR: Acute phase reactants

SAA: Serum amyloid A

ESR: Erythrocyte sedimentation rate

CAP: Community acquired pneumonia

ICAM-1: Intercellular adhesion molecule-1

ICAM-2: Intercellular adhesion molecule-2

fMLF: Formyl-methionyl-leucyl-phenylalanine

PRRs: Pattern recognition receptors

PAMPs: Pattern-associated molecular patterns

IFN-α: Interferon-alpha

IFN-γ: Interferon-gamma

TNF-α: Tumor necrosis factor-alpha

MAC: Membrane attack complex

HLA: Human leukocyte antigen

NK cells: Natural killer cells

ED: Emergency department

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SUMMARY

Follow-up of inflammatory markers after initiation of antibiotic therapy in emergency department - comparison of clinical practice and guidelines

Hana Franić

Inflammatory markers are commonly used laboratory determinants of infective and inflammatory conditions, especially those used in emergency department since they are widely available, affordable, and rapidly interpreted. Therefore, we have investigated CRP values and leukocyte count as two laboratory determinants for initiation of antibiotic therapy, as well as their relative and absolute differences within the 24 hours and effect of those differences on clinical outcome. We believed it was of critical importance to investigate this correlation in the setting of emergency department since that is where most acutely ill patients will initially present, but also due to very scarce and often unclear research that has been done in this subject so far.

Our study included 300 patients, with an average time between first and second CRP sample being 14 ± 6 hours, and the average time between antibiotic initiation and control CRP 11 ± 6 hours. We found no correlation between changes in values and the clinical picture of these patients, both regarding CRP and leukocyte values. This means that whether patients' condition was declining, improving, or staying the same, CRP control values were not significantly changing respective of those conditions. Regarding CRP control values corelation with clinical outcome, analysis showed statistically significant correlation between changes in absolute and relative CRP values and decision about hospitalization, discharge, observation or change in antibiotic therapy. Second statistical significance was found in case where we compared multiple variables influencing the clinical outcome, and that was that the decision about further treatment did correlate with change in leukocyte count. Since no correlation was found in all other data analysis (for example no correlation was found between clinical picture and clinical outcome), it only proves that clinical practice relies on incorrect assumption that changes in CRP values in less than 24h can correctly direct physician's decision on further course of treatment including, continuation or change in antibiotic therapy.

We concluded that often unnecessary CRP measurements are done, without any benefit of such practice in the emergency department. CRP samples are taken randomly in a sense that within

this 24-hour frame, most controls were taken within half of that time, indicating that physicians might re-check CRP levels just for their reassurance but essentially without those values influencing further treatment of the patient. We believe that data we gathered proved numerous unnecessary controls of CRP, but even more importantly that clinical decisions based on those incorrectly interpreted CRP changes, especially regarding antibiotic treatment, potentially does not benefit these patients.

Keywords: Inflammatory markers, C reactive protein, Leukocytes, Emergency department, Antibiotic therapy

SAŽETAK

Kontrola markera upale nakon početka antibiotske terapije u hitnom prijemu - usporedba prakse i smjernica

Hana Franić

Upalni markeri uobičajene su laboratorijske odrednice infektivnih i upalnih stanja, posebice oni koji se koriste u hitnoj službi jer su široko dostupni, pristupačni te se mogu brzo interpretirati. Stoga smo istražili vrijednosti CRP-a i broj leukocita kao dvije laboratorijske odrednice inicijacije antibiotske terapije, njihove relativne i apsolutne razlike unutar 24 sata te učinak tih razlika na klinički ishod. Smatrali smo da je od ključne važnosti istražiti ovu korelaciju u pozadini objedinjenog hitnog prijema jer se tamo inicijalno i javlja većina akutnih bolesnika, ali i zbog vrlo oskudnih i često nejasnih istraživanja koja su do sada provedena na ovu temu.

Ovo istraživanje obuhvatilo je 300 pacijenata, s prosječnim vremenom između prvog i drugog uzorka CRP-a od 14 ± 6 sat, a prosječnim vremenom između početka uzimanja antibiotika i kontrolnog CRP-a 11 ± 6,1 sat. Nismo pronašli korelaciju između promjena vrijednosti i kliničke slike ovih bolesnika, kako u pogledu CRP-a tako i vrijednosti leukocita. To znači da bez obzira na to da li se stanje bolesnika pogoršavalo, poboljšavalo ili ostajalo isto, kontrolne vrijednosti CRP-a nisu se značajno mijenjale u odnosu na ta stanja. Što se tiče korelacije kontrolnih vrijednosti CRP-a s kliničkim ishodom, analiza je pokazala statistički značajnu korelaciju između promjena apsolutnih i relativnih vrijednosti CRP-a i odluke o hospitalizaciji, otpustu, promatranju ili promjeni antibiotske terapije. Druga statistička značajnost ustanovljena je kada smo uspoređivali više varijabli koje utječu na klinički ishod, a to je da je odluka o daljnjem liječenju korelirala s promjenom broja leukocita. Budući da u svim drugim analizama podataka nije pronađena korelacija (na primjer, nije pronađena korelacija između kliničke slike i kliničkog ishoda), to samo dokazuje da se klinička praksa oslanja na pogrešnu pretpostavku da promjene vrijednosti CRP-a u manje od 24 sata mogu ispravno usmjeriti odluku liječnika o daljnjem tijeku liječenja uključujući i nastavak ili promjenu antibiotske terapije.

Zaključili smo da se često rade nepotrebna mjerenja CRP-a, a da takva praksa u objedinjenom hitnom prijemu nema nikakve koristi. Uzorci CRP-a uzimaju se nasumično u smislu da je unutar 24-satnog okvira većina kontrola uzeta unutar polovice tog vremena, što ukazuje da bi liječnici mogli ponovno provjeriti razine CRP-a samo radi vlastite sigurnosti, ali bez da ti rezultati u

konačnici utječu na daljnji tijek liječenja. Vjerujemo da su podaci koje smo prikupili dokazali brojne nepotrebne kontrole CRP-a, ali što je još važnije da kliničke odluke temeljene na tim netočno protumačenim promjenama CRP-a, posebice vezane za liječenje antibioticima, potencijalno ne koriste ovim pacijentima.

Ključne riječi: Upalni markeri, C reaktivni protein, Leukociti, Objedinjeni hitni prijem, Antibiotska terapija

1. PREFACE

1.1 C reactive protein and APRs

Since infections are one of the most common reasons for presentation to emergency department (abdominal, respiratory, urinary, and skin infections that are the most common) together with other common inflammatory conditions, we wanted to further explore how these conditions were processed in the setting of emergency room. As bacteria are number one causes of infections, and antibiotics our primary therapy in those cases we wanted to explore the background of adequate therapy initiation in these patients. The question arises whether treatment is based on clinical presentation (signs and symptoms) or on the laboratory values (CRP levels and leukocyte count as the most basic ones), or perhaps on both. Investigation of CRP as a guideline for initiation and more importantly as a measure of response to therapy is crucial, and this debateable opinion is a topic of a lot of research in the last 20 years. As our main goal was to compare the clinical practice and guidelines, along the way we discovered literature on direct use of CRP is scarce and often contradictory. Since exact guidelines about the correct use and interpretation of CRP values don't exist, there is an accepted clinical practice (proven by some studies regarding specific clinical conditions) that effect of antibiotic is evaluated by control CRP taken at least 24 hours after initiation of treatment, including even 48-72 hours.

C reactive protein (CRP) is synthesized by the liver as a response of an organism to any type of inflammation. This protein is a pentamer, named after C carbohydrate of pneumococcal antigen after it was discovered in 1930 at the Rockefeller University (1) Human CRP is made up of five identical subunits which bind to phosphocholine (PCh) in a $Ca2^{+}$ - dependent manner. (2) Being a reactive protein (acute phase reactant) means its concentration rises early in the course of the disease, and peaks within 48-72 hours. Once the hepatocytes are stimulated by cytokines, mostly IL-6, concentration of CRP rises within 4 to 6 hours and doubles every 8 hours. (3) The sole determinant of circulating CRP concentration is its synthesis rate, which increases proportionally with the intensity of inflammatory process stimulating CRP production, and vice-versa. (4) Once the CRP is released, it binds to polysaccharides in microorganisms, activating the classical complement pathway of innate immunity and commencing the host's defence. Important factors for rising of CRP are also some non-inflammatory determinants such as age, sex, and race. Any inflammation can elevate CRP levels, most commonly infections, but also a very large group of non-infectious inflammatory conditions such as autoimmune diseases,

malignant tumors, surgeries and traumas, burns, smoking, uremia, cardiac ischemia (Acute coronary syndrome), vigorous exercise and psychiatric diseases. (3)

Table 1. C reactive protein elevations in various conditions, according to “Clinical chemistry, Oxford handbook of clinical medicine”

MARKED ELEVATION	NORMAL TO SLIGHT ELEVATION
Bacterial infection	Viral infection
Abscess	Steroids/ Estrogens
Crohn’s disease	Ulcerative colitis
Connective tissue disorder (except SLE)	SLE
Necrosis (eg. Myocardial infarction)	Atherosclerosis
Neoplasia	Morbid obesity
Trauma	

CRP also acts as an opsonin. Mortensen and colleagues were the first to demonstrate CRP's ability to mediate the phagocytosis of sensitized erythrocytes, particularly in the presence of a complement source. This process, known as opsonization, is a key mechanism by which CRP contributes to the host defence against infections. (5) Opsonization is an immune process mediated by opsonins to tag foreign pathogens for elimination by phagocytes. These molecules overcome the repellent force between the negative cell walls and promote uptake of the pathogen by the macrophage, therefore aiding in antimicrobial destruction and preventing the spread of disease.(6) When investigating acute-phase reactants (APRs) important distinctions need to be made. There are two groups of proteins that are secreted in response to tissue inflammation: mediators and inhibitors. Respectively this means APRs are divided into proteins whose concentration increases and those whose concentration decreases in response to inflammatory stimuli.(4)

APRs is a heterogenous group which includes the following: CRP, Procalcitonin (PCT), serum amyloid A (SAA) protein, alpha-1 antitrypsin, fibrinogen, ferritin, haptoglobin, ceruloplasmin, complement components C3 and C4 and a nonprotein APR, Erythrocyte sedimentation rate (ESR). Normally there is a small quantity of these proteins in the plasma but in inflammatory synthesis of these proteins by the liver is increased, depending on the type of stimulus. The

mentioned increase is a process mediated by proinflammatory cytokines: Il-6, IL-1, TNF-alpha and Interferon gamma. Certain acute-phase proteins have been used to diagnose and follow the course of diseases or as tumor markers, therefore there is broad spectrum of clinical use of dynamics of APR.

Proteins decreasing in response to inflammation are albumin, transferrin, transthyretin, and retinol binding proteins (negative APRs). A reduction in albumin level is characteristic of conditions such as infection, malignancy, trauma, surgery and inflammatory disease, all states that will result with concomitant elevation of APR mediators. (7)

1.2 Inflammation and inflammatory response

In acute inflammation, host response will be initially mediated by interaction between the cells of innate immunity and the soluble molecules they secrete. The inflammatory response will begin with local tissue injury or infection, damaging the epithelial cells that consequently produce cytokines and antimicrobial peptides. These products will cause early infiltration of this local tissue with all types of phagocytic cells. Within this inflamed tissue other mediators such as leukotrienes, prostaglandins and kinins will cause vasodilation and increased vascular permeability, allowing increased transport of both fluid and inflammatory cells. Phagocytic cells at the site will release their pro-inflammatory cytokines, which will in turn act systemically on hypothalamus to produce fever, and on liver to stimulate production of APRs.(8)

Once the cytokines are released in the circulation, the transport of activated neutrophils and monocytes to the infection site will begin. Neutrophils are mobilized from the blood to sites of infection or inflammation through the leukocyte adhesion cascade. As endothelial cells near the affected area become activated, and express adhesion receptors like E- and P-selectins they will bind to glycoprotein ligands on neutrophils. This process will enable neutrophils to roll along the endothelium. Chemokines then activate the neutrophils, increasing the affinity of β2 integrins. The integrins bind to ligands such as intercellular adhesion molecule-1 (ICAM-1) and ICAM-2 on endothelial cells, resulting in firm adhesion of the neutrophils. Subsequently, neutrophils transmigrate into peripheral tissues. Once in the tissues, they follow chemoattractant gradients, such as formyl-methionyl-leucyl-phenylalanine (fMLF) and the anaphylatoxin C5a, to perform their functions.(9)

Inflammation is reflected by the laboratory findings with multiple patterns, most commonly as leukocytosis (caused by transport of activated neutrophils and monocytes to the infection site) and elevation of C-reactive protein levels. CRP acts as activator of complement, binding to Fc receptors. Interaction of CRP with Fc receptors results in generation of proinflammatory cytokines (Il-1, IL-6, TNF-alpha) that enhance the inflammatory response. Although IgG also serves as an activator of complement cascade that specifically recognizes distinct antigenic epitopes, CRP recognizes altered self and foreign molecules based on pattern recognition. Therefore, CRP acts as a surveillance molecule for altered self-molecules and certain pathogens. This pattern of recognition provides early defence and produces a proinflammatory signal and activation of the humoral, adaptive immune system.(5)

1.3 The immune system

Immunity as a term describes an ability to resist a particular disease, consequentially accomplishing protection of the organism from an infection. This is achieved either by preventing development of pathogenic organisms (which is mostly done by innate immunity) or by counteracting the effects of their products (adaptive immunity). The mentioned two types of immune system, immune and adaptive immunity, function in their own ways but also interact to provide optimal immunological defence. Innate immunity provides a fast and nonspecific response, while adaptive offers a slower but more precise response. (10)

Innate immunity

Innate immunity, programmed as a basic defence mechanism from any infection or disease, includes physical and anatomical barriers, phagocytic cells (neutrophils, monocytes, and macrophages), molecules such as acute phase reactants, and natural killer cells. Innate immunity resides on the principle of recognition of general structure of microorganisms not found in mammals and can produce the hosts response within minutes.

Physical barriers include tightly bound keratinized skin cells and hydrophobic fats that additionally repel water and microorganisms. Another type of barrier preventing microorganism growth is low ph value and low oxygen level. Lysozyme, ammonia and defensins as components of sweat also provide a type of barrier that acts on structural integrity of bacterial cell membranes together with their other antimicrobial properties.(11) Mucosal membranes of respiratory, gastrointestinal, and

urogenital tract are basic internal anatomical barriers, each with their specific properties, respectively respiratory cilia, gastric hydrochloric acid and amylase from the saliva, and unidirectional flow of urine together with the presence of antimicrobial factors in urine.(12) Additionally, microbiome composed of commensal endogenous bacteria provides yet another crucial type of barrier against the invading pathogens.

Phagocytes are, as their name emphasizes, specialized inflammatory cells responsible for phagocytosis, ingestion and destruction of microorganisms. These cells express Toll-like receptors, which assist in clearing a wide range of microbial pathogens and their products. Additionally, phagocytes serve as significant sources of both pro- and anti-inflammatory cytokines, thereby engaging in host defence through diverse mechanisms.(13) Neutrophils, monocytes and macrophages are all types of phagocytes that express surface receptors PRRs (Pattern recognition receptors) that will recognize PAMPs (pattern-associated molecular patterns). PAMPs are diverse molecules present as bacterial cell wall components, bacterial DNA and viral double-stranded RNA. (11) While the recognition of microorganisms is provided through PRRs, the process of engulfment itself is enhanced by opsonization. Opsonins include acute phase proteins such as CRP and complement, and antibodies produced by the adaptive immune system. These molecules accomplish the process of phagocytosis by binding both to the pathogen and phagocytes receptors, connecting the two to allow intracellular pathogen destruction followed by generation of pro-inflammatory cytokines.(11)

Cytokines are signalling proteins with multiple overlapping roles in cellular communication and recognition. (8)They significantly influence the immune system by regulating cell trafficking and the development of immune tissues and organs.(14) Cytokines and their signalling pathways lead to changes in gene transcription and cellular function, all because of their ability to bind specific receptors and activate downstream pathways.(8) Some of the most important cytokines in regulation of immune response include: Interferon-alpha (IFN-α), Interferon-gamma (IFN-γ), Tumor necrosis factor-alpha (TNF-α) and Interlukins-1,2,4,6,12,17,22. Their actions very significantly, including activation of all specific types of cells, increased expression of other cytokines, stimulation of recruitment and proliferation, maturation and antibody production and induction of apoptosis.

The complement system, comprising a tightly regulated network of proteins, plays a crucial role in host defence and inflammation. Its activation leads to opsonization of pathogens, facilitating

their removal by the phagocytes.(15) These proteins are produced by the liver and released into the circulation, where they can activate and initiate a rapid amplifying cascade. (8) The mechanisms of activation include the Alternate, Classical and Lectin pathway, all of which result in the activation of C3 component. C3 activates the final common pathway, creating a membrane attack complex (MAC) composed of C5-C9 components of complement.

Natural killer cells are unique type of lymphatic cells that have a major role in defence mechanisms from viral infections and tumours. They have features of both innate and adaptive immunity, respectively they are not antigen-specific, but they do morphologically resemble lymphocytes and recognize similar ligands(8)Since they have the ability to recognize human leukocyte antigen (HLA), NK cells remain tolerant to bodies own healthy cells. When some cells do become infected by virus or undergo malignant change, there is downregulation of HLA, and at that point NK cells attack those abnormal cells. The ways of attack differ, either mediated by perforins (pore-forming proteins) that NK secrete, or by proteolytic enzymes (granzymes) that eventually induce apoptosis. They also mediate their antiviral and anti-tumor effect by cytokines they produce, such as previously mentioned TNF-α and IFN-γ. (11)

Adaptive immunity

If the innate immune system fails to effectively combat a pathogen, the adaptive immune system is activated. It has three main characteristics: precise specificity, adaptability to various molecules, and memory for subsequent encounters. The adaptive response involves humoral immunity, where B cells produce antibodies, and cellular immunity, where T cells release cytokines to affect other cells and directly eliminate targets. These collaborate closely with the innate immune system to enhance overall immune effectiveness. (8) Lymphoid organs are vital parts of adaptive immunity. Primary lymphoid organs, such as the bone marrow and thymus, are involved in lymphocyte development and maturation. Secondary lymphoid organs, like the spleen, lymph nodes, and mucosa-associated lymphoid tissue, trap and interact with foreign substances. The thymus is responsible for T-cell maturation and is most active in early life. The spleen filters blood, facilitates phagocytosis, and synthesizes antibodies, while lymph nodes maximize exposure to lymph and play essential roles in B- and T-lymphocyte interactions. Mucosa-associated lymphoid tissue serves similar functions and includes tonsils, adenoids, and Peyer's patches. Lymphatics connect these tissues, facilitating lymph node access, fluid return to the venous system, and fat transport from the intestine.(8)

1.4 CRP response patterns to antibiotics

Given that CRP follows first-order elimination kinetics, relative changes in CRP levels might be more informative than absolute values. By utilizing the CRP-ratio, which reflects the relative changes in CRP concerning its initial concentration, patients can be categorized based on different response patterns, which have been shown to correlate with varying outcomes. Additionally, CRP levels are not significantly affected by common therapies or interventions such as systemic corticosteroids and renal replacement therapy(16)

Four distinct CRP response patterns to antibiotic therapy have been identified: fast, slow, unresponsive, and biphasic. These patterns correlate with different prognoses. Patients with "fast" and "slow" response patterns generally have better outcomes, while those with "unresponsive" or "biphasic" patterns tend to have poorer prognoses.(3) All these terms: fast, slow, unresponsive, and biphasic reflect the amount of time (specifically days) passed in which changes In CRP concentration were observed. For better understanding, here are provided explanations of these terms used in one study from 2018. that investigated CRP ration response to antibiotic therapy. (16) There, CRP levels were measured every other day from admission (D0) to Day 6 (D0, D2, D4, D6) in the PICU. The CRP-ratio was calculated relative to the D0 CRP value, and patients were retrospectively classified according to predefined CRP-ratio response patterns to antibiotics. So," fast" response CRP was characterized as CRP at D4 ≤0.4 of the D0 CRP concentration. "Slow" response was described by a continuous but slow decrease of CRP (CRP at D4 was >0.4 and at D6 was ≤0.8 of the D0 CRP). "Unresponsive" pattern designated that CRP levels remained >0.8 of the D0 CRP at all times, and "biphasic" response an initial CRP decrease to ≤0.8 of the D0 CRP followed by a secondary rise to >0.8 of the D0 CRP. Comparisons were made between survivors and non-survivors as well as among the four different CRP-ratio patterns.(16)

1.5 CRP and rational antibiotic therapy

Since CRP is now a widely used marker of infection, it is also useful as a clinical tool to identify patients who are unlikely to benefit from antibiotic treatment. Therefore, its role as a guiding aid for establishing rational prescribing decisions is rising. (1) In regards to using CRP in primary care several trials, including the 258 patients Netherlands trail ("Point-of-Care C-Reactive Protein Testing and Antibiotic Prescribing for Respiratory Tract Infections: A Randomized Controlled

Trial”), 431 Netherlands trail (“Effect of point of care testing for C reactive protein and training in communication skills on antibiotic use in lower respiratory tract infections: cluster randomized trial”) and a large European 6771 trail, confirmed that use of CRP in general practice can reduce unnecessary antibiotic prescribing in adult patients presenting with acute cough. The 2014 Cochrane review provided additional validation to these findings, assessing biomarkers as point-of-care tests for directing antibiotic prescriptions in primary care patients with acute respiratory infections.(1)

In summary, the use of CRP by GPs proves highly advantageous in managing adults with acute cough and serves as an effective measure for antimicrobial management. But these are one of the rare proven examples, and effects of CRP guided antibiotic treatment needs to be explored in other diseases and necessitate prospective validation across diverse demographics. Until such validation occurs, it's crucial to recognize that GP reliance on C-reactive protein can inform antibiotic decisions, provided it's applied within the appropriate patient population. (1)

1.6 CRP correlation to patients with pneumonia

Regarding serial CRP measurements in pneumonia patients’ findings indicate that consecutive CRP measurements are beneficial for monitoring antibiotic treatment in severe community-acquired pneumonia. A study from 2008. described a delayed normalization of CRP as a decline of <60% in CRP levels in 3 days and a decline of <90% in CRP levels in 7 days. This delayed normalization of CRP levels within the first 3 to 7 days suggested the possibility of inappropriate empirical antibiotic therapy. Patients whose CRP levels decreased by less than 60% in 3 days or less than 90% in 7 days faced a four to seven-fold higher risk of having received unsuitable antibiotic treatment. To conclude, consecutive measurements of C-reactive protein (CRP) are valuable during the first week of monitoring antibiotic treatment for severe community-acquired pneumonia. This is particularly true when considering the causative microorganism and the use of steroids. A delayed decline in CRP levels is associated with a higher risk of having received inappropriate antibiotic treatment.(17)

1.7 CRP and guidelines for its use

Since CRP is a nonspecific marker of inflammation, and its elevated values are found in many inflammatory conditions, establishing guidelines regarding its proper use and interpretation could improve clinical outcome in specific groups of patients. For example, a study from 2005.

discussed all possible indicators of lower respiratory tract infections in adults, and except for the physical exam findings (acute cough, fever, dyspnea and newly found focal chest sounds) they mentioned that CRP levels of >50 mg/L could increase the likelihood that the patient indeed has pneumonia.(18) Updated version suggested a bit different correlations of CRP with the diagnosis, respectively values of CRP less then 20mg/L in patients that had duration of symptoms shorter then 24h most likely excluded the presence of pneumonia, while values of CRP higher than 100mg/L made the diagnosis of pneumonia a likely.(19) Essentially, both studies emphasized the importance of CRP as a negative predictive value. The combination of signs, symptoms, and CRP is diagnostically valuable for detecting but especially for ruling out pneumonia. (19) The conclusion was that CRP values on its own do not provide much data but are very useful as an additional clinical prediction rule for pneumonia, as well as an indicator for further diagnostic investigation (chest radiography empiric antibiotic therapy). (20) Some studies on the isolated diagnostic value of CRP confirmed the diagnostic value of CRP, while the others concluded that there are no clear diagnostic values of CRP, again proving further studies and investigations are needed to provide accurate guidelines for CRP use. A study from 2007. investigated CRP and procalcitonin as predictors in patients with lower respiratory infections and found the specific values of these markers linked to diagnosis of pneumonia. Procalcitonin levels above 0.06 ng/ml and CRP levels of 20 mg/l or higher were linked to radiographic pneumonia, bacterial infection, and subsequent hospitalization. (21)However, their positive predictive values were too low to be clinically useful, again indicating their diagnostic value only when combined with other clinical signs of pneumonia. Since CRP values cannot accurately differentiate between bacterial and nonbacterial pneumonia and its association with severity of infection is questionable, its everyday usage is maybe exaggerated. However, the studies showed that clinical courses are closely reflected by CRP levels. CRP, interleukin 6, and procalcitonin have all shown independent prognostic potential. Due to high costs and unproven cost-effectiveness, only CRP is recommended as a routine laboratory diagnostic work-up. (18) In all hospitalized patients with lower respiratory infection (severe pneumonia) laboratory assessment should include leukocyte counts, CRP, and blood gas determination, but in cases of mild pneumonia usefulness of leukocyte counts and CRP is not proven.(18)

1.8 CRP in sepsis

Lately, a lot of research has been directed towards establishing the relationship between serial CRP measurement as a prognostic factor in outcome of septic patients. Since CRP levels are now widely used as a marker of septic conditions, interest in evaluating potential CRP measurements as an indicator of response to therapy has risen. A study from 2011 including 891 patients observed CRP as an early marker of community-acquired sepsis and concluded that CRP values after antibiotic initiation can estimate the clinical outcome in this group of patients. Daily measurements of CRP levels after the initiation of antibiotic treatment proved to be effective as early as day 3 in identifying patients with community-acquired sepsis who were at risk of poor outcomes. The rate at which CRP levels declined during the first five days in the ICU was strongly correlated with patient prognosis. Recognizing the pattern of CRP-ratio response was valuable in understanding the individual clinical course of patients. (22)Another study from 2008. was designed to investigate correlations between serial CRP measurements in septic patients and their response to antimicrobial therapy, as well as to discover the possibility of relationship between CRP levels and other clinical variables. This study highlighted both the usefulness and limitations of CRP concentrations. One of the findings was that an increase in CRP levels on the first day of treatment was associated with ineffective initial antibiotic therapy, bearing in mind that the sensitivity and specificity of this observation were relatively limited. That indicated a need for future investigations of the role of CRP in guiding therapy, and additionally comparison of the time course of CRP levels to other potential markers, such as procalcitonin. The study concluded that monitoring blood CRP concentrations in sepsis patients during the first 48 hours can help evaluate the response to initial antimicrobial therapy. Therefore, daily measurement of CRP is straightforward and cost-effective, aiding in the diagnosis of sepsis, assessing the response to antibiotic therapy, and determining prognosis.(23)

Other studies, like this one from 2019. claim otherwise. They identified three C-reactive protein (CRP) kinetic groups: fast response, delayed but fast response, and delayed and slow response. (Figure 1.) They found there were no statistically significant associations between CRP kinetics and early or late mortality, or antibiotic therapy duration. Although the appropriateness of antibiotic therapy did not significantly differ between the groups, no patient with inappropriate antibiotic therapy had a fast response pattern. Despite the importance of CRP in infection indicated by various studies, early CRP kinetics is not associated with response and prognostic assessment in critically ill patients. However, a fast response pattern tends to exclude initial inappropriate antibiotic therapy.(3)

Since this kind of data does not really exist in the context of emergency department (most studies are confined to specific conditions such as sepsis or pneumonia, or they focus on CRP usefulness in family medicine), and the data we have so far is often contradictory (like this regarding CRP in sepsis), further research is absolutely needed.

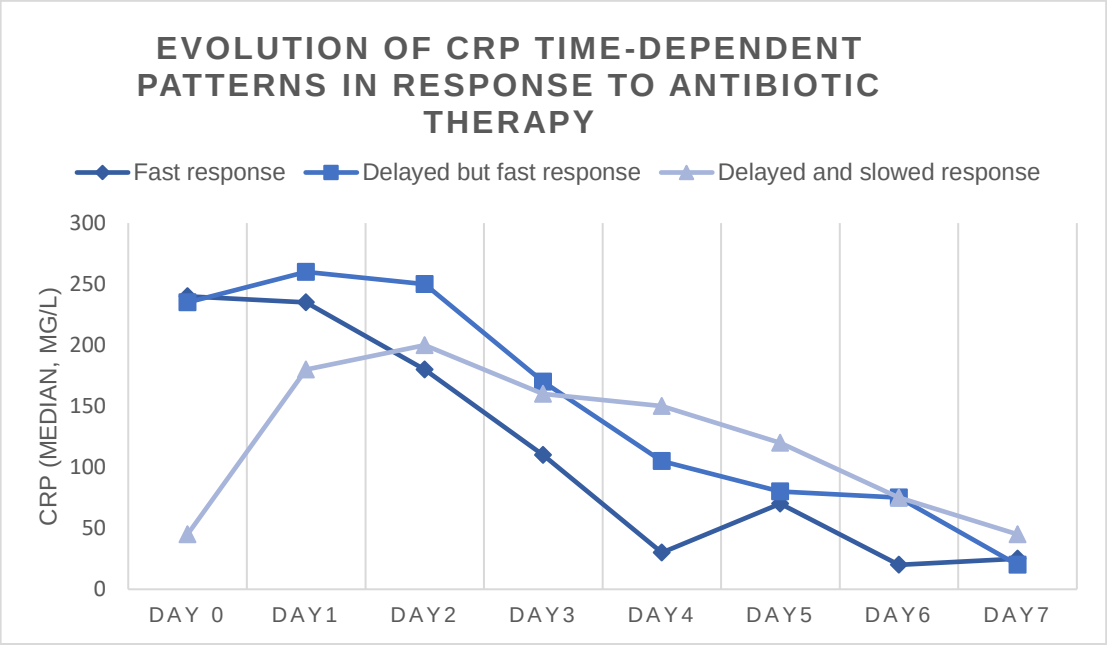

Figure 1.
Graph according to a study: *"Usefulness of Early C-Reactive Protein Kinetics in Response and Prognostic Assessment in Infected Critically Ill Patients: An Observational Retrospective Study"*

1.9 CRP and its control values

Very little literature has been found investigating the use of control CRP, described as a second CRP measurement taken several hours or in some cases days, after the initial one. One of the rare papers regarding this topic is an observational study done in Israel during a 9-year period, between 2007. and 2016. The goal of the study was to demonstrate that initial low CRP values do not necessarily exclude the presence of bacterial infection. What was interesting about that study was that the significant changes in CRP they demonstrated all occurred within the 12 hours or even less. This study was one of first to detail the dynamic changes in CRP levels during the initial hours of hospitalization, highlighting the necessity of further testing before making conclusions about the intensity of the inflammatory response in such patients. Also, the study suggested that irrespective of the infection type (cellulitis, pneumonia, septicemia, etc.),

individuals with initially low CRP concentrations tend to show significantly higher concentrations within a few hours. This increase can occur even during the evaluation and treatment period in the Emergency Department. These individuals showed a CRP increase that could reach concentrations 5 to 10 times higher than the initial level, presenting this rapid change in CRP as the main finding of the study. (24) What should be considered here is how this rapid incline of CRP values actually influenced further patient outcome. Did those patients, based on their CRP dynamics, maybe receive earlier antibiotic therapy, or were they hospitalised sooner. Or perhaps those rapid elevations of CRP just proved the existence of the initially suspected infection without any clinical consequences.

2. HYPOTHESIS

Early control of laboratory markers of inflammation is not correlating with early clinical course and or outcomes; however, it may influence admission/discharge decisions and/or prolong emergency department evaluation times.

3. OBJECTIVES

General objective of this research paper is to establish early dynamics (within first 24 hours) of inflammatory marker CRP and leukocyte count, its association with clinical course and influence on clinical practice in emergency departments.

Specific goals of this research:

1. To establish patterns of control samples for CRP levels and leukocyte count.
2. To establish if there is an association between the dynamics of the inflammatory markers and early clinical course.
3. To establish if there is an association between the dynamics of markers with clinical decisions made in the emergency department.
4. To establish the effect of the laboratory results (change in CRP and change in leukocyte count) on final clinical outcome of those patients.

4. MATERIAL AND METHODS

Adult (18 years of age and older) patients who were diagnosed with an infection presumed to be bacterial, started on antibiotic treatment and observed in the emergency department pending final decision about admission or discharge were considered for inclusion. Included were patients with respiratory infections, urinary tract infections and abdominal infections. Patients with other sites of infection or those with unknown or uncertain sites of infection were not included.

Patients diagnosed with sepsis (according to Sepsis 3 criteria) in the emergency department even if observed were not included since sepsis is considered an absolute indication for hospital admission.
Patients with immunosuppression expected an imminent mortal outcome and those in whom infection was not the primary and most important diagnosis (i.e. those with stroke and urinary infection or those with were. High probability of surgical intervention was also an exclusion criterion. Table 2 summarizes inclusion and exclusion criteria.

Patients selected according to the above criteria were identified in the Database of Emergency Department patients and cross-referenced against the Database of the Department of Laboratory Diagnostics to identify patients with at least 2 consecutive laboratory measurements of leukocyte number and CRP concentration within 24 hours.

For the identified patients, the following information was acquired: age at ED presentation, sex (female or male), type of infection, clinical condition at antibiotic initiation (generally poor or well), existence of indication for hospitalization at antibiotic initiation, Leukocyte count in first and second measurements, CRP concentration at first and second measurement, time interval between first and second laboratory evaluation and time from antibiotic initiation to second laboratory evaluation; clinical condition at the time of second laboratory measurements (improvement, worsening or unchanged).
Sample size was calculated with confidence level of 90% and alpha (margin of error) of 5%. Given these parameters calculated sample size was 273 which was set as minimum patient inclusion number.

Table 2. Inclusion and exclusion criteria

Inclusion criteria (must meet all)	Exclusion criteria
○ Adult (>18 years) patients ○ At least two Leukocyte and CRP measurements within 24 hours in the emergency department ○ Respiratory, urinary, or abdominal infection not requiring surgery ○ Antibiotic treatment started in the emergency department	○ Sepsis (according to Sepsis 3 criteria) ○ Immunosuppression ○ Imminent mortal outcome ○ Infection not the primary pathology ○ Unknown or uncertain site of intection ○ CNS infections, skin and soft tissue infections ○ Probable need for surgical intervention

Collected data were analyzed using MedCal® Statistical Software version 22.017 (MedCalc Software Ltd, Ostend, Belgium). Results are reported as absolute and relative frequencies for categorical variables and as means with standard deviations for continuous variables. Chi-squared test was used to compare categorical variables, T-test and one way ANOVA for continuous variables. Statistical significance was set at P=0.05

The author has no conflict of interest regarding the research conducted.

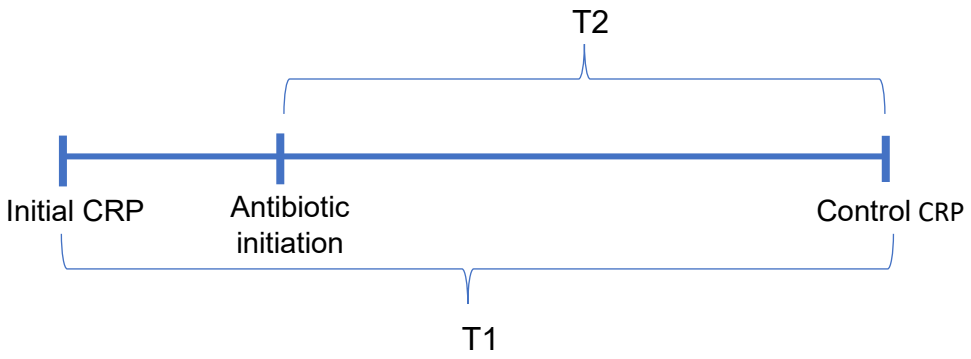

Figure 2: explanation of definitions delta T1 and T2 for better understanding of data presentation

5.RESULTS

A sample of 300 patients was included, with a median age of 54 years. There were slightly more female participants (167 patients). (Table 3)

Regarding the infection type, we divided our sample into three categories: the largest group of patients had respiratory infection (49%), followed by a group of urinary infection patients (22%), and lastly the smallest number of patients with abdominal infection (19%). (Table 3)

One of the major variables used in this study was clinical outcome. This term included four categories based on the possibilities of further treatment: patients who were hospitalised (7,3%), patients who were discharged from the emergency department without admission (26,35%), patients who were after initial examination in the ED kept for further observation (60,7%) and patients who received modification of their antibiotic therapy (5,7%). (Table 3)

Another variable we used was clinical picture. This term describes if there were changes in patients' status over the time spent in the emergency department. This epicrisis was described as a subjective clinical opinion rather than dependant on specific laboratory values. Three categories were used: patients that had improved, patients that had deteriorated, and patients that had no change regarding their clinical presentation.

Table 3. Main characteristics of the study sample.

Sex	F: 167 (55,7%), M: 133
Age	54 ± 23
Type of infection	
- respiratory	147 (49%)
- urinary	97 (22,3%)
- abdominal	56 (18,7%)
OUTCOME:	
Hospitalization	22 (7,3%)
Discharge	79 (26,35%)
Further observation	182 (60.7%)
Change in antibiotic therapy	17 (5,7%)
Immediate hospitalization	48 (16%)
Time in between first and control CRP (Delta t1)	13,9h ± 6,1
Time in between antibiotic administration and control CRP (delta t2)	10,9 ± 6,1

Important variables used in this study were delta t1 and delta t2. (Figure 2) Delta t1 is defined as time passed (in hours) in between initial and control CRP values. Its average value represents how much time on average passed between patient's arrival to the emergency department, since all our patients with infection had taken blood samples to establish initial CRP levels, and between second blood sample taken to reevaluate their CRP levels. Average delta t1 was 13.9 hours. (Figure 3)

Delta t2 is defined as time passed in between initiation of antibiotic therapy and the second blood sample taken for revaluation of CRP. Average delta t2 was 10,9 hours. (Figure 4)

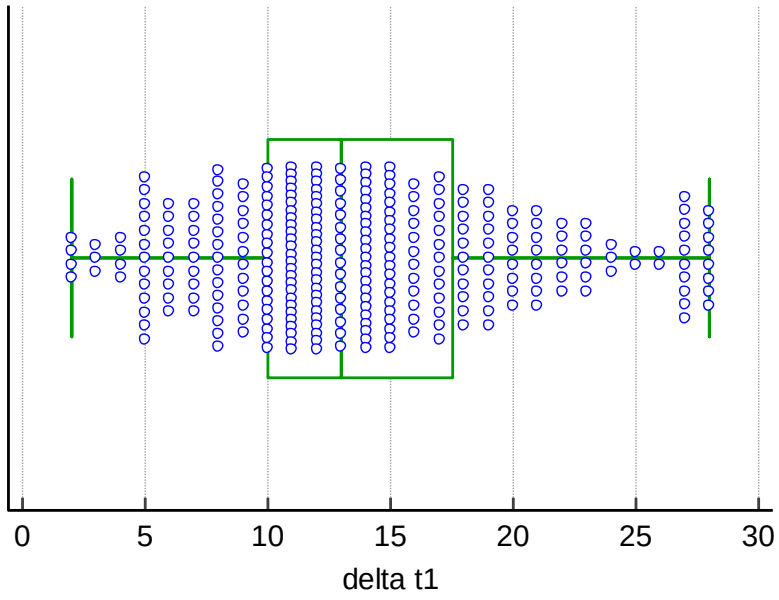

Figure 3. Graphic representation of time distribution between the sampling of the two CRP values taken for laboratory analysis (delta t1 in hours)

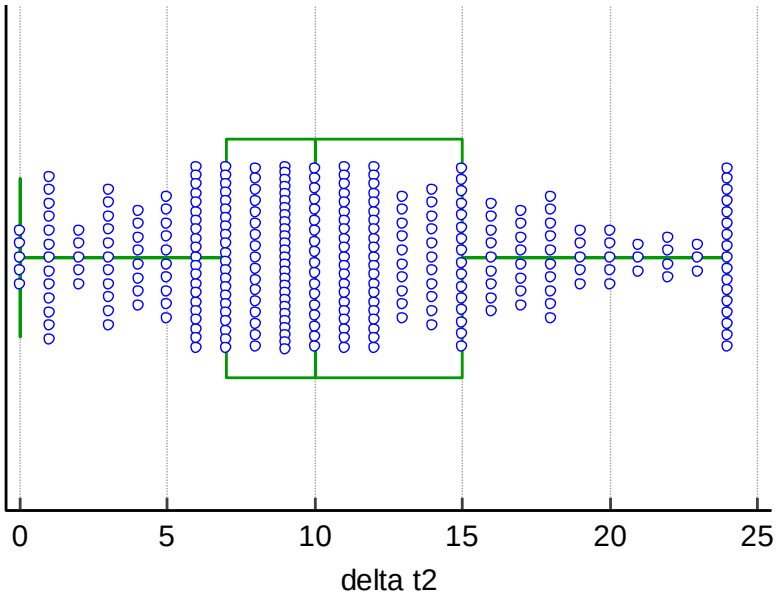

Figure 4. Graphic representation of time in between initial antibiotic administration and control CRP sample for laboratory analysis (delta t2 in hours)

CRP levels were measured twice, once after admission to the emergency department, and a second control sample was taken within the next 24 hours. The average difference in those two CRP measurements was 6,5 ± 33,6 mmol/L. We compared this CRP change in relation to the clinical picture and discovered that CRP differences were all very similar regardless of the different clinical pictures. Statistical analysis disproved our hypothesis that there would be notable differences in CRP changes relative to this patients' groups, therefore concluding that there is no statistically significant correlation between CRP changes and clinical picture. (p = 0,923)

Table 4. Change in CRP level depending on the clinical picture.

CRP average difference	6,5 ± 33,6
CRP difference in patients with worsening clinical picture	8,5 ± 24,7
CRP difference in patients with improving clinical picture	6,9 ± 34
CRP difference in patients with unchanged clinical picture	6,1 ± 32

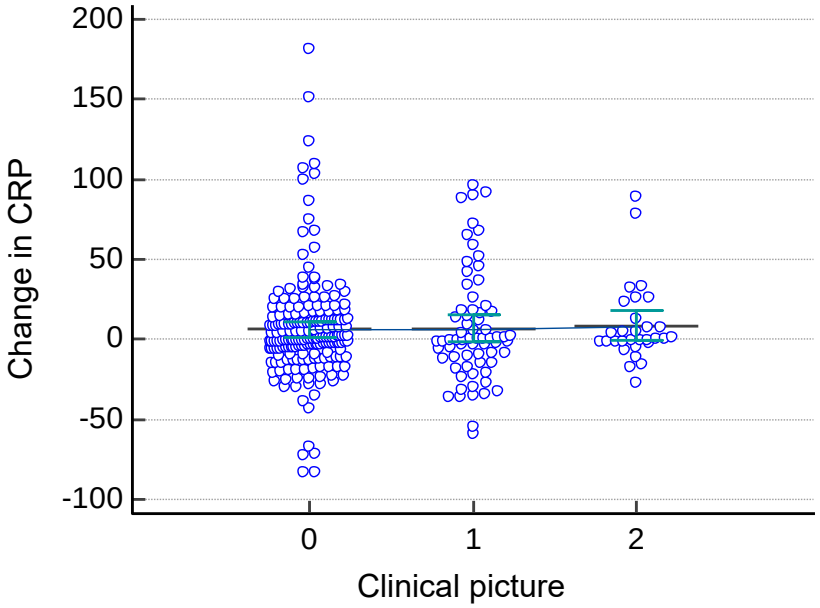

Figure 5. Change in CRP level (from initial to control) depending on the clinical picture (0 = unchanged, 1 = improved clinical picture, 2 = worsening clinical picture)

We also compared change in CRP in relation to the clinical outcome. Our hypothesis that changes in CRP will not notably differ regarding to the different clinical outcomes was disproved by this analysis, concluding that there was statistical significance in this case ($p< 0,001$). So, the amount of change in CRP levels did correlate with those specific clinical outcomes.

Table 5. Change in CRP level depending on the clinical outcome.

CRP difference in patients who stayed for Observation	1,0 ± 20,9
CRP difference in patients who were Discharged	-2,9 ± 22,3
CRP difference in patients who stayed for Hospitalization	41,5 ± 53,7
CRP difference in patients who had Change in antibiotic treatment	64,2 ± 48,5

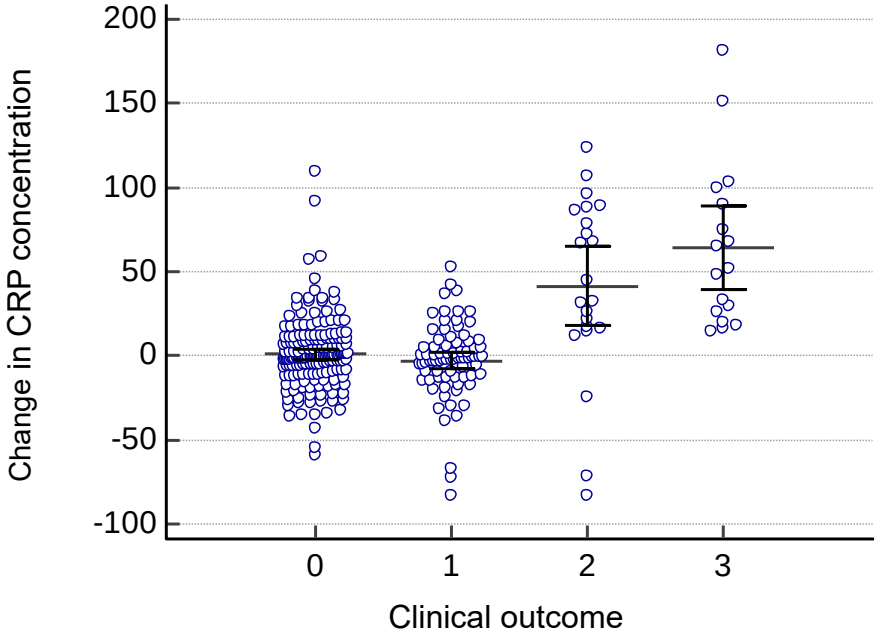

Figure 6. Comparison of change in CRP concentration depending on end decision for patient (ANOVA P<0.001), 0 = further observation, 1 = discharge, 2 = hospitalization, 3 = change of antibiotic therapy

Leukocyte count was also measured twice. First value was obtained after initial admission to the emergency department, and the second, control value one was taken within the next 24 hours. We compared relation between changes in those leukocyte counts (delta L) and the clinical picture of these patients and found there were no statistically significant correlations between these two variables. (p = 0,443)

Table 6. Change in leukocyte levels (delta L) depending on the clinical picture.

Leukocytes average change	-0,8 ± 2,9
Delta leukocytes in patients with improved clinical picture	-1,2 ± 3,5
Delta leukocytes in patients worsening clinical picture	-0,8 ± 2
Delta leukocytes in patients with unchanged clinical picture	-0,7 ± 2,9

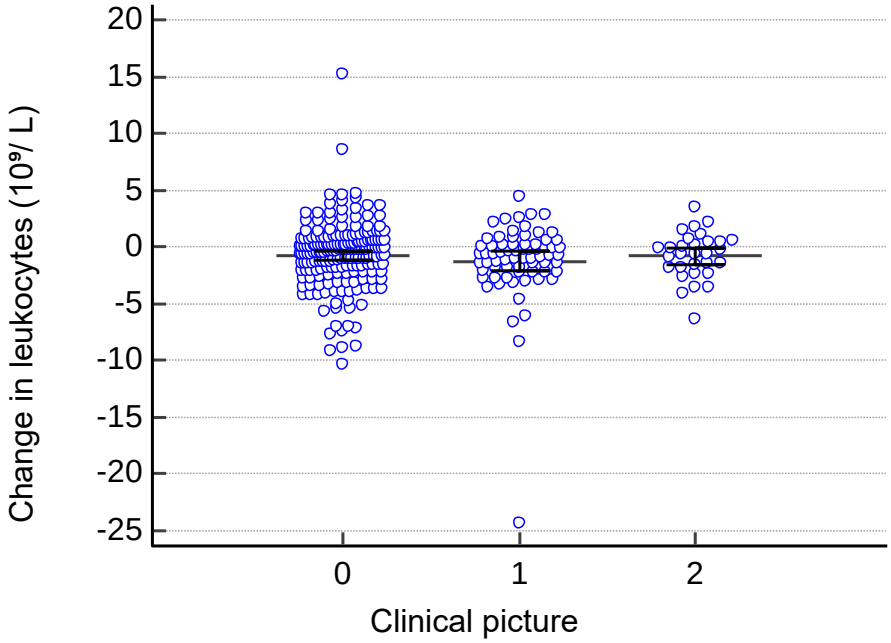

Figure 7. Difference in leukocyte levels depending on clinical condition, clinical condition: 0 = unchanged, 1= improved clinical picture, 2= worsening clinical picture

Corelation between leukocyte count and the clinical outcome was also explored. The data proved our hypothesis that clinical outcome in these patients will not significantly depend on the changes in leukocyte count. Therefore, the conclusion was that that correlation between change in leukocyte count and clinical outcome was statistically insignificant (p= 0,476)

Table 7. Change in leukocyte count depending on the clinical outcome

Change in leukocyte levels in patients left for further observation	-1,1 ± 3,2
Change in leukocyte levels in patients who were discharged	-0.5 ± 2,8
Change in leukocyte levels in patients who were hospitalized	-0,6 ± 2,1
Change in leukocyte levels in patients who had change of antibiotic therapy	-0,3 ± 2,4

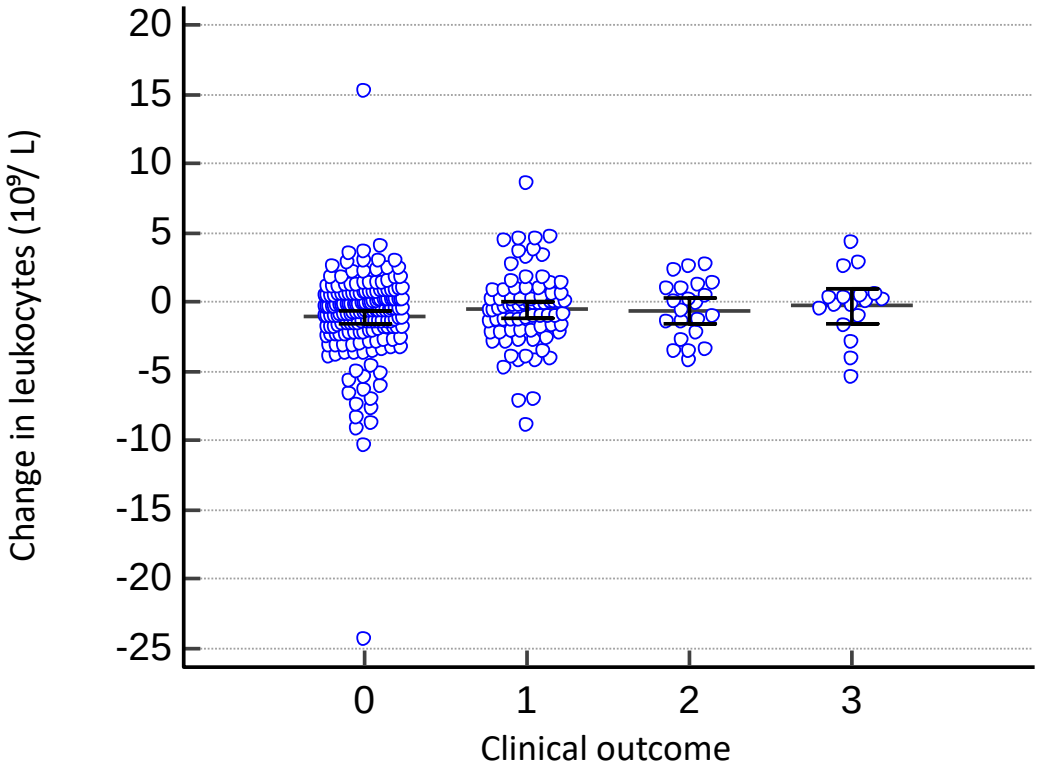

Figure 8. Difference in leukocyte count depending on the decision on further treatment (clinical outcome) (0 = further observation, 1 = discharge, 2 = hospitalization, 3 = change of antibiotic therapy)

Association between the two major variables, clinical picture and clinical outcome was also explored. Out of 182 patients (61%) who were retained for further observation in the ED (group clinical outcome 0), 119 had unchanged clinical picture, 44 of them improved, and 19 of them had worsening of their condition. In the group of patients who were discharged (group clinical outcome 1), that consisted of 79 patients (26%), 56 of them had no change in their clinical picture, 14 improved, and 9 had worsening of their condition. In case of patients who were hospitalised (group clinical outcome 2), containing 22 patients (7%), 15 of them had no change in their clinical picture, 5 patients improved, and 2 had worsened. Lastly, in the group who had received a new antibiotic (group clinical condition 3) that consisted of 17 patients (6%), 11 of them had no change in their clinical picture, 6 patients improved, and none of them had worsening of their status. (Table 8.)

Table 8. Association between clinical condition and clinical outcome

	Clinical outcome				
Clinical picture	0	1	2	3	
0 (no change)	119	56	15	11	201 (67.0%)
1 (improvement)	44	14	5	6	69 (23.0%)
2 (worsening)	19	9	2	0	30 (10.0%)
	182 (60.7%)	79 (26.3%)	22 (7.3%)	17 (5.7%)	300

Table 9. Statistical data regarding the association between clinical condition and clinical outcome.

Chi-squared	4.358
DF	6
Significance level	P = 0.6284
Contingency coefficient	0.120

According to table 9. there was no statistical significance found between the clinical outcome and clinical picture. Therefore, we can draw the conclusion that due to this incoherence between these two variables (clinical outcome and clinical picture), the following end decisions: whether patients were retained for further observation, discharged, hospitalised, or received a new antibiotic therapy, were not made based on clinical picture of this patients, but on the amount of changes in CRP values (delta t1).

Table 10: Multiple regression for correlation between decision on clinical outcome and difference between clinical and laboratory values

Variable	r-coefficient	T	P
Control CRP	-0.0002718	-0.517	0.6059
Relative change in CRP concentration	0.004434	6.927	<0.0001
Absolute change in CRP concentration	0.003835	2.192	0.0291
Change in leukocyte count	0.02928	2.151	0.0323
Type of infection	0.08590	1.593	0.1122
Clinical picture	-0.009276	-0.152	0.8794

When multiple data were compared to establish the influence of all used variables on the decision of clinical outcome, three variables showed statistical relevance (Table 10). As stated, the amount of change in CRP levels did correlate with the clinical outcomes, both the absolute (P = 0.0291) and the relative change (P <0.0001). Another statistically significant correlation was the one between change in leukocyte count and clinical outcome (P = 0.0323). Other variables such as control CRP (second measurement of CRP) or type of infection were not found to have statistically significant correlation with the decision on clinical outcome.

Relative changes in CRP levels showed no correlation with clinical picture, p = 0.600 (Figure 9.)

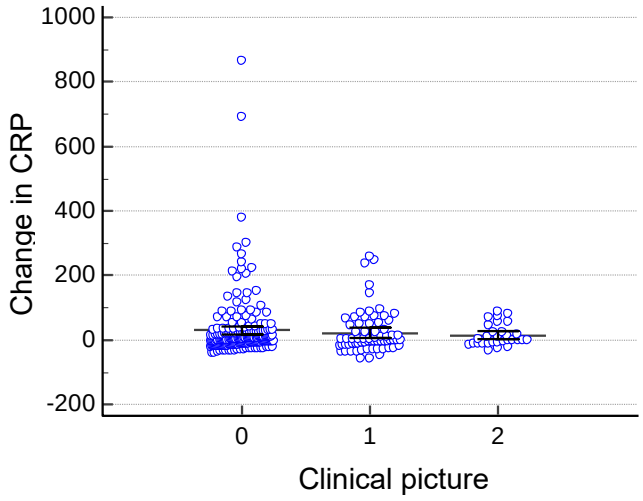

Figure 9. Relative changes in CRP in correlation with clinical picture (0 = unchanged clinical picture, 1 = improved clinical picture, 2 = worsening of clinical picture)

Relative changes of CRP levels in relation to clinical outcome were statistically significant (P<0.001), meaning that the decision on clinical outcome in these patients was based on relative changes in CRP. (Figure 10)

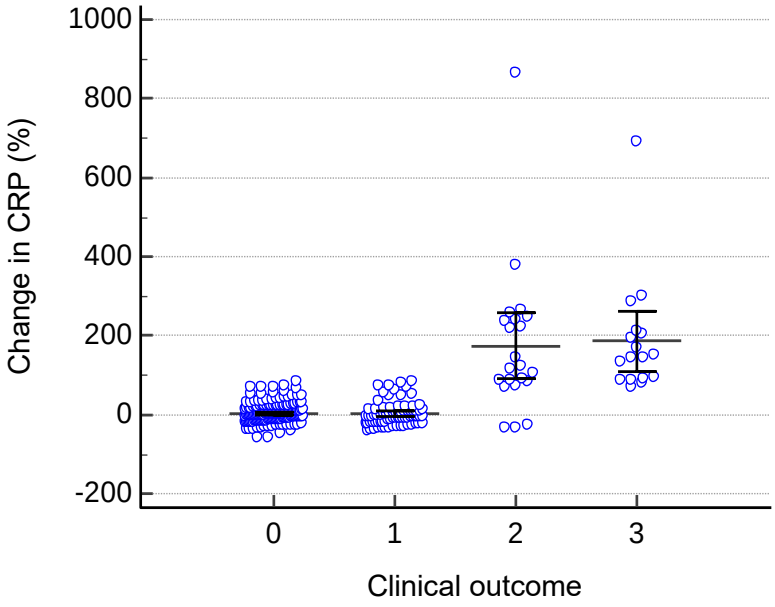

Figure 10. Relative changes in CRP in correlation to clinical outcome. (0 = further observation, 1 = discharge, 2 = hospitalization, 3 = change of antibiotic therapy)

6.Discussion

Since some studies suggest the importance of CRP and other laboratory markers of infection, especially in regard with diagnosis and treatment of those patients, we considered further exploration of these correlations was necessary. We were also interested in how clinical practice is functioning based on those premises. In this case, a rather dysfunctional pattern was discovered, in which most clinicians in the emergency department operate in their own ways, without any established protocols to follow. Also, the data gained from this study leads to two very important questions. First, if it is beneficial in the clinical practice that the decision about further treatment is only based on laboratory data of CRP dynamics and not on the clinical picture that is assessed by the physician. Secondly, and more importantly, can this decision in clinical practice truly be relied on this narrow time window of CRP changes. Although the conclusion that clinical outcome was dependent on changes in CRP might initially sound reasonable, if we analyse this data further, we need to consider that those changes in CRP were observed only in a brief time frame, that averaged at 13,9 hours, and that the average change in CRP was 6,5 ± 33,6 mg/L. Compared to guidelines and established clinical practice, these numbers seem too small to make a significant background that decisions on further patient treatment can be based on.

We believe rational CRP measurements could be of great importance in clinical practice, but in specific conditions that, according to the research so far, have not been clearly established.

The strengths of this specific research would be a relatively large number of patients and a big number of observed variables. On the other side, weaknesses would be that all these data were extracted from a single hospital center and therefore the patients are of uniform ethnicity, that the study was done retrospectively, and that criteria that determined some of the variables were unclear (for example the decision regarding hospitalization).

7.Conclusions

It could be concluded that often unnecessary CRP measurements are done, without any benefit of such practice in the emergency department. CRP samples are taken randomly in a sense that within this 24-hour frame, most controls were taken within half of that time, indicating that physicians might re-check CRP levels just for their reassurance but essentially without those values influencing further treatment of the patient. We believe that data we gathered proved numerous unnecessary controls of CRP, but even more importantly that clinical decisions based on those incorrectly interpreted CRP changes, especially regarding antibiotic treatment, potentially do not benefit these patients.

Finally, although statistical analysis showed clear findings, due to some limitations of the study these data should be interpreted with caution.

8.Acknowledgements

Primary I would like to officially thank my mentor, prof Gornik for taking on this project and hopefully continuing this research further in the future. Also, I would like to thank the employees of the clinical department for laboratory diagnostics who enabled access to research the database of laboratory values, the sheer work couldn’t have been done without them.

In this way, I would like to express my gratitude to everyone who supported me and believed in me during this challenging part of my education. Special thanks to my household for their extraordinary support, and to my dear colleagues who made all these years much more enjoyable.

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10.Biography

Hana Franić is a final year medical student in the University of Zagreb. She is a long-time member of the student surgical section, and since the student section for emergency medicine was founded, an active member there. She participated in multiple conferences in the last few years (such as “OMI Satellite Symposium in Cardiac Surgery”, “The International Scientific and Training Conference of Polish Society for Vascular Surgery” and “7th Emergency medicine congress with International Participation”), as well as in multiple student’s congresses. Since her interest in emergency medicine grew over time, she started student volunteering on an ambulance emergency medicine shifts, as well as in the emergency department. She has done several courses on trauma education and reanimation in ambulatory emergency organized by STEP. She hopes to one day, regardless of the field of medicine she will be mostly focused on, to participate in development, integration, and education, preferably using her English background of education to explore European medicine and bring innovations back to Croatia.