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Increased perioperative C-reactive protein and decreased postoperative albumin is associated with acute posttraumatic osteomyelitis in patients with high-energy tibial fractures

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ABSTRACT

Background: Early diagnosis of acute posttraumatic osteomyelitis (POM) is of vital importance for avoiding devastating complications. Diagnosing POM is difficult due to the lack of a highly specific and sensitive test, such as in myocardial infarct, stroke and intracranial bleeding. Serum inflammatory markers, C-reactive protein (CRP), procalcitonin (PCT), white blood cells (WBC) can support clinical findings but they are not able to differentiate between inflammatory response to infection and the host response to non-infection insult with high specificity and sensitivity.
Aim: The objectives of the study were to investigate whether the biochemical and immunoinflammatory patient profile could facilitate postoperative monitoring, guide the antibiotic treatment and timing of revision surgery.
Patients and methods: This prospective nonrandomised cohort study included 86 patients after high-energy injury to the shin requiring primary surgical treatment (open or closed reduction and internal fixation of tibial fracture). Values of the biochemical and immunoinflammatory profile were measured on admission (ADD), first postoperative day (POD1) and fourth-postoperative day (POD4).
Results: We discovered on our sample that the development of POM is associated with increased CRP on ADD, POD1 and decreased albumins on POD4. Further studies are needed to prove that these differences can be useful in diagnosing the risk of infection. The assessment of other important risk factors such as: the extent of soft tissue damage, multiple fractures, transfusion rate, need for conversion primary external fixation to intramedullary (IM) nailing or locking plate fixation can empower our clinical judgment of POM.
Conclusions: We can improve prediction of posttraumatic osteomyelitis by using the perioperative inflammatory biomarker CRP in combination with postoperative albumins levels and other associated independent risk factors.

Introduction

Post-traumatic osteomyelitis (POM) is a serious complication occurring in 0.4–7% of operations performed in orthopaedic and trauma surgery [1,2]. POM is an exogenous osteomyelitis and can be described as the result of injury or nosocomial infection after the operation of fracture allowing pathogens to enter the bone, proliferate in traumatized tissue, and cause subsequent bone infection. Its incidence is six cases per 100,000 person-years and increases due to a rise in predisposing conditions such as diabetes mellitus and peripheral vascular diseases [3,4]. One of the most common injuries sustained after road traffic accidents is a tibial

Abbreviations: POM, posttraumatic osteomyelitis; No POM, control group; CRP, C-reactive protein; PCT, procalcitonin; ADD, admission; POD1, first postoperative day; POD4, fourth-postoperative day; WBC, white blood cells; SIRS, systemic inflammatory response syndrome; CARS, compensatory anti-inflammatory response syndrome; ASA, American Society of Anaesthesiology physical status classification; NPWT, negative-pressure wound therapy; EF, external fixator; CI, confidence interval; EF conversion, external fixation then conversion to plate or intramedullary nail after recovery of soft tissue.

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fracture. These fractures are associated with high-energy trauma and, due to the poor surrounding soft tissue envelope, the tibia is more susceptible to bone defects and post-traumatic complications. The most frequent single site infection in extremity osteomyelitis is the tibia, with an incidence of up to 40% [5]. Bone infection morbidity is principally the consequence of sustained primary contamination at presentation in open fracture patients and secondary contamination in closed fracture patients that underwent open reduction and internal fixation (ORIF). The force necessary to produce fracture also means considerable soft-tissue injury, with oedema, necrosis, hematoma and foreign bodies that potentiate bacterial virulence. Secondary injuries during surgical procedure with hematoma, tissue oedema and utilization of implants for osteosynthesis also contribute to the development of bone infection.

The up-regulation of the immune system functions following trauma has been given the term systemic inflammatory response syndrome (SIRS) and is characterized by local and systemic release of pro-inflammatory cytokines, arachidonic acid metabolites, complement factors, acute phase proteins and activation of the coagulation system [6]. Compensatory anti-inflammatory response syndrome (CARS) is simultaneously triggered by the release of anti-inflammatory mediators [7]. An imbalance of these dual immune responses may be a possible source for increased susceptibility to infections [8]. POM is a clinical diagnosis definitively confirmed by microorganisms isolated from bone biopsy specimens and hystopathologic examination. Plain-film radiography is the basic examination that may support the clinical suspicion of bone infection [9]. Detection of active infection can be very difficult in bones altered by processes that have affected the bone structure and metabolism, such as prior trauma or surgical procedures. Further imaging procedures, such as CT scanning, MRI, ^{111}In-labeled leukocyte scintigraphy or SPECT/CT scan can be helpful in diagnosis but the limited accuracy of these methods after extended osteosynthesis has to be taken into consideration [10].

In terms of biochemical assessment, CRP and procalcitonin (PCT) have been commonly used in infection and sepsis diagnostics [11]. One of the main limitations of CRP is a slow response to certain insult, reaching its maximum value 48 h later. PCT is detectable within 4–6 h after its induction, reaches its peak within 24 h then starts to decline [12]. Using PCT, bacterial infection can be better differentiated from a systemic inflammatory response of other aetiology, with higher sensitivity and specificity than CRP and PCT also has good prognostic value [11]. Other autocoids that have been used for diagnosis of infection include cytokines such as tumour necrosis factor alpha (TNF-α), interleukin-6 (IL-6), interleukin-10 (IL-10).

In the herein study we aimed to investigate amongst others, whether the biomarkers CRP, PCT, TFN-α, IL-6 and IL-10 could predict the development of acute POM in patients who have sustained high-energy tibia fracture.

Patients and methods

Study design, setting, and data source

The present observational study, designed as a prospective nonrandomised cohort study to follow up the development of post-traumatic osteomyelitis on a population of patients after high-energy injury to shin and surgical management of tibial fracture, was conducted at the Traumatology Department of the University Clinical Centre Ljubljana Slovenia from January 2012 to December 2014. Patients' data about treatment were collected using an adapted questionnaire in the emergency department, operating room and hospital ward. On admission to hospital, personal details, mechanism of injury, type of fracture (Gustilo classification for open fracture), site of fracture (AO/OTA classification for long bones fracture) and soft tissue injury severity assessment were recorded. Each patient was assessed preoperatively according to the American Society of Anaesthesiology physical status classification [13]. In the operating room, each patient received systemic antibiotic prophylaxis for Gram positive and negative bacteria on induction of anaesthesia and prior to skin incision or, in the case of open fracture, on admission to the emergency department. A standardized protocol for general and epidural anaesthesia was used. During the operation, the anaesthesiologist recorded the length of the procedure, blood loss and the volume of transfusion. We also recorded the type of fracture fixation, soft tissue reconstruction and application of negative-pressure wound therapy (NPWT).

POM as an acute exogenous osteomyelitis most frequently appears with the typical inflammation signs over the period of 1 week to 12 weeks post fracture fixation and it can be overlap with surgical site infection (SSI). The diagnosis of POM after tibial fracture operation was based on assessment of clinical, laboratory findings and diagnostic procedures.

Patients who developed post-traumatic osteomyelitis were additionally assessed before the inclusion into POM group by completing an osteomyelitis questionnaire which captured: infection's occurrence in days after surgery, intraoperative bone and soft tissue sampling, types of cultured bacteria, meeting the CDC/NHSN surveillance definition criteria for osteomyelitis [14], antibiotics therapy in days and histopathological proof of osteomyelitis. Follow-up data were obtained from the appropriate outpatient medical records. The Republic of Slovenia National Medical Ethics Committee approved this protocol study (No. 38/05/04).

Inclusion and exclusion criteria

Inclusion criteria were high-energy injury to proximal, shaft or distal tibial fracture requiring primary surgical treatment (open or closed reduction and internal fixation of tibial fracture).

Exclusion criteria were: ankle fracture, patella fracture, avulsion fracture of the knee, malignant neoplasm and pathological tibial fracture, systemic autoimmune disease of connective tissue, immature patients under 15 years of age (children), immunocompromised patients.

Laboratory and sample collecting methods

Laboratory analyses of peripheral venous blood on admission (blood sample ADD), 24 h after surgery (blood sample POD1) and fourth-day after surgery (blood sample POD4) included biochemical analysis, complete blood count, C-reactive protein (CPR), procalcitonin (PCT), albumin/protein level, prothrombin time and international normalized ratio (INR) (only on admission) and for determination of cytokines: tumour necrosis factor alpha (TFN-α), interleukin-6 (IL-6), interleukin-10 (IL-10).

Biomarkers measurement

WBC count (reference range $4–10 \times 10^9$/L), WBC differential (neutrophil count $1.50–7.40 \times 10^9$/L, lymphocyte count $1.10–3.50 \times 10^9$/L) and hematocrit (reference range 0.390–0.500) were analysed with a haematological blood analyser LH75 (Beckman Coulter). The immunobiochemic analyser Modular Analytics SWE (Roche Diagnostics) was used for serum samples analysis. The serum concentration of CRP (reference range 0–5 mg/L) was measured by the immunoturbidimetric method, PCT (reference range 0–0.5 μg/L) by the electrochemiluminiscence method and albumins (reference range 35–52 g/L) by the bromcresol green method.

Assessment of patients' immune status

Whole venous blood was collected into vacutainer tubes containing EDTA. Samples were processed for flow cytometry. For surface staining, the standard whole-blood staining methodology as prescribed by the manufacturer (BDBiosciences) was used. For detecting regulatory T cells, samples were stained for surface antigens with a mix of anti-CD25-PE/ anti-CD127-APC/ anti-CD4-PE-Cy™7. All antibodies were obtained from BDBiosciences (Mountain View, Ca, USA). Cells were analysed on FACSCantoII™ Flow Cytometer (BDBiosciences) equipped with blue (488-nm solid-state) and red (633-nm helium-neon) laser. Digital data was acquired with FACSDiva software (BDBiosciences) and analysed using FlowJo software (Tree Star Inc.,).

Determination of cytokines level in serum: tumour necrosis factor (TFN-alpha), interleukin-6 (IL-6), interleukin-10 (IL-10) and lymphocyte populations

We used commercially available enzyme-linked immunosorbent assay (ELISA) kits for measurement of concentration of TNF-α (Milenia Biotec, Germany), IL-6 and IL-10 (Thermo Scientific, USA) according to the manufacturer's instructions.

Statistical analysis

Numerical variables were summarized with medians and interquartile ranges (IQR), categorical variables with frequencies and percentages.

In order to avoid problems with missing data, the association between osteomyelitis and other covariates was assessed through univariate analyses. For categorical covariates, we used chi-squared test or Fisher's exact test (if expected frequencies were below 5). For numerical covariates, we used Mann-Whitney U test due to asymmetric shape of the distributions. We used logarithm on PCT, IL-6, IL-10 and TNFα on ADD, POD1 and POD4 because of extremely asymmetric shape of distributions. Results are in Tables 1 and 2.

In Table 2, the univariate predictive value of the covariates for the prediction of osteomyelitis was assessed calculating the area under the receiver operating characteristic curve (AUC, ROC) together with 95% confidence interval (CI) using DeLong method. To avoid false-positive results because of so many hypotheses tested, the P values were adjusted for multiple testing using a permutation procedure (free step-down resampling method with 1 million permutations of the outcome) [15].

Table 1
Comparison of Patients and Surgical Characteristics between Osteomyelitis and Non-osteomyelitis group.

Characteristics	No POMs N = 66	POM N = 20	POM/total (%)	P-value
Age (years)	51.0	49.5	/	0.602
Median (IQR)	(37.2-61.2)	(44.5-61.8)		
Gender				
Female	22 (33.3%)	4 (20.0%)	4/26 (15%)	0.255
Male	44 (66.7%)	16 (80.0%)	16/60 (27%)	
Tibia Fracture				
Isolated	56 (84.8)	9 (45.0%)	9/65 (14%)	0.001 *
Multiple sites, Polytrauma	10 (15.2)	11 (55.0%)	11/21 (52%)	
Type of fracture				
Open	21 (31.8%)	11 (55.0%)	11/32 (34%)	0.060
Closed	45 (68.2%)	9 (45.0%)	9/54 (17%)	
Site of fracture				
Distal Tibia- Pilon	18 (27.3%)	9 (45.0%)	9/27 (33%)	0.198
Proximal Tibia	10 (15.2%)	4 (20.0%)	4/14 (29%)	
Tibial Shaft	38 (57.6%)	7 (35.0%)	7/45 (16%)	
Soft tissue damage #				
Impaired	17 (25.8%)	12 (60.0%)	12/29 (41%)	0.005*
Not impaired	49 (74.2%)	8 (40.0%)	8/57 (14%)	
Concomitant internal disease				
Yes	31 (47.0%)	10 (50.0%)	10/41 (24%)	0.812
No	35 (53.0%)	10 (50.0%)	10/45 (45%)	
ASA score #				
1	27 (40.9%)	4 (20.0%)	4/31 (13%)	0.093
2	33 (50.0%)	11 (55.0%)	11/44 (25%)	
3	6 (9.1%)	4 (20.0%)	4/10 (40%)	
4*	0	1 (5.0%)	1/1 (100%)	
Type of OS				
1 Plate	26 (39.4%)	7 (35.0%)	7/33 (21%)	<0.001*
2 IMN	27 (40.9%)	1 (5.0%)	1/28 (4%)	
3 EF conversion	4 (6.1%)	7 (35.0%)	7/11 (64%)	
4 EF	9 (13.6%)	5 (25.0%)	5/14 (36%)	
Blood Transfusion				
Yes	18 (27.3%)	11 (55.0%)	11/29 (38%)	0.016* (1)
No	48 (72.7%)	9 (45.0%)	9/57 (16%)	

Legend:
No missing data observation.
Soft tissue damage #.
Impaired: extensive soft-tissue damage frequently with compromised vascularity with or without severe wound contamination, the fracture pattern is complex with marked fracture instability.
Not impaired: clean wound of less than 1 cm in size with little or no contamination, the wound results from a perforation from the inside out by one of the fracture ends injuries have a skin laceration larger than 1 cm, but the surrounding tissues have minor or no signs of contusion with no dead musculature presented.
ASA score # ASA 3 and ASA 4 were unified due to only one patient in ASA 4 group.
(1) For testing the difference in units of blood transfusion (numerical variable).

Table 2
Comparison of Different Immunoinflammatory Parameters between Non-osteomyelitis and Osteomyelitis Group.

PARAMETER (Normal value, Units)	No POM	N/median (IQR)	POM	N/median (IQR)	AUC (95% CI)	P-value	Adjusted P-value
CD25++CD4 (Treg) ADD (1-5%)	34	1.050 (0.80–1.40)	5	1.000 (1.00–1.10)	0.526 (0.231-0.822)	0.849	0.999
CD25++CD4 (Treg) POD4	28	1.500 (1.00–2.125)	6	1.300 (1.20–1.40)	0.539 (0.352-0.725)	0.768	0.999
WBC ADD (4-10x109/L)	56	10.155 (7.775–12.60)	18	10.750 (8.250–13.328)	0.551 (0.395-0.707)	0.520	0.997
WBC POD1	40	8.550 (7.075–9.975)	17	9.600 (7.700–10.500)	0.609 (0.450-0.768)	0.197	0.942
WBC POD4	38	7.800 (6.625–9.600)	17	8.800 (8.100–10.400)	0.624 (0.470-0.778)	0.145	0.902
CRP ADD (0-5 mg/L)	32	5.00 (5.00–29.75)	13	55.000 (7.000–96.000)	0.689 (0.499-0.878)	0.047	0.618
CRP POD1	32	47.500 (26.75-72.75)	16	97.000 (52.250–134.500)	0.684 (0.503-0.864)	0.040	0.567
CRP POD4	31	43.00 (13.00–78.00)	17	65.000 (27.000–123.000)	0.609 (0.437-0.781)	0.215	0.946
PCT ADD, log (0-0.50μg/L)	20	−2.996 (-3.507– (-2.626))	6	−2.611 (-2.921-(−2.329))	0.721 (0.471-0.970)	0.104	0.834
PCT POD1, log	25	−2.813 (-3.219– (-2.408))	6	−1.172 (-2.771-1.127)	0.720 (0.381-1.000)	0.098	0.834
PCT POD4, log	27	−2.813 (-3.363– (-2.592))	5	−2.659 (-2.813-(-2.040))	0.659 (0.319-1.000)	0.262	0.950
ALBUMIN ADD (32-55 g/L)	1	17.000	5	33.000 (25.000-35.000)	NA	NA	NA
ALBUMIN POD1	28	35.500 (32.75–39.00)	10	31.000 (29.000-35.250)	0.679 (0.476-0.881)	0.097	0.834
ALBUMIN POD4	22	39.000 (34.00–41.00)	7	27.000 (26.500-33.000)	0.838 (0.650-1.000)	0.008	0.128
PROTEINS ADD (65-80 g/L)	1	36.000	4	58.000 (51.250-60.500)	NA	NA	NA
PROTEINS POD1	19	58.000 (51.00–61.00)	8	54.500 (51.000-58.000)	0.572 (0.328-0.817)	0.558	0.997
PROTEINS POD4	12	65.500 (54.25-68.00)	8	54.500 (50.500-62.000)	0.724 (0.479-0.969)	0.096	0.834
IL-6 ADD, log (< 3.94 pg/L)	44	0.727 (0.422–1.256)	7	1.172 (0.899-1.535)	0.701 (0.523-0.879)	0.090	0.828
IL-6 POD1, log	32	0.072 (-0.528– 0.637)	6	0.424 (0.380-0.694)	0.690 (0.528-0.852)	0.144	0.902
IL-6 POD4, log	27	0.765 (0.148–1.308)	5	0.531 (0.095-0.854)	0.578 (0.299-0.857)	0.586	0.997
IL-10 ADD, log (< 10.9 pg/L)	43	1.157 (0.824-1.859)	7	2.440 (1.732-2.784)	0.714 (0.498-0.931)	0.071	0.765
IL-10 POD1, log	32	1.352 (0.963–2.327)	6	1.753 (0.799-2.630)	0.503 (0.218-0.788)	0.984	0.999
IL-10 POD4, log	27	1.433 (0.652–2.390)	5	1.463 (1.401-3.991)	0.607 (0.242-0.973)	0.452	0.995
TNFα ADD, log (4.76-12.4 pg/L)	41	0.993 (0.588–1.449)	7	0.850 (0.502-0.940)	0.641 (0.470-0.812)	0.237	0.948
TNFα POD1, log	29	1.044 (0.495–1.670)	6	1.168 (0.805-1.371)	0.532 (0.270-0.794)	0.810	0.999
TNFα POD4, log	25	1.406 (1.075–1.730)	5	1.233 (1.026-1.775)	0.516 (0.186-0.846)	0.911	0.999

Legend: We do not test association for variables with only one patient per group.

The difference was considered statistically significant at $P < 0.05$. All analyses were performed with R statistical software, version 3.3.2.

Results

A total of 86 patients were included in the study, 60 males (69.8%) and 26 females (30.2%). After open reduction and internal fixation (ORIF) of tibial fracture (nailing, plating or external fixation (EF)) in our prospective study 20 cases were diagnosed with POM. The characteristics of the patients, tibial fracture and surgical procedures are shown in Table 1.

Classification of tibial fractures, associated fractures and injuries

The most frequent site of fracture was tibial shaft fracture (52.3%, 45 cases) followed by distal tibial Pilon fracture (31.4%, 27 cases). In the POM group, distal tibia was the predilection site of infection (9 cases, 45%) compared to the No POM group (18 cases, 27.3%). However, site of fracture was not significantly associated with osteomyelitis ($p = 0.198$). Multiple sites fractured and polytraumatized patients were more likely to develop POM (11 cases, 55.0%, in POM vs 10 cases, 15.2%, in No POM; $p = 0.001$).

Injury features, concomitant diseases and age of POM group

Out of 20 patients that developed POM, 11 had sustained an open fracture (55.0%) and 9 a closed one (45.0%). Fall from a height was the main mechanism of injury (8 patients, 40.0%) followed by traffic accident (6 patients, 30.0%) and workplace accident (4 patients, 20.0%). Nine patients had an isolated tibial fracture and the others had multiple site long bone fracture or were polytraumatized. Half of the POM group patients had concomitant disease (cardiovascular, respiratory disease, diabetes, drug or alcohol dependence). The median age of the POM group was 49.5 years (IQR 44.5–61.8 years). There was no statistically significant difference compared to the No POM group (median age 51 years (IQR 37.2–61.2 years), (P-value 0.602).

Perioperative levels of serum immunoinflammatory markers

Inflammatory marker values after surgical procedures were elevated, as expected, reaching a peak value on POD1 (CRP, PCT) and later decreasing (Fig. 1, Table 2). The level of CRP on admission was higher in the POM group compared to non POM group (P –value < 0.05). The median CRP in the No POM group on ADD was 5 mg/L (IQR 5–29.8 mg/L), on POD1 47.5 mg/L (IQR 26.8–72.8 mg/L) and on POD4 43.0 mg/L (IQR 13–87 mg/L). In comparison, the median CRP of the POM group on ADD was 55.0 mg/L (IQR 7.0–96.0 mg/L), on POD1 97.0 mg/L (IQR 52.3–134.5 mg/L) and on POD4 65.0 mg/L (IQR 27.0–123.0 mg/L). ROC analysis was used to compare biomarkers CPR, PCT, WBC count. The highest diagnostic accuracy for POM on ADD was for PCT (AUC = 0.72, 95% CI: 0.47-0.97) and on POD1 also PCT (AUC = 0.72, 95% CI: 0.38–1).

The serum level of albumin on POD4 was significantly lower in POM than in NO POM group (AUC 0.84, 95% CI: 0.65–1, $p = 0.008$, adjusted $p = 0.128$). In contrast to the No POM group, there was even a fall instead of arise on our sample.

Operative fracture treatment, duration of antibiotic treatment and intraoperative pathogenic microorganism culture

The surgical procedures performed for open reduction and fracture stabilization were plating (33 cases), intramedullary nailing (28 cases), EF (14 cases) and EF converted to plate or IMN (11 cases). We found a significant difference ($P < 0.001$) between the No POM and POM groups regarding type of osteosynthesis. Using EF and EF converted to plating or IMN we have in POM group 5 cases (25.0%) and 7 cases (35.0%), respectively, and in No POM group 9 cases (13.6%) and 4 cases (6.1%), respectively. We also evaluated the performance status of patients before surgical procedures using the ASA score. There was no significant difference between groups in the recorded

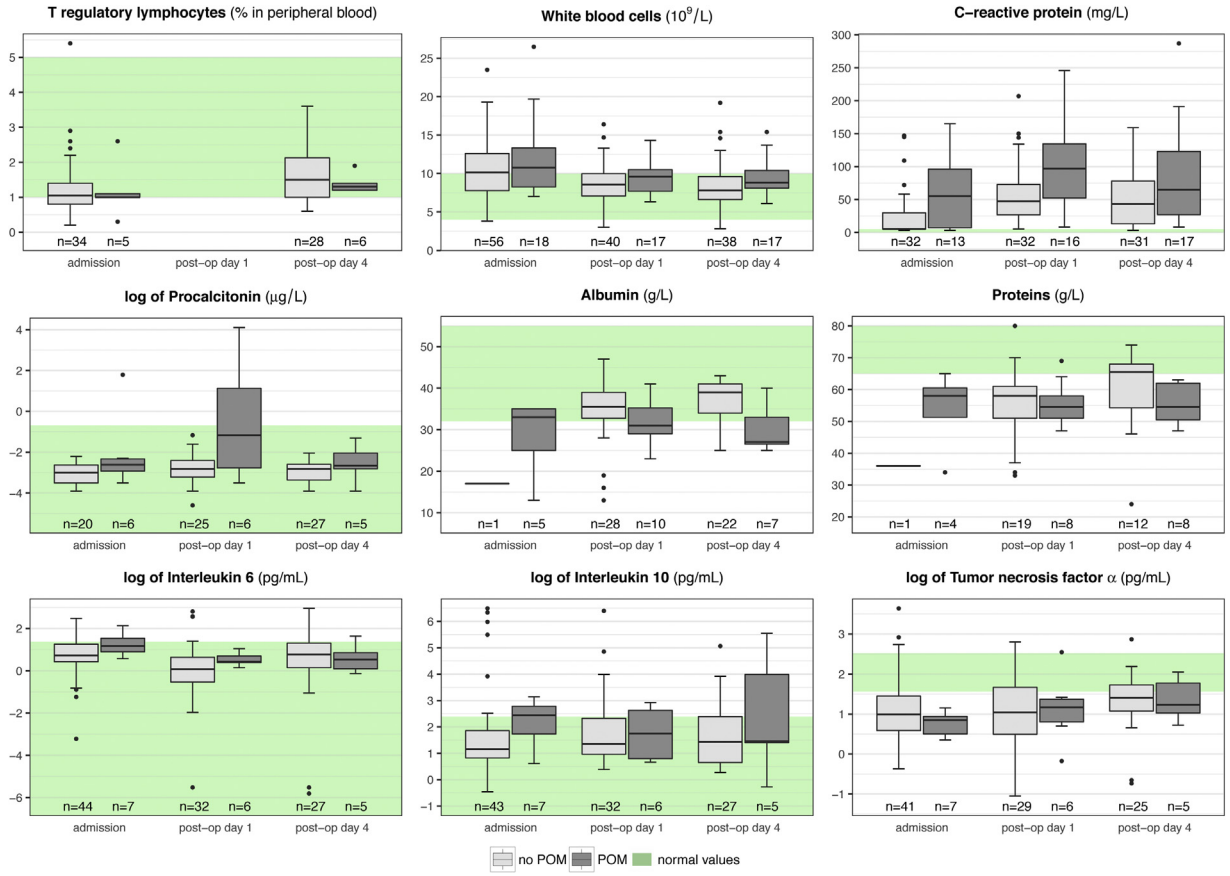

Fig. 1. Inflammatory marker values after surgical procedures in posttraumatic osteomyelitis (POM) versus no-POM group on admission (ADD), first postoperative day (POD1) and fourth-postoperative day (POD4).

scores ASA. In the POM group, we also found a greater number of transfused patients (11 patients, 55%; No POM group 18 patients, 27.3%) there was a significant difference in unit count per patient ($P = 0.016$) (6 unit (IQR 2–8.5 units) in POM group and 3.5 unit in No POM group (IQR 2–5.5 units). We reviewed the clinical data for intravenously used antibiotic for inpatient perioperative prophylaxis and treatment of POM and outpatient oral antibiotics treatment. The median duration of antibiotics therapy for the No POM group was 7 days (IQR 3–14 days) (45.5% of patients, treated for other source infection) and 47 days (IQR 21.5–62.8 days) (all patients) for the POM group. The number of all patients receiving antibiotic therapy was 50 (58.1% of patients). *Staphylococcus aureus* (68%) was identified as a single cause or in polymicrobial bone infection. Pseudomonas aeruginosa, *Escherichia coli* and other Gram-negative anaerobe bacillus accounted for 28% [16].

Conclusion

The following factors were significantly associated with an increased incidence of POM on our sample: extent of soft tissue injury, multiple fracture/polytraumatized patient, amount of transfusion, type of osteosynthesis, CRP serum level on ADD and POD1, serum albumins level on POD4. Further studies are needed to prove association with CRP on ADD and POD1 and fall of serum albumins on POD4 in population (adjusted P-values are larger than 0.10, Table 2).

Discussion

Tibial fracture after high-energy trauma to the shin and surgical management is a common site of infection. Postoperative bone infection is difficult to diagnose due to the lack of specific/sensitive standard diagnostic laboratory methods. The gold standard is blood culture and bone specimen culture to confirm POM but it lacks sensitivity (only 40–60%) and the results are available after 2–3 days.

The present study aim was to identify additional more sensitive markers for POM during the perioperative period. On our sample, we found significantly elevated levels of CRP before surgery (ADD) and first day after surgery (POD1) in POM group compared to No POM group (both $P < 0.05$). Another significant difference between groups was the level of albumins on POD4 ($P = 0.008$). However, these differences between POM and No POM groups were not significant after the adjustment of p values for multiple testing. In our attempt to find additional inflammatory and immune markers of the POM evolution we measured peripheral blood concentration of cytokines (TFN-α, IL-6, IL-10) and T cell subsets. With so many parameters, our study was underpowered to confirm the differences between groups in population, however we have found pronounced POM/No POM differences in IL-10 and Tregs concentration means. New independent study is needed to confirm described differences.

In a recent study, Stucken et al reported that the predicted probabilities of perioperative infection achieved 86% when associated with positive tests of WBC, ESR, and CRP [17]. In similar study (Maharajan K) PCT at cut-off of 0.4 ng/ml was demonstrated 85% sensitive and an 87% specific marker in the diagnosis of septic arthritis and acute osteomyelitis, with predictive value 76% [18]. In contrast studies on an adult population (Fottner [19], Martinot [20]) and on a paediatric population (Butbul-Aviel [21], Faesch [22]) PCT was demonstrated to be a poorly sensitive marker with high specificity at a cut-off of 0.5 ng/ml. Considering the low value of sensitivity, PCT can not be used as a screening test for identifying bone and joint infections in

children. In agreement, in our study we also did not find any statistically significantly elevated levels of PCT in POM compared to control group.

Serum prealbumin and albumin are acute-phase proteins and their serum level is the result of albumin liver production, intake of essential amino acids, loss through gut, renal function. Hypoalbuminemia is also a sign of acute and chronic inflammatory states [23]. No study has directly correlated albumin or prealbumin levels with the severity of POM. In our study, we found that albumin levels on POD4 were significantly lower in the POM group (P = 0.008, adjusted P = 0.128, AUC 0.84, 95% CI: 0.65–1). In a retrospective cohort study performed in South Korea (670 patients), the CRP/albumin ratio on admission was an independent predictor of mortality in patients with severe sepsis or septic shock [24].

We obtained no significant differences between POM/No POM groups in serum IL-6, IL-10 and TNFα in high-energy tibial fractured population. IL-6 and TNF-a achieve higher positive rates than other inflammatory markers for diagnosis in patients with POM, although they are still not widely used in routine laboratory parameters [5]. IL-6 release is triggered by tissue damage or infection with a rapid onset, peaking within 2 h after trauma, and similarly, IL-10 peaks within 4 h following trauma, and the levels decrease rapidly. Since the timing of surgical procedure and sample collection has not been uniformly related to traumatic event, hence the variability of IL-10 and IL-6 levels in our studied population [25]. Pape et al. [26] compared patients with an isolated femoral shaft fracture to polytraumatized patients both treated by femoral nailing. The results demonstrated a significant increase in pro-inflammatory cytokines in correlation with the degree of blood loss. Femoral nailing was found to have a significant impact on inflammatory response, and led to a marked increase in IL-6 concentrations [27].

In addition to the microbial characteristics, host defence status and physical patient performance, the risk of POM is dominated by local factors related to the wound (extent of soft-tissue injury, location of the fracture in tibia and use of ORIF (open reduction, internal fixation) or external fixation) [28]. The choice of ORIF is strongly correlated with the general patients condition, the extent of soft tissue injury, fracture localization and type of fracture, so in POM group we have a reasonably tendency of more EF use (5 patients, 25%) comparing to No POM group (9 patients, 13.6%). The high part of patients with EF conversion (7 patients, 35%) performed after soft tissue recovery in POM group could warn us that we should be precocious of pin track infection after EF, in still persistent deep soft infection.

Finally we can emphasize that perioperative dynamics of CRP particular the significant increased on first postoperative day comparing the admission value and lower albumin value on forth postoperative day should be warning sign for treating surgeon to evaluate other risk factors and perform the revision. Routine perioperative assessment of CRP and albumin in patients with high-energy tibial fracture could be adjuvant tool in POM prevention.

Limitations of this study include a relatively small sample (86 patients) with uneven groups (20 patients in POM group) and frequent missing values for multiple independent factors, and variation in surgical techniques due to different surgeon in charge. Strength includes a prospective clinical study design with interesting question that remains challenging for treating surgeons and having potential serious consequences for patients with high-energy tibial fracture.

Authors' contributions

According to the definition given by the International Committee of Medical Journal Editors (ICMJE), the authors listed above qualify for authorship based on making one or more of the substantial contributions to the intellectual content of article: MG, AI conception and design of the study. MG acquisition of the data, MG, AI, NRG, LL analysed and interpreted the data. AI, NRG, LL participated in drafting of the manuscript. MC was involved in critical revision of the manuscript. All authors approved the final submitted version of manuscript.

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Ethics approval and consent to participate

Ethical approval was obtained prior to study start by the corresponding ethic review board. The Republic of Slovenia National Medical Ethics Committee approved this protocol study (No. 38/05/04). Informed consent was obtained written at follow-up investigation of each patient included.

Competing interests

The authors declare that they have no competing interests.

Content of publication

Not applicable.

Availability of data and materials

The data that were gathered and analysed during current study are not publicly available. Corresponding author can any time provide all the necessary data on request.

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