Citokinski odgovor pri bolnikih, zdravljenih z metodo odprtega trebuha zaradi hude sepse, povzročene z dogajanjem v trebušni votlini

Interleukin response in patients treated with abbreviated laparotomy for severe intraabdominal sepsis

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Izvleček

Uvod: *Pro- in protivnetni citokini igrajo pomembno vlogo pri trebušni sepsi. Študije kažejo, da je poznejši protivnetni odziv za bolnika s trebušno sepso škodljivejši kot začetni pro-vnetni odziv. Zato smo preučevali serumske vrednosti protivnetnih in pro-vnetnih interlevkinov pri bolnikih s trebušno sepso, ki smo jih zdravili z metodo odprtega trebuha.*

Metode: *Izvedli smo prospektivno raziskavo 42 bolnikov, zdravljenih z metodo odprtega trebuha. Bolniki so bili razdeljeni v dve skupini: visoko tvegano skupino (več kot dve menjavi sistema do dokončnega zapiranja trebuha – 24 bolnikov) in skupino z nižjim tveganjem (dve ali manj menjavi sistema do zapiranja trebuha – 18 bolnikov). Izmerili in izračunali smo vrednosti in razmerja med pro- in protivnetnimi citokini prvi dan in deseti dan po prvem posegu.*

Abstract

Background: *Pro- and anti-inflammatory cytokines play an important role in abdominal sepsis. Studies suggest that the anti-inflammatory response is more detrimental to the patient with abdominal sepsis than the initial pro-inflammatory response. We therefore studied the serum levels of pro-inflammatory and anti-inflammatory interleukins in patients with abdominal sepsis treated by abbreviated laparotomy.*

Methods: *We performed a prospective study of 42 patients treated by abbreviated laparotomy. The patients were divided into a high-risk (more than two procedures before abdominal closure) group (24 patients) and a low-risk (two or fewer procedures) group (18 patients). The differences and correlations between the serum levels of pro-inflammatory*

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Rezultati: *Smrtnost je bila bistveno višja v skupini z visokim tveganjem (41,7-% v skupini z visokim tveganjem v primerjavi s 5,6-% v skupini z nizkim tveganjem; p = 0,012). V skupini z visokim tveganjem (22,5 pg/ml (IQR 5,25)) so bile ravni IL-10 v serumu bistveno višje kot v skupini z nizkim tveganjem (12,15 pg/ml (IQR 6,725)) (p = 0,012). Starost je bila pomembno povezana s smrtnostjo (p = 0,007). Logaritmična vrednost ravni IL-10 v serumu prvi dan (HR: 2,5; 95 % IZ: 1,109–5,638; p = 0,027) in mejna vrednost IL-10 (HR: 3,816; 95 % IZ: 1,047–13,910; p = 0,042) sta bili v multivariatni analizi pomembno povezani s slabšim potekom bolezni.*

Zaključek: *Bolniki, ki imajo prvi dan po posegu večji protivnetni odziv, imajo tudi dolgotrajnejši potek in višjo stopnjo umrljivosti. Koncentracija IL-10 v serumu prvi dan po operaciji lahko napove slabši potek bolezni pri teh bolnikih in bi lahko bila uporaben pripomoček pri načrtovanju zdravljenja.*

Results: *The mortality was significantly higher in the high-risk group (41.7% vs. 5.6% in the low-risk group; p = 0.012). IL-10 serum levels were significantly higher in the high-risk group (22.5 pg/mL (IQR 5.25)) compared to the low-risk group (12.15 pg/mL (IQR 6.725)) (p = 0.012). Age was significantly correlated with mortality (p = 0.007). The logarithmic value of IL-10 serum levels on day one (HR: 2.5; 95% CI: 1.109–5.638; p = 0.027) and the IL-10 cut-off value (HR: 3.816; 95% CI: 1.047–13.910; p = 0.042) were significantly correlated with worse disease course in multivariate analysis.*

Conclusion: *Patients who exhibit a greater anti-inflammatory response on day one are at increased risk of a protracted course and higher mortality. IL-10 serum levels on day one after surgery predict a worse disease course in these patients and could be a useful marker of abdominal sepsis.*

INTRODUCTION

Both morbidity and mortality in patients who have undergone surgery for severe abdominal sepsis and who were treated with abbreviated laparotomy (AL) and temporary abdominal closure (TAC) are alarmingly high.[1-5] Even the expeditious treatment of the cause of abdominal sepsis sometimes cannot save patients from their demise. In our previous study, we showed that the mortality rates in patients after ten to 15 days of protracted treatment following AL and TAC rise exponentially despite adequate treatment.[6] We postulated that after ten days these patients enter a state that has been described appropriately as immunological exhaustion and can develop tertiary peritonitis or multiple organ failure.6 Our hypothesis was that the severe pro-inflammatory reaction activated a disproportionally high anti-inflammatory response that is activated between 10 and 15 days after surgery. This mechanism, which aims to quench the initial surge of pro-inflammatory cytokines, is actually more detrimental to the patient than the initial inflammation. Measurement of serum levels of interleukin 6 (IL-6) and interleukin 10 (IL-10) could therefore predict the course and prognosis of severe abdominal sepsis in patients treated with AL and TAC. To identify the patients at risk of a protracted course of abdominal sepsis and consequently likely to experience higher mortality, we studied the serum levels of pro-inflammatory IL-6 and anti-inflammatory IL-10 in patients after these procedures.

PATIENTS AND METHODS

Patients

This prospective study included 42 patients with severe intraabdominal sepsis admitted to the department for Abdominal and General Surgery at our University Clinical Centre. The enrolment occurred in the operating room after the decision was made to perform AL with TAC and planned laparotomy. It was followed by the principle of intraabdominal sepsis treatment consisting of two steps: i) source control and ii) damage control. In the source control step,

the cause of intraabdominal sepsis was treated with an appropriate surgical approach (resection of the damaged viscus, suturing, faecal diversion, removal of necrotic tissue). In the damage control step, a thorough washing of the abdominal cavity with sterile normal saline was undertaken, necrotic tissue removed as a step in reducing the infective burden, and finally, the laparotomy was left open and a negative pressure device applied. TAC was achieved with a negative wound pressure device that was applied in all patients using the same technique. The abdominal viscus was covered with a sterile permeable foil that prevented ingrowth into the polyurethane sponge and fistula formation (visceral protective layer). The second layer consisted of a permeable sterile polyurethane sponge that was placed below the abdominal wall. This sponge was in close contact with the third layer of permeable polyurethane sponge that was placed at the level of the laparotomy. This third layer was sealed off with an adhesive abdominal drape onto which an interface pad was applied. This was connected with tubing set to a negative wound pressure device (RENASYS, Smith and Nephew, London UK). The dressing was regularly changed at 48-hour intervals until the abdominal cavity was free from infective material and the source of the sepsis definitely treated. The negative pressure was held between 90 and 125 mmHg between dressing changes. For further analysis, patients were allocated to one of two groups. The first group consisted of patients who only required one or two additional negative wound pressure device changes before definitive laparotomy closure. This group was defined as the low-risk group (18 patients). Patients who required three or more negative wound device changes or who died at any time during the treatment regardless of the number of dressing changes were included in the second group. This group was defined as the high-risk group (24 patients).

The primary endpoint of the study was analysis of the difference between serum levels of pro-inflammatory IL-6 and anti-inflammatory IL-10 on days one and ten between high-risk and low-risk groups. The secondary endpoints were the correlations between IL-6 and IL-10 serum levels and different clinical parameters, and mortality rates in patients with different IL-6 and IL-10 levels. All patients' data was prospectively collected and stored in the hospital database. Informed consent was waived because of practical problems. Most of the patients were operated on in emergency situations and it was impossible to ask incapacitated patients for informed consent. However, the study was approved by the Institutional Review Board (UKC-MB-KME-18-05/16).

Serum Interleukin-6 and Interleukin-10 measurement

Serum samples were collected from the patients on the first day after the initial operation requiring negative pressure therapy and on day ten. Whole blood samples were collected into tubes and centrifuged at 2,700 × g for 10 min. Serum was then removed and frozen at -80 °C until the final analysis. For the determination of IL-6 and IL-10 levels, we used a solid-phase, enzyme-labelled chemiluminescent sequential immunometric assay (Immulite 1000 analyzer, Siemens Healthcare Diagnostics Inc., Newark, NJ, USA) according to the manufacturer's instructions.

Statistical analysis

Based on the results of Inukai et al. and Waio et al.[2,18], we expected a 40% mortality rate in the high-risk group and 4% mortality in the low-risk group. To achieve a statistical power of 80% to detect an effect at an α-level of 5%, at least ten patients were needed in each group. We included a total of 42 patients which ensured a statistically adequately powered study.

Normally-distributed continuous variables are expressed as mean ± SD and variables without a normal distribution as median ± IQR. All variables were tested for normality distribution with Q-Q Plots. Discrete variables are expressed as absolute number and percentage. For comparison of normally-distributed continuous variables, Student's t-test and one-way ANOVA were used; otherwise, the Mann-Whitney U-test was used. For comparison of discrete variables, the χ^2-test was used. Correlations between different parameters were analysed with the Pearson's test. Variables that were found to be significant and variables with a p value below the threshold of 0.4 were included in multivariate analysis. Correlations between a continuous outcome and multiple predictors were analysed with the linear regression model, while correlations between a discrete outcome and multiple predictors were analysed using a logistic regression model. For the level of significance,

a p value of < 0.05 was selected. Statistical analysis was performed using SPSS v. 20 (IBM SPSS Statistics for Windows, Armonk, NY, USA). Graphs of interleukin serum concentrations were plotted using Excel 2010 for Windows 10 (Microsoft Corporation, Redmond, WA, USA).

RESULTS

Patients

The baseline characteristics of patients allocated to TAC treatment are presented in Table 1. From the 43 patients originally included, one was excluded from the study because he was transferred to another hospital for definitive care. Of the remaining 42 patients, IL-6 and IL-10 samples were obtained at day one in all cases. If a patient died because of sepsis before the second sample could be obtained on day ten, only one sample was analysed. The second sample on day ten was obtained from 34 (80.9%) patients. The mean age of the included patients was 62.9 ± 16 years. The main cause leading to the requirement for the operation was stercoral peritonitis that occurred in 19 (44.2%) patients. In most of the patients, the abdominal cavity was contaminated without adhesions which corresponded to stage Ib of the Bjork classification (18 (41.9%)). The mortality in the patient population was 25.5%, and the laparotomy was successfully closed on day 7.18 ± 7.24 in survivors. Primary closure was achieved in all surviving patients, and no surgical complications were observed. With the

Table 1. *Baseline characteristics of patients allocated to TAC treatment.*

	All patients treated with TAC	Patients treated with TAC		p
		Low-risk patients (less than three TAC changes)	High-risk patients (three or more TAC changes)	
Age [years±SD]	62±15.9	62.89±14	63.33±17.8	NS
Cause of peritonitis [n (%)] Purulent Stercoral Biliary Pancreatitis Intestinal ischemia	12 (27.9) 19 (44.2) 5 (11.6) 3 (7) 4 (9.3)	9 (50) 5 (27.8) 1 (5.6) 2 (11.1) 1(5.6)	3 (12.5) 13 (54.2) 4 (16.7) 1 (4.2) 3(12.5)	NS
Number of TAC changes [n±SD]	2.74±2.55	1.28±0.46	3.92±2.9	<0.0001*
Severity of peritonits [n (%)] Bjork Ia Bjork Ib Bjork Ic Bjork IIb Bjork IIc	8 (18.6) 18 (41.9) 15 (34.9) 1 (2.3) 1 (2.3)	6 (33.3) 5 (27.8) 7 (38.9) 0 (0) 0 (0)	2 (8.3) 12 (50) 8 (33.3) 1 (4.2) 1 (4.2)	NS
Mortality [n (%)]	11 (25.6)	1 (5.6)	10 (41.7)	0.009*
IL-6 day one [pg/mL (IQR)]	631 (2065)	575 (116.35)	670 (245.9)	NS
IL-6 day ten [pg/mL (IQR)]	30.5 (71.45)	25.4 (10.1)	44.65 (16.8)	NS
IL-10 day one [pg/mL (IQR)]	16.5 (22.5)	12.15 (6.725)	22.5 (5.25)	0.012*
IL-10 day ten [pg/mL (IQR)]	5.5 (7.32)	5 (5)	6.05 (5.15)	NS

NS-nonspecific

exception of one patient who wished to finish treatment at another hospital, there were no protocol violations. The study ended on January 27, 2019, when the last patient was allocated to treatment.

The interleukin levels were the highest on day one after the initial operation and then returned to baseline levels by day ten after surgery, regardless of the number of reoperations. The median serum levels of IL-6 were 585 pg/mL (IQR 3551.5) on day one and 38.45 pg/mL (IQR 78.4) on day ten after surgery (Figure 1a). The median serum levels of IL-10 were 17.15 pg/mL (IQR 20.63) on day one and 6.7 pg/mL (IQR 7.6) on day ten after surgery (Figure 1b). The ratio of IL-10:IL-6 on day one was the highest in patients with pancreatitis (13.37 (IQR 28) and lowest in patients with purulent peritonitis (0.82 (IQR 3.26); p = 0.008).

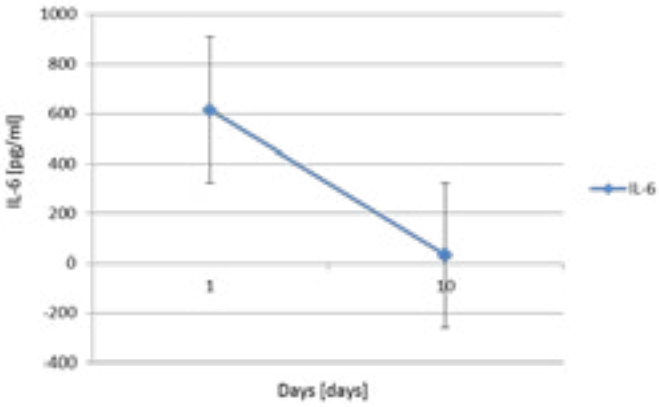

Figure 1.a) *IL-6 serum levels on days one and ten of patients allocated to TAC treatment.*

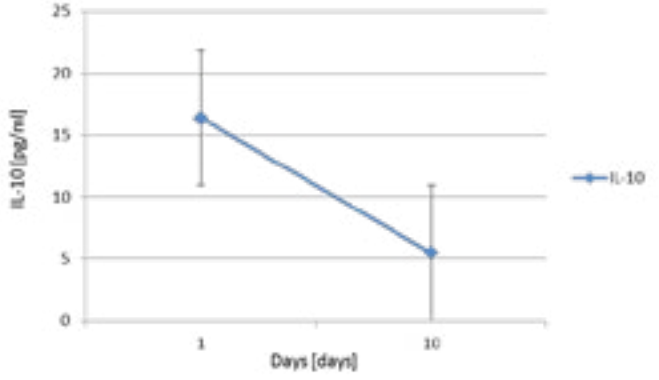

Figure 1.b) *IL-10 serum levels on days one and ten of patients allocated to TAC treatment.*

Comparison of clinical parameters and differences in IL-6 and IL-10 serum levels between low-risk and high-risk groups

The distribution and interleukin levels in the low-risk and high-risk groups are presented in Table 1. There were no statistically-significant differences in age, cause of peritonitis or severity of peritonitis according to the Bjork classification distribution. The average number of TAC changes in the low-risk group was 1.28 ± 0.46, while it was 3.92 ± 2.92 in the high-risk group ($p < 0.0001$). Mortality was significantly higher in the high-risk group (41.7% in the high-risk group vs. 5.6% in the low-risk group; p = 0.012). Although the patients in the high-risk group had higher IL-6 serum values on day one than patients in the low-risk group (high-risk group: 670.5 pg/mL (IQR 245.9) vs. low-risk group: 575 pg/mL (IQR 116.35); p = 0.213), this difference did not reach statistical significance. The serum values of IL-6 on day ten were equal in both groups (Figure 2a). This implied that the IL-6 levels had returned to baseline by day ten after surgery, regardless of the severity of the initial disease or the cause of peritonitis. Compared to the low-risk group (12.15 pg/mL (IQR 6.725); p = 0.012), IL-10 serum levels were significantly higher in the high-risk group (22.5 pg/mL (IQR 5.25)). Similar to IL-6, IL-10 serum values had also returned to baseline levels by day ten (Figure 2b).

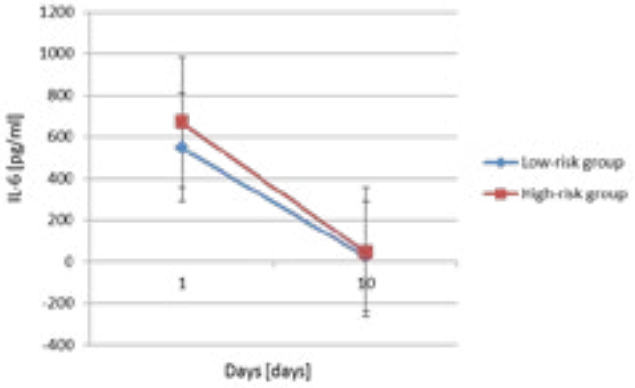

Figure 2.a) *IL-6 serum levels on days one and ten in high-risk and low-risk groups.*

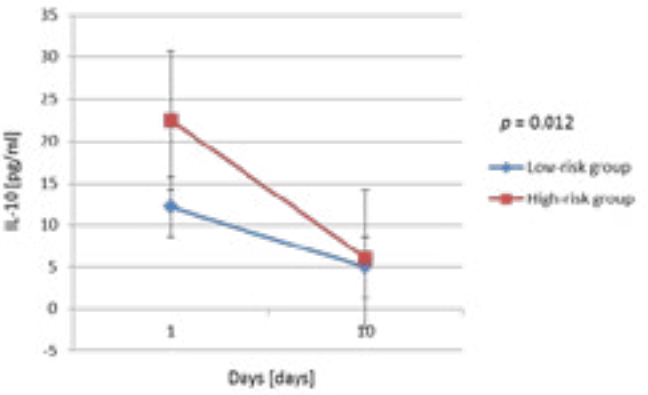

Figure 2.b) *IL-10 serum levels on days one and ten in high-risk and low-risk groups.*

Correlations between IL-6 and IL-10, clinical characteristics, outcome and multivariate analysis

Significant correlations were observed between IL-6 and IL-10 on day one after surgery ($p < 0.0001$). The serum levels of IL-6 on days one ($p = 0.044$) and ten ($p = 0.041$) were found to be significantly correlated with age. Age was also significantly correlated with mortality ($p = 0.007$). We observed a significant positive correlation between mortality and more than three dressing changes – "high-risk group" ($p = 0.008$). The type of peritonitis was significantly correlated with the ratio between IL-10 on day one and IL-6 on day one ($p = 0.008$) and similarly with the IL-6 day one to IL-6 day ten ratio ($p = 0.016$). The ratio of IL-10 to IL-6 on day one determines the relative proportion of the anti-inflammatory response to the pro-inflammatory response. Lower ratios signify a proportionally greater pro-inflammatory response. The IL-6 day one to IL-6 day ten ratio gives a normalised IL-6 value that indicates the initial rise of the pro-inflammatory IL-6 as a response to sepsis. Table 2 presents correlations between different parameters.

Table 2. *Correlations between clinical parameters and serum IL-6 and IL-10 levels of patients allocated to TAC treatment.*

	IL-6(day 1)	IL-6(day 10)	IL-10(day 1)	IL-10(day 10)	Age	Type of peritonitis	Severity of peritonitis	Number of changes	High-risk group	Mortality
IL-6(day 1)		NS	<0.0001*	NS	0.044*	NS	NS	NS	NS	NS
IL-6(day 10)	NS		NS	NS	0.041*	NS	NS	NS	NS	NS
IL-10(day 1)	<0.0001*	NS		NS	NS	NS	NS	NS	NS	NS
IL-10(day 10)	NS	NS	NS		NS	NS	NS	NS	NS	NS
Age	0.044*	0.041*	NS	NS		NS	NS	NS	NS	NS
Type of peritonitis	NS	NS	NS	NS	NS		NS	NS	NS	NS
Severity of peritonitis	NS	NS	NS	NS	NS	NS		NS	NS	NS
Number of changes	NS	NS	NS	NS	NS	NS	NS		NS	NS
High-risk group	NS	NS	NS	NS	NS	NS	NS	NS		0.008*
Mortality	NS	NS	NS	NS	NS	NS	NS	NS	0.008*	

NS-nonspecific

Receiver operating characteristic (ROC) curve analysis was used to determine threshold levels of IL-10 on day one for a worse course of sepsis. For the cut-off, a serum level of 15 pg/mL was chosen with an area under the curve (AUC) of 0.728 (p = 0.012). The sensitivity and specificity for prediction of a worse course were 70.8% and 61.1% respectively.

All significant factors were included in the multivariate analysis. The linear regression model confirmed a significant correlation between IL-6 and age (HR: 0.308; 95% CI: 0.000–0.001; p = 0.044). Figure 3 shows a scatter plot of the IL-6 serum levels on day one and age with a regression line. From the included parameters in the logistic regression model, the logarithmic value of serum IL-10 levels on day one (HR: 2.5; 95% CI: 1.109–5.638; p = 0.027) and the IL-10 cut-off value (HR: 3.816; 95% CI: 1.047–13.910; p = 0.042) were significantly correlated with worse sepsis course.

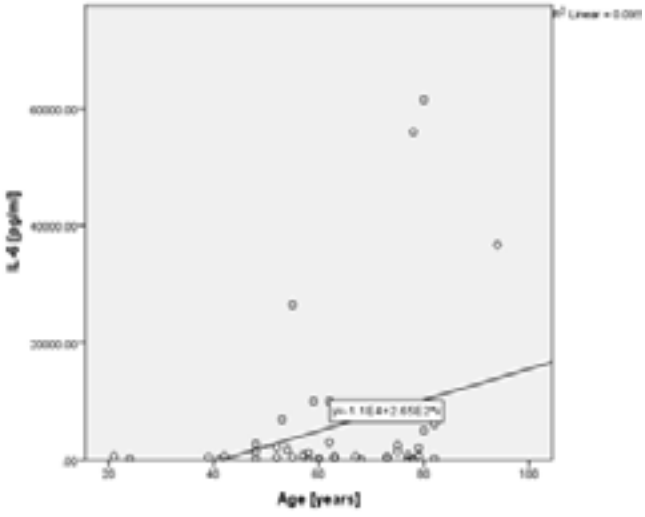

Figure 3. *Scatter plot of the IL-6 serum levels on day one and age of patients allocated to TAC treatment.*

DISCUSSION

In order to identify patients at risk for a protracted course of abdominal sepsis and higher mortality, we investigated the postoperative inflammatory response and the IL-6 and IL-10 serum levels as markers of severity of the inflammatory response. In our previous study, we showed that more than six TAC device changes are a significant predictor of mortality in patients with severe abdominal sepsis.6 The negative impact of prolonged TAC treatment is evident by the significantly higher morbidity of patients in the present study with more than three TAC changes and prolonged treatment. Our results even indicate that the number of TAC changes has a stronger impact on the disease course than the cause of peritonitis, the gravidity of peritonitis and age. This is surprising, since some forms of intraabdominal sepsis have been shown to have a worse prognosis.[3] Comorbidities, age and the general condition of the patients have also been proven to be significant factors in the prognosis of patients with severe sepsis.[2] Therefore, other factors must have played a more important role in patients' prognosis in our study. As both the high- and low-risk groups in our study were matched for age, cause of peritonitis and severity of peritonitis, the surgical treatment and the immunological response to the surgery must have played a more important role in prognosis.

The course of sepsis in surgical patients differs to that in patients with non-surgical disease.[17] The surgical treatment itself causes an immunological response that can be detrimental for the patient. Some patients with catastrophic intraabdominal sepsis are characterised by a protracted course at the end of which, despite adequate treatment of the original causative agent, tertiary peritonitis and multiple organ failure usually ensues. We propose that the trigger for the therapy failure is the exaggerated anti-inflammatory response activated around day ten after AL (abdominal lavage) and TAC.

Until recently, the accepted model of the host immune response to sepsis was biphasic.[7] In the first phase after infection, the systemic inflammatory response targets the causative organisms aiming to remove the virulent agents.[7] The surviving patients enter an immunosuppressive phase in which they can succumb to tertiary peritonitis despite adequate treatment of the primary cause of sepsis.[7] In our patient group, we also noticed a rise of pro-inflammatory IL-6 on day one after surgery. The IL-6 levels then decreased to baseline by day ten. However, high-risk patients in our study had only insignificantly higher levels of pro-inflammatory IL-6 than low-risk patients on day one.

While the pro-inflammatory response was greater in the high-risk group, this difference did not reach the level of significance. This is somewhat counter-intuitive, because we would expect a higher inflammatory response in patients with a worse course of sepsis. Many studies have shown that the increase of IL-6 on the first day is prognostic for higher morbidity.[9,11,16] In these studies, however, heterogeneous groups of patients were studied, many of which did not need surgical treatment.[9,11,16] This shows that a different mechanism beside the pro-inflammatory response might have a more detrimental effect on the disease course in severe abdominal sepsis in patients treated with AL and TAC. We also observed that the level of IL-6 response is significantly associated with age, which could account for a more heterogeneous response in patients with abdominal sepsis. Therefore, the serum IL-6 levels on day one might be too unreliable to predict a worse course in patients treated with AL and TAC.

In our study group, we found significantly higher levels of IL-10 in patients with worse disease course, but the levels of IL-10 were increased much sooner than expected. We noticed a correlation between IL-6 and IL-10 already on day one, implying that the inflammatory and anti-inflammatory cascades are activated simultaneously in the initial phase of severe abdominal sepsis. Similar observations were made by Tamayo et al., Cavaillon et al. and Rodriguez-Gaspar et al., which also support the model of simultaneous activation of pro- and anti-inflammatory responses.[12,14] In our study, the anti-inflammatory cytokine IL-10 peaked on day one after surgery and was significantly higher in patients with worse disease course. These levels dropped to baseline by day ten and were similar to those of the low-risk group on day ten. This supports the observations that the anti-inflammatory response occurs simultaneously with the pro-inflammatory response, as reported by Tamayo et al., Cavaillon et al. and Rodriguez-Gaspar et al.[12,14] In addition, we observed that this anti-inflammatory response plays a much more important role in determining the further course and the outcome of severe abdominal sepsis than the pro-inflammatory response. The logarithmic function of serum IL-10 levels was found to be a significant predictor for a high-risk course of severe abdominal sepsis in multivariate analysis. By ROC analysis, we determined the threshold level of serum IL-10 to be 15 pg/mL for the high-risk course. This threshold level proved to be a significant predictor of a worse course of abdominal sepsis in multivariate analysis. The greater impact of the anti-inflammatory cytokine IL-10 in patients with sepsis was also observed by Li et al.[15] They also showed that the IL-10 to T-lymphocyte ratio is a significant predictor of mortality.15 IL-10 might be a marker of excessive TH2 cell subset activation. Many recent studies have shown that upon engaging with the major histocompatibility complex II on the surface of antigen-presenting cells, different T cell subsets are activated.[19] The largest group of T cells in the body is the CD4+ T cell population, most of which are the so-called T helper cells (TH). The response to antigens varies according to the balance of two main TH subsets, TH1/TH2. In some cases, there is an overexpression of TH2cells, specifically the regulatory TR1 cells. These cells produce IL-10 that quells the T-cell response. This is in accordance with the results of our study. In future studies, it might be valuable to search for the exact mechanism responsible for the excessive TH2 activation in severe abdominal sepsis.

Another important implication of our findings is that due to the early IL-10 response in severe intraabdominal sepsis, serum IL-10 levels could serve as a convenient marker for worse prognosis in patients treated with AL and TAC devices.

From the results presented in our study we can conclude that the anti-inflammatory response plays a very important role in the course of severe intraabdominal sepsis in patients with AL and TAC devices. Patients who exhibit a greater anti-inflammatory response on day one are at higher risk for a protracted course and higher mortality rates, and high IL-10 levels on day one could serve as an important marker for worse prognosis.

REFERENCES

1. Kirkpatric AW, Roberts DJ, Faris PD, et al. Active negative pressure peritoneal therapy after abbreviated laparotomy. The intraperitoneal vacuum randomized controlled trail. Annals of Surgery 2015;262(1):38–46.https://doi.org/10.1097/SLA.0000000000001095.
2. Inukai K, Usui A, Yamada, et al. Open abdominal management for perforative peritonitis with septic shock: a retrospective analysis on usefulness of a standardized treatment. Eur J Trauma Emerg Surg 2019;1–6. https://doi.org/10.1007/s00068–019–01132–2.
3. Muresan MG, Balmos IA, Badea I, Santini A. Abdominal sepsis: An Update. J Crit Care Med 2018;4(4):120–125.https://doi.org/10.2478/jccm-2018–0023.
4. Kushimoto S, Miyauchi M, Yokota H, Kawai M. Damage control surgery and open abdominal management: Recent advances and our approach. J Nippon Med Sch 2009;76(6):280–290.
5. Godat L, Kobayashi Leslie, Costantini T, Coimbra R. Abdominal damage control surgery and reconstruction: world society of emergency surgery position paper. World Journal of Emergency Surgery 2013;8(53): 1–7.
6. Krebs B, Jagric T. Does negative-pressure wound therapy for the open abdomen benefit the patient? A retrospective cohort study. Adv Skin and Wound Care 2017;30(6):256–260. https://doi.org/10.1097/01.ASW.0000516196.19330.6f.
7. Ward NS, Casserly B, Ayala A. The compensatory anti-inflammatory response syndrome (CARS) in critically ill patients. Clinical Chest Med 2008;29:617–25.https://doi.org/10.1016/j.ccm.2008.06.010.
8. Roberts D, Jenne CN, Ball CG, et al. Efficiancy and safety of active negative pressure peritoneal therapy for reducing the systemic inflammatory response after damage control laparotomy (the intraperitoneal Vacuum Trial): study protocol for a randomised controlled trial. Trials 2013;14:141-127. https://doi.org/10.1186/1745–6215–14–141.
9. Wiersinga WJ, Leopold SJ, Cranendonk DR, van der Poll T. Host immune response to sepsis. Virulence 2014;5(1):36–44. https://doi.org/10.4161/viru.25436
10. Flohe SB, Agrawal H, Schmitz D, Gertz M, Flohe S, Schade FU. Dendritic cells during polymicrobial sepsis rapidly mature but fail to initiate a protective Th1-type immune response. J Leukoc Biol 2006;79:473–481.https://doi.org/10.1189/jlb.0705413.
11. Boomer JS, To K, Chang KC, et al. Immunosuppresion in patients who die of sepsis and multiple organ failure. JAMA 2011;306(23):2594–2605. https://doi.org/10.1001/jama.2011.1829.
12. Tamayo E, Fernandez A, Almensa R, et al. Pro- and anti-inflammatory responses are regulated simultaneously from the first moments of septic shock. Eur Cytokine Netw 2011;22(2):82–7. https://doi.org/10.1684/ecn.2011.0281.
13. Cavallion JM, Adib-Conquy M, Fitting C, Adrie C, Payen D. Cytokine cascade in sepsis. Scand J Infect Dis 2003;35:535–44.
14. de Pablo R, Monserrat J, Reyes E, et al. Mortality in patients with septic shock correlates with anti-inflammatory but not pro-inflammatory immunododulatory molecules. J Intensive Care Med 2011;26:125–32. https://doi.org/10.1177/0885066610384465.
15. Li X, Xu Z, Pang X, Huang Y, et al. Interleukin-10/lymphocyte ratio predicts mortality in severe septic patients. PLoS One. 2017; 12(6):e0179050. https://doi.org/10.1371/journal.pone.0179050
16. Hotchkiss RS. Sepsis-induced immunosuppression: from cellular dysfunctions to immunotherapy. 2013 Nat Rev Immunol. 2013;13(12):862–874. https://doi.org/10.1038/nri3552.
17. Siekmann W, Eintrei C, Magnuson A, et al. Surgical and not analgesic technique affects postoperative inflammation following colorectal cancer surgery: a prospective randomized study. Colorectal Dis 2017;19(6):186–95.https://doi.org/10.1111/codi.13643.
18. Xiao Z, Wilson C, Robertson HL, et al. Inflammatory mediators in intra-abdominal sepsis or injury – a scoping review. Critical Care, 2015; 19(373): 1-13. DOI: 10.1186/s13054–015–1093–4.
19. Bonilla FA, Oettgen HC. Adaptive immunity. J Allergy Clin Immun, 2010; 125:S33–40.