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The systemic impact of a surgical procedure in older oncological patients

Matthijs Plas [a], Jacco J. de Haan [b], Hanneke van der Wal-Huisman [a], Abraham Rutgers [c], Anthony R. Absalom [d], Geertruida H. de Bock [e], Barbara L. van Leeuwen [a, *]

[a] University of Groningen, University Medical Center Groningen, Department of Surgery, Hanzeplein 1, 9700, RB, Groningen, the Netherlands
[b] University of Groningen, University Medical Center Groningen, Department of Medical Oncology, Hanzeplein 1, 9700, RB, Groningen, the Netherlands
[c] University of Groningen, University Medical Center Groningen, Department of Rheumatology and Clinical Immunology, Hanzeplein 1, 9700, RB, Groningen, the Netherlands
[d] University of Groningen, University Medical Center Groningen, Department of Anesthesiology, Hanzeplein 1, 9700, RB, Groningen, the Netherlands
[e] University of Groningen, University Medical Center Groningen, Department of Epidemiology, Hanzeplein 1, 9700, RB, Groningen, the Netherlands

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ABSTRACT

Background: An excessive inflammatory response accounts partially for the increased morbidity and mortality seen in elderly surgical patients. The aim of this study was to investigate the association between a range of pre- and peroperative factors and the extent of the inflammatory response, and to identify patients at risk of a greater inflammatory response following surgery.
Methods: Patients 65 years and older undergoing a surgical procedure for a solid malignant tumour were prospectively included in an observational cohort study. Inflammatory markers were measured in plasma samples pre- and postoperatively: C-reactive protein (CRP), Interleukin-1 beta (IL-1β), IL-6, IL-10, IL-12, and Tumour necrosis factor alpha (TNF-α). Preoperative and postoperative inflammatory factor assay results were compared, and associations between inflammatory markers and pre- and peroperative factors were explored using multivariate linear regression analysis.
Results: Between July 2010 and April 2014, plasma samples of 224 patients were obtained. Median age was 72 (65–89) years and 108 (48.2%) patients were male. The predominant diagnosis was carcinoma, 156 (69.6%). Anaesthesia duration was associated with increase in CRP, IL-1β and IL-6; intracavitary surgery with increase in IL-6; blood loss with decrease in CRP and IL-1β; total fluid volume administered with a decrease in IL-1β and disease stage was associated with increase in IL-6.
Conclusions: The perioperative inflammatory response is related more to surgical characteristics rather than to preoperative factors (with the exception of disease stage). Elderly oncological patients undergoing longer lasting, intracavitary surgical procedures for more advanced disease stages develop the most intense inflammatory response.

Introduction

Over the next decades the global burden of cancer will increase, with over 20 million new cancer cases expected annually as early as 2025 [1]. The majority of new patients with cancer are elderly [2]. Due to the combination of a growing cancer incidence, ageing of the population, and surgery continuing to be the principle treatment for many solid tumors, the number of elderly patients undergoing surgery as part of cancer treatment is expected to increase strongly. With advancing age, the immune system declines in reliability and efficiency, leading to greater susceptibility to a pathological course of an inflammatory response. This process is called “inflammaging” [3–5]. In a surgical setting, where tissue barriers are breached, tissue damage activates the immune system leading to a systemic inflammatory response [6,7]. Although intended to be protective by eliminating invading pathogens and repairing damaged tissue, an excessive inflammatory response can cause collateral tissue

* Corresponding author. University of Groningen, University Medical Center Groningen, Department of Surgery, Groningen, HPC BA31, P.O. Box 30.001, 9700, RB Groningen, the Netherlands.
E-mail address: b.l.van.leeuwen@umcg.nl (B.L. van Leeuwen).

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damage and lead to pathology [8]. The systemic inflammatory response can be investigated straight-forward by assaying circulatory inflammatory markers, such as cytokines and other proteins [9]. Tumour necrosis factor-alpha (TNF-α) is one of the first detectable cytokines during an immune response, regulating the release of both pro- and anti-inflammatory mediators [10]. Important pro-inflammatory cytokines are Interleukin-1 beta (IL-1β), crucial for host-defense responses to infection and injury, and Interleukin-6 (IL-6) that is a prognostic factor for postoperative outcome in trauma patients [11,12]. Interleukin-10 (IL-10) is a strong anti-inflammatory cytokine in the acute phase that suppresses the release of Interleukin-12 (IL-12) that is crucial in preserving a responsive immune system in the postoperative period. In clinical practice, C-reactive protein (CRP), an acute phase protein produced by the liver in response to IL-6, is a standard clinical marker of inflammation [13]. Postoperative complications in elderly patients are associated with higher morbidity and mortality rates and can affect quality of life [14,15]. An excessive inflammatory response following surgery may account partially for the increased morbidity and mortality seen in elderly surgical patients. Nowadays, frailty, comprehensive geriatric assessments, pre- and rehabilitation programs, and multidisciplinary collaborations are getting attention in the elderly, all aimed to improve the postoperative outcome. However, there is still a lack of knowledge concerning the differences in physiological response to the surgical procedure itself in the elderly. The aim of the current study, a prospective cohort study of elderly patients undergoing oncological surgery, was to investigate pre- and peroperative factors associated with the extent of the inflammatory response, and to identify those patients at risk of a greater inflammatory response following surgery.

METHODS

The PICNIC cohort

The data used for this study is a sub-set of data gathered during the prospective observational study, 'PICNIC' (PostoperatIve Cognitive dysfunctioN In elderly Cancer patients), conducted from July 2010 until April 2014 at the University Medical Center Groningen (UMCG, Groningen, the Netherlands) [16,17]. This study was approved by the Medical Ethical Committee of the UMCG, and registered in the Dutch Clinical Trial Database (trial number NL31486.042.10). Patients aged 65 years and over, admitted to the UMCG for an elective surgical resection of a solid tumour (including gynaecological tract, digestive tract, soft tissue) were recruited. Written informed consent was obtained from all participants according to local regulations and data collection was conducted according to the declaration of Helsinki. Exclusion criteria of the 'PICNIC' study included: any physical condition potentially impeding compliance with the study, such as a severe visual or auditory impairment or a recent history of stroke (or other preoperative cognitive deficits) and insufficient understanding of the Dutch language. Of 307 patients included in the 'PICNIC' study, 14 patients were incorrectly included and 19 patients withdrew consent, so that data from 274 patients were available for analysis.

Blood plasma sampling and biochemical analyses

Blood samples were collected preoperatively, before induction of anaesthesia (T0) and at wound closure at the end of surgery (T1). The collection of blood was combined with blood withdrawals for standard care via (venous) lines placed for the surgical procedure. After blood samples were centrifuged at 2600 G for 10 min, plasma was aspirated and stored at −80 °C. For the current study, only patients (n = 224) with blood plasma sampled at both sampling moments were included. The surgery-evoked inflammatory response was evaluated by calculating the changes in plasma inflammatory markers. The following biomarkers were assessed for the current analysis; CRP, IL-1β, IL-6, IL-10, IL-12 and TNF-α. Analyses were performed in batches by Haemoscan ® (Groningen) using sandwich ELISA technique for interleukins, developed by BioLegend (San Diego, CA) and high sensitivity ELISA (Dakopatts, Glostrup, Denmark) for CRP.

Outcomes and determinants

Primary outcomes were plasma level alterations of inflammatory markers CRP, IL-1β, IL-6, IL-10, IL-12 and TNF-α during surgical procedures. As a measure of the surgery-evoked inflammatory response, preoperative results of the inflammatory factor assays were subtracted from the postoperative outcomes (ΔCRP, ΔIL-1β, ΔIL-6, ΔIL-10, ΔIL-12 and ΔTNF-α). Secondary outcomes were the preoperative plasma levels of the assessed inflammatory markers CRP, IL-1β, IL-6, IL-10, IL-12 and TNF-α. Determinants considered were: age, gender, BMI, smoking state, comorbidities according to the Charlson Comorbidity Index (CCI), diabetes, COPD, hypertension, renal failure, cardiac problems, neo-adjuvant treatment, disease stage, immunosuppressive use, surgery duration, intracavitary surgery, blood loss, red blood cell (RBC) transfusion and epidural use.

Definitions and data collection

All clinical data such as age, gender, BMI, tumour type, disease stage, CCI, comorbidities, neo-adjuvant treatment and the surgical characteristics were prospectively collected. Steroids, nonsteroidal anti-inflammatory drugs (NSAIDs), disease-modifying anti-rheumatic drugs (DMARDs) and/or biologicals were considered immunomodulating drugs and as such registered in our dataset. Data about immunomodulating medication use and smoking were collected retrospectively by reviewing the electronic medical record (EMR). Smoking status was classified as: non-smoker, smoker and ex-smoker. Propofol administration during the maintenance phase of anaesthesia was defined as intravenous anaesthesia, whereas use of iso-, sevo- or desflurane maintenance was defined as inhalational anaesthesia. A surgical procedure in the thoracic or abdominal cavity was defined as intracavitary surgery.

Data analysis and statistics

Continuous data are presented as median and range, as the data were non-normally distributed. Categorical data are presented as number and percentages. Differences of the plasma levels of the inflammatory markers between sampling moments were explored to investigate the inflammatory response to the surgical procedure, by performing a Wilcoxon signed rank test. Logarithmic transformation was applied on the inflammatory response data (for the perioperative inflammatory response after subtraction), to reduce skewness and to approach normal distribution. Linear regression analyses were performed to evaluate which determinants were associated with the primary (surgery-evoked inflammatory response) and secondary (preoperative plasma levels of inflammatory markers) outcomes. All determinants were included in univariate analysis. If determinants were found significant ($p < 0.1$) in univariate analyses, multivariate linear regression analyses was performed. Step-by-step elimination of the least significant variable with backward selection was used for developing a multivariate model including only statistical significant variables. Post-hoc testing was executed according to the Bonferroni correction

method to correct for multiple testing in univariate analyses [18]. Results from linear regression analyses (B and 95% CI's) are represented in 10log scale. *P*-values <0.05 were considered to be statistically significant for multivariate testing. Data analyses were performed using IBM SPSS Statistics version 23 (IBM Corporation, Armonk, NY) and GraphPad Prism version 5.04 (GraphPad Software, San Diego, CA).

RESULTS

The demographic, tumour and surgical characteristics of 224 patients, included in the current analysis, are shown in Table 1. The median age of those included was 72 (65–89) years and 108 (48.2%) patients were male. Median score for the Charlson Comorbidity Index (CCI) was 3 (2–9). Hypertension was the most frequently noted comorbidity, in 76 (34.1%) patients of the study population. Of those included, 19 (8.5%) patients used immunomodulating medication. Histological diagnosis was carcinoma in 156 (69.6%) patients, sarcoma in 29 (12.9%) patients and melanoma in 25 (11.2%) patients. Most patients (176 (78.9%)) did not receive neo-adjuvant therapy (chemotherapy, radiation therapy or a combination) as part of their cancer treatment. All disease stages (I, II, III and IV) were represented in this cohort and in 11 (5.0%) patients histological examination did not show malignant disease postoperatively. One hundred and fifty three (68.3%) patients underwent surgery in the thoracic or abdominal cavity.

Table 1
Patient, tumour and surgical characteristics.

Patient and tumour characteristics	Included in current analysis (n = 224)
Age (years)	72 (65–89)
Gender	
Female	116 (51.8%)
Male	108 (48.2%)
BMI	26.3 (18.7–39.5)
Smoking	
No	164 (83.7%)
Yes	21 (10.7%)
Former	11 (5.6%)
Charlson Comorbidity Index (CCI)	3 (2–9)
Diabetes	46 (20.6%)
COPD	24 (10.7%)
Hypertension	76 (34.1%)
Renal failure	7 (3.1%)
Cardiac problems	32 (14.3%)
Immunomodulating drug use	19 (8.5%)
Tumour type	
Carcinoma	156 (69.6%)
Sarcoma	29 (12.9%)
Melanoma	25 (11.2%)
Other malignancy	3 (1.3%)
No malignancy	11 (4.9%)
Neo-adjuvant treatment	
None	176 (78.9%)
Chemotherapy	21 (9.4%)
Radiation	8 (3.6%)
Combination	18 (8.1%)
Disease Stage	
Benign	11 (4.9%)
I	54 (24.1%)
II	55 (24.6%)
III	60 (26.8%)
IV	44 (19.6%)
Surgical characteristics	
Intracavitary surgery	
No (Skin/Extremities/Neck)	71 (31.7%)
Yes (Abdomen/Thorax)	153 (68.3%)
Anaesthesia type	
Intravenous	145 (70%)
Inhalational	62 (30%)
Blood loss (ml)	150 (0–8300)
RBC 's transfusion (#)	0 (0–10)
Anaesthesia duration (min)	199.5 (40–1132)
Total transfusion (ml)	2000 (0–16000)
Epidural	113 (50.4%)
Median (range) & number (%)	

Inflammatory marker plasma levels

The plasma concentrations of inflammatory markers CRP, IL-1β, IL-6, IL-10, IL-12 and TNF-α are shown in Table 2. Preoperative plasma concentrations, those at wound closure and the perioperative change are presented. A significant difference for plasma levels between sampling moments was seen for the inflammatory markers CRP, IL-1β, IL-6 and IL-10 (Fig. 1).

Factors associated with baseline plasma concentrations

Univariate linear regression analyses showed that patient and tumour characteristics, including comorbidities and neo-adjuvant treatment, were not significantly associated with baseline plasma concentrations of the inflammatory markers (supplemental Table).

Factors associated with perioperative change in plasma concentrations

Chemoradiation as neo-adjuvant treatment was associated with a perioperative increase in plasma concentrations of IL-6 in univariate analyses (Table 3). Major surgery was found to be associated with perioperative increase in IL-6 and IL-10, whereas intracavitary surgery was only associated with perioperative increase in IL-6. Blood loss and the number of RBC's transfused were associated with perioperative decreases in CRP and IL-1β, and an increase in IL-6. Anaesthesia duration was associated with the perioperative increase in IL-6 and IL-10. Total fluid transfusion was associated with the perioperative decrease in CRP and IL-1β, and increase in IL-6, and IL-10. Lastly, epidural use was associated with the perioperative increase in IL-6. No other patients or tumour characteristics were found to be associated with changes in the inflammatory markers (Table 3).

Multivariate linear regression analysis showed that different surgical characteristics, and disease stage, were associated with the perioperative changes of the inflammatory markers CRP, IL-1β and IL-6 (Table 4). Anaesthesia duration was associated with increase in CRP, IL-1β and IL-6; intracavitary surgery was associated with increase in IL-6; blood loss was associated with decrease in CRP and IL-1β; total fluid transfusion was associated with IL-1β and disease stage was associated with increase in IL-6. Multivariate modelling for IL-10 did not reveal independent associations. Multivariate modelling for the perioperative inflammatory response of IL-12 and TNF-α was not performed as these markers did not show a

Table 2
Peroperative plasma cytokine levels (n = 224).

Marker	Baseline (T0)	Wound closure (T1)	Δ (T1-T0)	*p-value**
CRP	5.7 (0–204)	5.0 (0–189)	−0.6 (-117–143)	<0.001
IL-1β	0.0 (0–33)	0.6 (0–33)	0.4 (-23–14)	<0.001
IL-6	0.0 (0–652)	88.6 (0–2386)	73.2 (-13–2386)	<0.001
IL-10	13.0 (0–1565)	56.0 (0–1648)	34.5 (-544–1378)	<0.001
IL-12	0.0 (0–1746)	0.0 (0–1437)	0.0 (-309–73)	0.743
TNF-α	0.0 (0–1056)	0.0 (0–1156)	0.0 (-147–910)	0.151

Variable is denoted as median (range).
*Differences between the two blood plasma samples were tested with the Wilcoxon signed rank test. A p-value of <0.05 was considered significant.

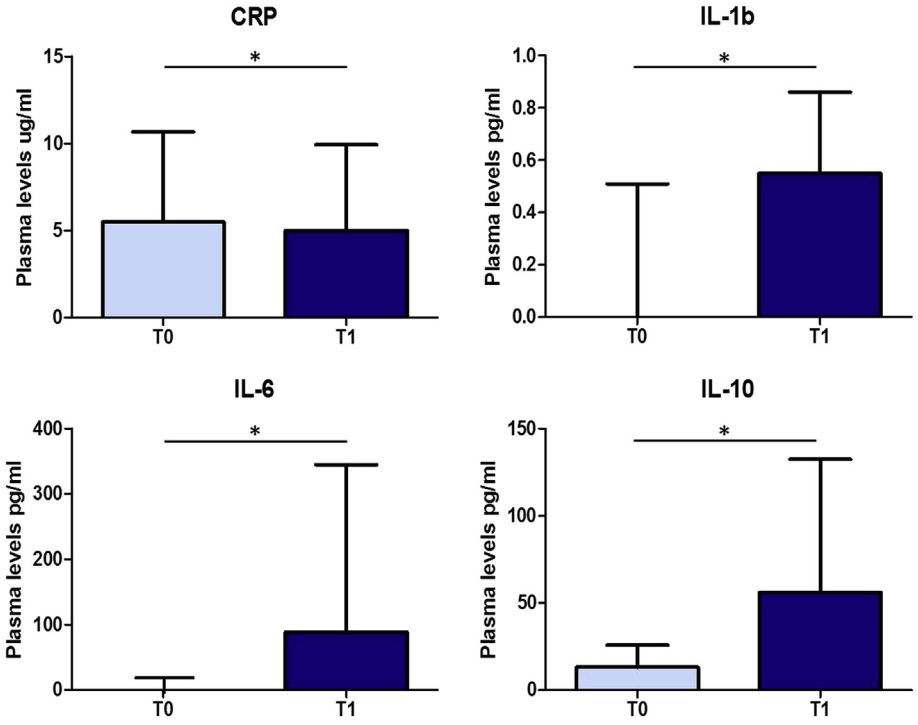

Fig. 1. This figure depicts plasma levels (median and interquartile range) of different inflammatory markers preoperatively (T0) and at would closure (T1). The shown inflammatory markers showed a significant change between samplings moments.

Table 3
Univariate linear regression analyses of the peroperative inflammatory response(Δ cytokine blood plasma levels) (n = 224) (10Logaritmic transformation).

Patient and tumour variables	CRP	IL-1β	IL-6	IL-10
	B (95%CI)	B (95%CI)	B (95%CI)	B (95%CI)
Age	0.001 (−0.003–0.01)	0.002 (−0.001–0.01)	−0.01 (−0.02–0.01)	0.00 (−0.004–0.01)
Gender	0.03 (−0.01–0.07)	0.02 (−0.02–0.06)	0.10 (−0.09–0.30)	−0.01 (−0.07–0.04)
BMI	0.00 (−0.001–0.001)	0.00 (−0.001–0.001)	−0.002 (−0.01–0.002)	0.00 (−0.001–0.001)
Smoking				
No	1	1	1	1
Yes	0.03 (−0.04–0.10)	0.02 (−0.04–0.09)	0.14 (−0.20–0.47)	0.01 (−0.08–0.11)
Former	0.01 (−0.09–0.10)	0.004 (−0.08–0.09)	0.34 (−0.11–0.79)	0.03 (−0.10–0.15)
Charlson Comorbidity Index	0.004 (−0.01–0.02)	0.01 (−0.01–0.02)	−0.003 (−0.06–0.06)	0.01 (−0.01–0.02)
Diabetes	0.01 (−0.05–0.06)	0.02 (−0.03–0.06)	0.07 (−0.17–0.31)	0.02 (−0.05–0.08)
COPD	0.01 (−0.06–0.08)	0.01 (−0.05–0.07)	−0.02 (−0.33–0.29)	0.01 (−0.08–0.09)
Hypertension	0.01 (−0.04–0.05)	0.02 (−0.02–0.06)	0.18 (−0.02–0.39)	0.04 (−0.02–0.10)
Renal failure	0.02 (−0.11–0.15)	0.003 (−0.11–0.11)	0.19 (−0.36–0.75)	0.04 (−0.12–0.20)
Cardiac problems	0.02 (−0.04–0.08)	0.01 (−0.04–0.06)	−0.29 (−0.56–0.01)	−0.03 (−0.11–0.05)
Neo-adjuvant treatment				
None	1	1	1	1
Chemotherapy	0.03 (−0.05–0.10)	0.01 (−0.06–0.07)	0.18 (−0.14–0.50)	0.03 (−0.06–0.13)
Radiation	0.02 (−0.01–0.13)	0.01 (−0.09–0.11)	0.17 (−0.33–0.67)	0.07 (−0.08–0.22)
Chemoradiation	−0.01 (−0.09–0.07)	0.01 (−0.06–0.08)	**0.80 (0.46–1.15)**	0.08 (−0.03–0.18)
Disease stage				
Benign, I & II	1	1	1	1
III & IV	0.02 (−0.03–0.06)	0.02 (−0.01–0.06)	0.23 (0.04–0.42)	−0.01 (−0.07–0.05)
Immunosuppressive use	0.01 (−0.06–0.09)	0.01 (−0.06–0.08)	−0.08 (−0.42–0.27)	0.01 (−0.09–0.10)
Surgical variables				
Intracavitary surgery	−0.02 (−0.07–0.02)	−0.01 (−0.05–0.03)	**0.87 (0.69–1.04)**	0.05 (−0.01–0.11)
Blood loss (liters)	**−0.15 (-0.16–0.13)**	**−0.11 (-0.13–0.09)**	**0.35 (0.24–0.46)**	0.04 (0.01–0.07)
RBC's transfusion	**−0.11 (-0.13–0.10)**	**−0.10 (-0.11–0.08)**	**0.17 (0.07–0.27)**	0.02 (−0.01–0.05)
Anaesthesia duration (hours)	−0.003 (−0.01–0.004)	−0.003 (−0.01–0.004)	**0.19 (0.17–0.22)**	**0.02 (0.01–0.03)**
Total transfusion (liters)	**−0.03 (-0.04–0.02)**	**−0.03 (-0.04–0.02)**	**0.22 (0.19–0.26)**	**0.03 (0.01–0.04)**
Epidural	−0.01 (−0.06–0.03)	−0.02 (−0.06–0.02)	**0.60 (0.43–0.78)**	0.07 (0.02–0.13)
Anaesthesia type				
Intravenous	1	1	1	1
Inhalational	0.03 (−0.02–0.08)	0.02 (−0.03–0.06)	0.13 (−0.09–0.34)	0.03 (−0.04–0.09)

Table 4
Multivariate linear regression analyses of the peroperative inflammatory response(Δ cytokine plasma levels) (n = 224) (10Logaritmic transformation).

Variable	CRP	IL-1β	IL-6
	B (95%CI)	B (95%CI)	B (95%CI)
Anaesthesia duration (hours)	**0.02 (0.01–0.02)**	**0.03 (0.02–0.03)**	**0.16 (0.14–0.18)**
Intracavitary surgery			**0.47 (0.33–0.62)**
Blood loss (liter)	**−0.17 (-0.19–0.15)**	**−0.14 (-0.17–0.12)**	
Total transfusion (liter)		**−0.02 (-0.03–0.003)**	
Disease stage			
Benign, I & II			**1**
III & IV			**0.14 (0.01–0.26)**
	R^2 0.615	R^2 0.605	R^2 0.607

significant perioperative response as shown in Table 2.

Discussion

Surgery in elderly oncological patients leads to the release of pro- and anti-inflammatory cytokines as part of immune system activation. This study shows that surgical characteristics rather than preoperative factors, like demographic and patient characteristics (with the exception of disease stage), determine the extent of the perioperative inflammatory response. Patients undergoing longer surgical procedures, intracavitary surgery or with more progressive disease, show the greatest inflammatory response to surgery. This is especially marked for IL-6.

The remodeling of the immune system in elderly as a result of life-long antigenic burden, is known as inflammaging [5]. The process of inflammaging leads to systemic priming of immune cells preoperatively and therefore cytokine response to inflammatory stimuli might be more pronounced [3,19]. In the current study, however, advancing age was not found to be an independent factor associated with a greater perioperative inflammatory response. The effect of ageing on the perioperative inflammatory response might be better demonstrated when comparing young patients with elderly, rather than searching for differences in those of 65 years and over. Literature is inconclusive about the influence of age on the cytokine response [20]. In a study comparing elderly patients with younger patients undergoing abdominal surgery, elderly patients (age 75–90 years) showed an increased and delayed IL-6 response to surgical trauma compared to young adults (age 36–60 years) [21]. Furthermore, in patients undergoing total hip arthroplasty, those over 65 years of age showed higher levels of IL-6 following surgery compared with middle-aged (40–65 years) patients [22].

Tissue damage (through trauma or surgery) leads to the activation of the immune system followed by cytokine release [23,24]. In our study, intracavitary surgery was independently associated with the extent of the surgery-evoked inflammatory response [9]. It is known that plasma levels of IL-6 reflect the extent of operative trauma. Our current findings show that intracavitary surgery leads to a more pronounced IL-6 response, likely because more tissue is damaged compared to more superficial procedures (thyroid, skin, breast and extremities). Studies have reported that laparoscopic interventions or minimally invasive procedures are associated with a tempered perioperative inflammatory response compared to open procedures, which inflict more tissue damage [25–27].

The observed associations between anaesthesia duration and the magnitude of the inflammatory response does not necessarily reflect a causal relationship. As more extensive surgical procedures require a longer anaesthesia duration, it is plausible that extensive surgery causes a greater extent of surgical tissue trauma and thereby causes higher plasma levels of IL-6 following surgery. The exposure to anesthetic drugs can even reduce the inflammatory response to surgery; compared to inhalational drugs (sevoflurane), intravenous drugs (propofol) reduce the response and expression of IL-6 [28]. Interestingly, literature shows that the choice of anesthetic drug may even influence long-term cancer outcome, with the suggestion that propofol has beneficial anti-inflammatory effects during surgery, which improve survival [29].

Patients with disease stages III & IV showed a greater inflammatory response to surgery. It is plausible to assume that in these patients, more affected tissue had to be resected during the surgical procedure and more tissue is exposed to injurious stimuli. In our study patients with disease stages III & IV seemed to have longer surgical procedures when compared to patients with benign, stage I or stage II disease however differences in duration of surgery were not significant. Circulating levels of inflammatory cytokines (IL-6) have previously been associated with disease stage of oncological patients [30]. Increased blood loss was found to be associated with a less pronounced perioperative inflammatory response for plasma levels of CRP and IL-1β. The observed finding for these two markers might be due to dilution of blood plasma as a result of the combination of blood loss and increased perioperative fluid transfusion to maintain cardiac output. However, this finding was not observed for the other inflammatory markers. Interestingly, a study comparing goal-directed fluid therapy to limitless administration of intravenous fluid during surgery, found a significant difference in plasma levels of IL-6 [31]. The findings suggested that unrestrained administration of intravenous fluid during surgery induces a more excessive inflammatory response [32].

In accordance with other studies, no difference in plasma levels of IL-12 and TNF-α between both sampling moments was observed in the current study. TNF-α is a known mediator of the perioperative inflammatory response, and is described in literature as a rapid response to acute injury. The combination of a median anaesthesia duration of 199.5 min in our study and a half-life of TNF-α less than 20 min, might have resulted in a failure to detect elevated plasma levels of TNF-α as result of the blood sampling interval [9]. Due to variation in the duration of surgical procedures in the current analysis, the plasma sample moment at wound closure might be taken before, during or after the peak response of the analysed markers. Previous research reports that injury in humans leads to a diminished capacity to produce IL-12, similar to our finding that perioperative increase in IL-12 plasma levels was not observed [33–35]. In a study investigating changes in plasma cytokines in response to musculoskeletal surgical trauma, a significant decrease for IL-12 plasma levels was observed at the end of surgery and subsequent period [36]. As marker of the inflammatory response, IL-10 is reserved a unique position. Although considered an anti-inflammatory cytokine, IL-10 possesses pro-inflammatory properties and has the ability to differently affect the function of several immune cells [37,38]. It is notable that elevation of different cytokines can indicate different etiologies of the inflammatory response. The elevation of one inflammatory cytokine may be

induced by an entirely separate mechanism when compared to another, which might explain the current findings.

Evaluation of the study

The strength of the current study is the size of the study population. As far as we know, the current cohort is the largest cohort in which the surgery-evoked inflammatory response has been explored in an elderly oncological population. A weakness is the limited number of blood sampling points. Addition of more plasma sampling moments during the surgical procedure and in the postoperative course would have facilitated the production of a time-response curve per inflammatory marker, and a better assessment of the relationship between the inflammatory response following surgery and postoperative recovery in elderly. The influence of the perioperative inflammatory response on postoperative outcomes is clinically relevant information and is of surplus value to report in future projects. The optimal selection of the inflammatory markers is subject to debate. The inflammatory markers assessed in the current study were chosen based on pathway, mechanism and hypothesis. We intently did not use multiplex assays which simultaneously measure multiple markers as this could lead to incidental findings, not easily related to the assumed mechanism.

Future perspectives and clinical implications

The consequences of the perioperative inflammatory response have not been examined in this study. It is important to keep in mind that IL-6 is part of a greater, complex network so that current conclusions are limited to the associations found in the current study. Further investigation of the effects of IL-6 on postoperative recovery is required. This may lead to the development of potential interventions to interfere with this intricate mechanism (such as perioperative tocilizumab treatment for blocking IL-6 receptors), improving perioperative care and outcome for the elderly surgical oncological patient. It also underlines the potential benefit of minimally invasive procedures in this patient category, which likely benefits those at risk for an excessive inflammatory response, as cytokine release might be less pronounced. In gastric cancer patients, minimally invasive procedures attenuated the inflammatory response and older gastric cancer patients demonstrated better postoperative outcomes compared to those undergoing open surgery [39,40]. This underscores the importance of exploring the effect of minimally invasive surgery (MIS) in all older surgically treated oncological patients. Furthermore, it would be of interest to explore the inflammatory response in younger patients and compare results and postoperative outcomes with the elderly. Attention to optimise patients preoperatively (including prehabilitation) is important but should not replace further research for solutions to decrease the systemic inflammatory impact of the surgical procedure itself in elderly.

Conclusion

In conclusion, this prospective study showed the activation of the immune system in response to surgery in elderly by comparing preoperative and postoperative plasma levels of different inflammatory markers. A perioperative inflammatory response was observed for CRP, IL-1β, IL-6 and IL-10. The perioperative inflammatory response is influenced by surgical characteristics rather than by preoperative factors, including neo-adjuvant treatment and comorbidities but with the exception of disease stage. Elderly oncological patients undergoing longer lasting, intracavitary surgical procedures for more advanced stage of disease, seem to develop the greatest inflammatory response, represented by increased plasma levels of IL-6. The effect of this surgery-evoked inflammatory response on postoperative outcome in this population still has to be determined.

Conflicts of interest and source of funding

No grant from any funding agency in the public, commercial, or not-for-profit sectors was obtained. The authors report no proprietary or commercial interest in any concept discussed in this article.

Appendix A. Supplementary data

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