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IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2020

Link to publication in University of Groningen/UMCG research database

The association between the inflammatory response to surgery and postoperative complications in older patients with cancer; a prospective prognostic factor study

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ARTICLE INFO

ABSTRACT

Background: Accurate prognostic biomarkers would substantially improve surgical planning and decisions making yet no studies have been reported exploring the inflammatory response in surgically treated older patients with cancer. The aim of this study was to explore inflammatory biomarkers as potential prognostic factors for postoperative complications within 30 days in older patients with cancer.
Method: Patients 65 years and older undergoing surgery for removal of a solid malignant tumour were included in an observational cohort study. All complications occurring up to 30 days postoperatively were documented prospectively. 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). Associations between inflammatory markers and postoperative complications were explored using logistic regression analysis.
Results: Between July 2010 and April 2014, plasma samples of 224 patients were collected. Median age was 72 (65–89) years and 116 (51.8%) patients were female. Approximately half of the patients developed postoperative complications (49.6%) of whom 62 patients (55.9%) developed >1 complication. An independent prognostic effect was observed for the inflammatory biomarkers IL-6 and IL-10 for the occurrence of postoperative complications.
Conclusion: The perioperative inflammatory response is associated with complications, independently from patient and surgical factors which are also associated with outcome. Research is warranted towards further exploration of the perioperative inflammatory response with the aim to improve perioperative care and outcome, and might help to improve surgical planning and decision making for older patients with cancer.

1. Introduction

Although older patients diagnosed with cancer may benefit from surgical treatment, they are more susceptible to the complications of surgery and anaesthesia than younger patients [1]. The frequency of postoperative complications in older patients undergoing elective surgery for solid tumour removal is relatively high, with incidences reported of >50% during the first 30 days postoperatively [2,3]. When postoperative complications occur in older patients, they are more likely to lead to adverse outcomes such as disability, loss of independence, diminished quality of life, high health care costs, and death [4,5]. Having prognostic factors established and available to assist with prognosis would be helpful in treatment planning and decision-making in older patients with cancer [6].

Multiple patient-related factors as well as the severity of the surgical procedure itself are associated with adverse postoperative outcomes [7]. Literature shows that pre-existing comorbidities and sex-related differences are associated with outcome in different surgical populations, and that frail patients have a significantly higher morbidity after elective surgical procedures compared to fit patients [8–10]. It is likely that the immune system has a role in the pathogenesis of postoperative complications but few inflammatory biomarkers are established to further estimate the risk of postoperative complications across populations

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[11]. Tissue damage inflicted during surgery induces a systemic inflammatory response which is coordinated by the immune system and mediated by endogenous mediators such as C-reactive protein (CRP), Interleukin-1β (IL-1β), IL-6, IL-10, IL-12 and Tumour necrosis factor-alpha (TNF-α) [12]. CRP is an acute phase protein and is used as a marker for tissue damage and inflammation [13]. IL-1β, IL-6, IL-10 and IL-12 are inflammatory cytokines, which can exert anti- and/or pro-inflammatory effects and are often used as marker for the inflammatory response to trauma [14,15]. TNF-α is an early mediator in the immune response after injury [16,17]. This systemic inflammatory response is thought to play a role in the development of postoperative complications, particularly in those of an inflammatory nature (e.g., delirium, surgical site infection, pneumonia, urinary tract infection, etc.) [18–21]. These inflammatory biomarkers might be useful as prognostic factors for the occurrence of postoperative complications.

Accurate prognostic inflammatory biomarkers would substantially improve surgical planning and decision making yet no studies have been reported exploring the inflammatory response in surgically treated older patients with cancer. Therefore, in this exploratory prognostic factor study we aimed to explore inflammatory biomarkers as potential prognostic factors for postoperative complications within 30 days, in a well-defined prospective cohort consisting of consecutively recruited older patients undergoing surgery as part of oncological treatment.

2. Methods

2.1. The PICNIC Cohort

This prospective clinical study to investigate associations of inflammatory biomarkers and postoperative (inflammatory) complications in older patients with cancer is a sub-study of the observational study 'PICNIC' (PostoperatIve Cognitive dysfunctioN In elderly Cancer patients), conducted at the University Medical Center Groningen (UMCG, Groningen, the Netherlands) [7,22,23]. The study was registered on the Dutch Clinical Trial Database (trial number NL31486.042.10) and approved by the Medical Ethical Committee of the UMCG. The aim of 'PICNIC' was to identify predictors of postoperative outcome in older patients with cancer, with special focus on physical and cognitive functioning. Written informed consent was obtained from every patient enrolled in the study. Patients were enrolled in the study from July 2010 until April 2014.

2.2. Patients and Clinical Data Collection

Patients aged 65 years and over referred to the UMCG for an elective resection of a solid tumour were considered eligible and were recruited for participation. Any physical condition potentially hindering compliance with the study protocol, such as (but not restricted to) severe visual or auditory impairment or a recent history of stroke or pre-existing cognitive impairment and insufficient understanding of Dutch language, were exclusion criteria of the 'PICNIC' study. Preoperatively the Mini-Mental State Examination (MMSE) was assessed for all patients for systematic screening for pre-existing cognitive impairment. Data collection was conducted following the Declaration of Helsinki. Privacy was guaranteed by using coded data in the analysis. Patient characteristics such as age, sex, BMI, tumour type, disease stage, comorbidities according to the Charlson Comorbidity Index (CCI), frailty according to the Groningen Frailty Indicator (GFI), neoadjuvant treatment and the surgical characteristics were prospectively collected during the study period.

2.3. Postoperative Complications

All complications occurring up to 30 days postoperatively were documented prospectively in the Case Report Form (CRF) using clear pre-defined criteria (Clavien-Dindo Classification) [24]. A subsequent search of the UMCG complication registry confirmed that all complications captured by the registry were also captured by our study. To guarantee the quality and validity of the registration, further actions were undertaken as careful monitoring is necessary [25]. In 2018, the patient records of all patients in whom complications were recorded, were reviewed. Discharge letters from the Electronic Medical Record (EMR) system, and all hardcopy patient files relevant to the hospital admission for the surgical procedure were reviewed by a research physician. All sections of the hardcopy patient files were examined page by page, including but not restricted to nursing-, consultant-, and progress notes. As traditional classification of complications by severity (Clavien-Dindo Classification) is not the most appropriate when exploring inflammatory biomarkers as potential prognostic factors for the postoperative course in a theory driven approach in the current study, postoperative complications were categorized as either non-inflammatory or inflammatory in nature retrospectively. Complications in which the immune system was thought to have played a role were considered inflammatory complications. In doubtful cases, the complication was discussed within the study group, and the complication was then defined as inflammatory or non-inflammatory according to the consensus opinion. Complications were considered inflammatory when diagnostic tests confirmed the occurrence of an infection (by cultures, radiographic findings or laboratory results) or when therapy was initiated by clinical suspicion of an infection. If complications were not considered as infectious, but with an assumed role of the immune system, they were assigned to the inflammatory subgroup. Examples include postoperative ileus, postoperative delirium and anastomotic leakage [26–28]. Postoperative delirium was considered an inflammatory complication as several cytokines are involved in the occurrence of delirium postoperatively [29]. If a patient had multiple complications, of which at least one was of an inflammatory nature, then the patient was assigned to the inflammatory complication group.

2.4. Sampling and Biochemical Analyses

Blood samples were collected at two moments: 1) preoperatively before anaesthesia induction (T0), and 2) at wound closure (T1). After blood samples were centrifuged at 2600 G for 10 min, plasma was aliquotted and stored at −80 °C. For current analysis, only patients with blood plasma collected at both sampling moments were included (Fig. 1). The following inflammatory biomarkers were determined in plasma: C-reactive protein (CRP) (Lower limit of detection (LLD): 0.001 μg/ml), Interleukin-1β (IL-1β) (LLD: 1,27 pg/ml), IL-6 (LLD: 0,00 pg/ml), IL-10 (LLD: 3,28 pg/ml), IL-12 (LLD: 5,07 pg/ml), and Tumour necrosis factor-alpha (TNF-α) (LLD: 6,49 pg/ml). Analyses were performed in batches (measured in singular) by Haemoscan® (Groningen) using sandwich ELISA technique for interleukins, developed by BioLegend (San Diego, CA) and high sensitivity CRP ELISA (Dakopatts, Glostrup, Denmark) for CRP. As a measure of the inflammatory response following surgery, postoperative levels (T1) of the inflammatory biomarkers (CRP, IL-1β, IL-6, IL-10, IL-12 and TNF-α) were used for analyses and adjusted for preoperative levels (T0). Preoperative blood samples were collected in the morning on the day of surgery.

2.5. Outcomes

Primary outcome of the current study was the association between inflammatory biomarkers (CRP, IL-1β, IL-6, IL-10, IL-12 and TNF-α) and the occurrence of complications and inflammatory complications within 30 days postoperatively. Secondary outcomes were to explore inflammatory biomarkers as potential prognostic factors for postoperative complications while controlling for known confounders.
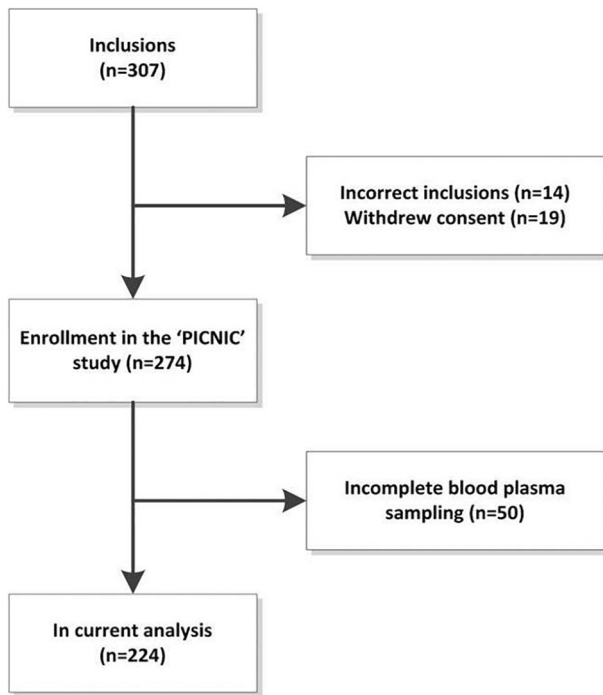
Fig. 1. Study flowchart.

2.6. Statistical Analyses

Characteristics (preoperative, surgical and biomarker) of all patients, patients developing complications, patients developing inflammatory complications and patients without complications were described. Median and interquartile range of postoperative levels (T1) of inflammatory markers were presented. The occurrence of each postoperative complication (non-inflammatory and inflammatory) was reported per complication (number and percentage) (see supplemental Table 2). Univariable and multivariable logistic regression analyses were used to: 1) explore associations between the inflammatory biomarkers and complications (yes vs. no) within 30 days postoperatively, 2) explore associations between the inflammatory biomarkers and inflammatory complications (yes vs. no) within 30 days postoperatively. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated. A theory driven approach for exploratory factor analysis was used for forward selection of variables. First, a null-model was developed with factors associated with postoperative complications based on literature and theory. The included variables were: sex (female or male), GFI (score), CCI (score) and type/intensity of surgery (superficial or intra-abdominal/thoracic). To elucidate a potential independent prognostic effect for each inflammatory biomarker, multivariable regressions analyses was used, while controlling for confounders [30]. Logarithmic transformation was applied on inflammatory biomarker data (for preoperative levels (T0) and postoperative levels (T1)) to approach normal distribution by reducing skewness. *P*-values <.05 were considered to be statistically significant. Inflammatory biomarkers found associated with outcome in univariable analyses were used in multivariable analyses. Statistical analyses were performed using IBM SPSS software, version 23.0 (IBM Corporation, Armonk, NY). Figures were designed with GraphPad Prism version 7.02 (GraphPad Software, San Diego, CA) and Adobe Illustrator, CS6 (Adobe Systems Incorporated, San Jose, CA).

3. Results

Of the 307 patients included in the 'PICNIC' study, 14 (4.6%) were incorrectly included, and 19 (6.2%) withdrew their consent before the

start of the surgical procedure. Subsequently, 50 patients of the 274 included in the 'PICNIC' study were excluded from the current analysis due to incomplete blood plasma sampling. Data of the remaining 224 patients (73%) are presented in the current analysis (Fig. 1).

3.1. Characteristics of the Included Patients

Patient and surgical characteristics are shown for all patients (*n* = 224), for patients with complications (*n* = 110) and for patients with an inflammatory complication (*n* = 62) in Table 1. The patients from the 'PICNIC' study excluded due to incomplete blood plasma sampling did not differ from the included patients in characteristics (in patient nor surgical characteristics), which is shown in supplemental Table 1.

3.2. The Postoperative Course

Of the 224 older patients with cancer included in the current analysis, 110 (49.1%) developed complications postoperatively, among whom, 62 (56.4%) developed more than one complication. In total 252 complications occurred, of which 145 (57.5%) were non-inflammatory and 107 (42.4%) were considered inflammatory complications. Detailed description of the nature of the complications in the study population is shown in supplemental Table 2.

3.3. Inflammatory Biomarker Analysis

Postoperative plasma concentrations of inflammatory biomarkers for all patients, patients with complications, patients with inflammatory complications and patients without complications are shown in Table 1, preoperative plasma concentrations are not shown. The inflammatory biomarkers IL-12 and TNF-α did not show a peroperative change in plasma levels (most values remained under the detection limit) and were not used for further analysis.

3.4. Clinical and Inflammatory Factors Associated with Complications

Univariable logistic regression analyses showed that different inflammatory biomarkers (CRP, IL-6 and IL-10) were associated with the occurrence of postoperative complications (see Table 2). Clinical factors such as male sex, a higher CCI score, receiving neoadjuvant chemoradiation and more extensive surgery (anaesthesia duration, type of surgery, amount of blood loss and amount of fluid transfusions) were associated with the occurrence of postoperative complications. For the occurrence of specific inflammatory complications, the inflammatory biomarkers IL-6 and IL-10 and clinical factors male sex, a higher CCI score and more extensive surgery, were found associated.

Multivariable logistic regression analysis showed that known clinical factors such as sex, comorbidities and extensive surgery were also in the current study associated with outcome, except frailty (see Table 3) and was considered as null-model. Multivariable models showed an independent prognostic effect for the inflammatory biomarkers IL-6 and IL-10 (adjusted for the confounders from the null-model) for the occurrence of postoperative complications (see Table 3a). When exploring an independent prognostic effect for the inflammatory biomarkers for the occurrence of inflammatory complications, only an effect was observed for Il-6 (adjusted for the confounders from the null-model) as shown in Table 3b.

4. Discussion

The data we present here show that there is a prognostic factor association between the inflammatory biomarkers IL-6 and IL-10, and the occurrence postoperative complications in older patients with cancer. A total number of 252 complications were registered, of which 107 (42.3%) were considered to be immune system related. Male sex, the number of comorbidities and the extent of surgery were found

Table 1

Characteristics of all patients, patients developing complications and patients developing inflammatory complications N(%), unless specified otherwise.

	All patients (n = 224)	Patients with at least one complication (n = 110)	Patients with at least one inflammatory complication (n = 62)	Patients without complications (n = 114)
Age (years)[a]	72 (68–78)	72 (68–78)	72 (68–79)	72 (68–78)
Sex				
Female	116 (51.8%)	45 (40.9%)	22 (35.5%)	71 (62.3%)
Male	108 (48.2%)	65 (59.1%)	40 (64.5%)	43 (37.7%)
GFI[a]	2 (1–4)	2 (1–4)	2 (1–4)	2 (1–4)
CCI[a]	3 (2–5)	4 (1–4)	4 (3–6)	3 (2–4)
Neo-adjuvant treatment				
None	177 (79%)	82 (74.5%)	46 (74.2%)	95 (83.3%)
Chemotherapy	21 (9.4%)	8 (7.3%)	2 (3.2%)	13 (11.4%)
Radiation	8 (3.6%)	5 (4.5%)	3 (4.8%)	3 (2.6%)
Chemoradiation	18 (8%)	15 (13.6%)	11 (17.7%)	3 (2.6%)
Disease stage				
Benign, I and II	118 (53.4%)	59 (53.6%)	32 (51.6%)	59 (52.7%)
III and IV	103 (46.6%)	51 (46.4%)	30 (48.4%)	53 (47.3%)
Anaesthesia duration (minutes)[a]	199.5 (121–339)	282 (154.75–437.5)	319 (174–464.25)	150 (98.75–227.75)
Type of surgery				
Superficial	71 (31.7%)	23 (20.9%)	14 (22.6%)	48 (42.1%)
Intra-abdominal/thoracic	153 (68.3%)	87 (79.1%)	48 (77.4%)	66 (57.9%)
Blood loss (liters)[a]	0.15 (0.03–0.475)	0.3 (0.1–0.65)	0.3 (0.1–0.8)	0.1 (0–3)
RBC's transfusions[a]	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)
Total transfusions (liters)[a]	2 (1–3.5)	3 (2–4.5)	3.5 (1.75–5)	1.6 (1–3)
Epidural	113 (50.4%)	63 (57.3%)	34 (54.8%)	50 (43.9%)
Biomarkers				
T1 – CRP[a]	5.03 (2.10–9.95)	7.95 (3.7–12.24)	7.54 (3.53–11.91)	3.92 (1.14–6.57)
T1 – IL-1β[a]	0.55 (0.34–0.86)	0.57 (0.36–0.87)	0.57 (0.36–0.91)	0.54 (0.32–0.82)
T1 – IL-6[a]	88.57 (0–344.82)	228.16 (23.68–549.21)	309.79 (21.34–588.81)	0 (0–161.17)
T1 – IL-10[a]	56 (18–132.5)	95.5 (37.25–189.75)	107 (29–235.5)	32.5 (13–83.5)
T1 – IL-12[a]	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)
T1 – TNF-α[a]	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)

[a] Data shown as median (interquartile range). Postoperative values (T1) of the inflammatory biomarkers are shown as a measure of the inflammatory response following surgery. *GFI* Groningen Frailty Indicator, *CCI* Charlson Comorbidity Index, *RBC* Red blood cell, *CRP* C-reactive protein, *IL* interleukin, *TNF-α* tumour necrosis factor-α.

associated with outcome in older patients with cancer undergoing surgery which lays in line with literature (the association was not observed for frailty).

4.1. Current findings in contrast to literature

Circulating IL-6 was first proposed as a useful marker for predicting postoperative complications more than 25 years ago [31]. This cytokine is produced soon after surgical trauma and plasma levels increase in the period following surgery. The finding that plasma levels of IL-6 are associated with the occurrence of postoperative complications is consistent with published literature [32–34]. Few studies have investigated the association between IL-6 and postoperative complications, although long-term changes of plasma levels of IL-6 (postoperative day 1) were associated with an increased risk of postoperative complications [35]. As a biomarker of the inflammatory response, IL-10 has an unusual position. Although considered an anti-inflammatory cytokine, it also possesses pro-inflammatory properties and has the ability to differently affect function of various immune cells [36,37]. In the current study associations with patient, surgical and inflammatory mediators with the occurrence of postoperative complications were observed. We hypothesize that patient and surgical factors have an influence on the occurrence of postoperative complications, but also on the inflammatory response to surgery itself (see Fig. 2). The number of patients experiencing postoperative complications in the current study is consistent with other studies reporting complication rates in older patients with cancer undergoing surgery [38,39].

Based on our data, older patients with cancer are predisposed by their comorbidities scored by the CCI for the development of complications in the postoperative course. The CCI was designed to quantify the risk of mortality over a one-year period after inpatient admission to the hospital by a weighted score computed by presence or absence of 19 comorbidities [40]. Given previous reports that found comorbidity as a predictor of outcomes in different surgical oncological populations, it

is not unexpected that comorbidities were found to be associated with postoperative complications in older patients [8,41,42]. Our study underscores that older men are at increased risk compared to women for the development of complications [43,44]. The distinction in complications rates might be a result of biologic sex-differences. However, other studies show conflicting results [9,43,45].

In literature frail patients are prone to postoperative complications when compared to fit patients [46]. In the current study an association of frailty with the occurrence of postoperative complications was not observed. The lack of association might be explained by the assessment of frailty as it remains controversial how to identify frailty [47]. In the current study the GFI was used for assessment of frailty [48]. Most patients were affected in GFI score as result of the oncological disease, however the study population was relatively fit. In literature 42% of older patients with cancer with any stage of solid or hematological malignancy are considered frail, in contrast to the 28.7% in our study (with a GFI score ≥ 4) [49]. However, the lack of association might also be the result of selection bias, as it is likely that patients with the most worse health status are prone to drop out of the study during follow-up or even before surgery or were not eligible for surgical treatment in the first place [50].

4.2. Future Perspectives and Clinical Implications

The possibilities for future research into the inflammatory response following surgery are twofold: 1) evaluating the prognostic value of inflammatory biomarker analysis for a complicated postoperative course and 2) identifying potential targets for preventive immunomodulating interventions. For example, a recent study in mice demonstrated that IL-6 is implicated in the pathophysiology of perioperative neurocognitive decline and that blockade of the IL6-receptor by tocilizumab attenuated neurocognitive decline [51]. Especially in the oncological population, steps aiming at prevention and early detection of postoperative complications are important. The recovery from

Table 2
Factors associated with postoperative complications and with inflammatory complications, univariable logistic regression analysis.

	Complications (yes vs no) (n = 110 vs n = 114)	Inflammatory complications[b] (yes vs no) (n = 62 vs n = 162)
	OR (CI)	OR (CI)
Biomarkers[a]		
CRP	**3.88 (1.30–11.61)***	2.28 (0.78–6.67)
IL-1β	0.71 (0.18–2.77)	0.88 (0.20–3.95)
IL-6	**2.03 (1.58–2.62)***	**1.80 (1.36–2.39) ***
IL-10	**2.27 (1.44–3.57)***	**2.08 (1.25–3.45) **
IL-12	2.11 (0.71–6.20)	1.64 (0.57–4.73)
TNF-α	1.36 (0.71–2.61)	0.85 (0.40–1.81)
Age (years)	1.02 (0.98–1.07)	1.03 (0.98–1.08)
Sex		
Female	1	1
Male	**2.4 (1.40–4.08) **	**2.5 (1.37–4.61) **
GFI	0.93 (0.80–1.09)	1.003 (0.85–1.19)
CCI	**1.29 (1.09–1.53) **	**1.38 (1.17–1.65) **
Neo-adjuvant treatment		
None	1	1
Chemotherapy	0.71 (0.28–1.81)	0.30 (0.07–1.34)
Radiation	1.93 (0.45–8.33)	1.71 (0.39–7.43)
Chemoradiation	**5.79 (1.62–20.72) **	**4.48 (1.64–12.23) **
Disease stage		
Benign, I and II	1	1
III and IV	0.96 (0.57–1.63)	1.09 (0.61–1.96)
Anaesthesia duration (minutes)		
<180	1	1
≥180	**3.45 (1.98–6.0) ***	**3.55 (1.84–6.85) ***
Type of surgery		
Superficial	1	1
Intra-abdominal/thoracic	**2.75 (1.52–4.97) **	1.86 (0.95–3.66)
Blood loss (liters)	**2.05 (1.08–3.90) ***	**2.01 (1.15–3.52) ***
RBC's transfusions	1.25 (0.87–1.79)	1.21 (0.90–1.61)
Total transfusions (liters)	**1.61 (1.34–1.95) ***	**1.39 (1.18–1.64) ***
Epidural	1.69 (0.99–2.87)	1.26 (0.70–2.27)

* $p < .05$, ** $p < .01$, *** $p < .001$ (bold values are considered significant). *OR* odds ratio, *CI* 95% confidence interval, *GFI* Groningen Frailty Indicator, *CCI* Charlson Comorbidity Index, *CRP* C-reactive protein, *IL* interleukin, *TNF-α* tumour necrosis factor-α

[a] Plasma levels of the inflammatory biomarkers were divided by a factor 100 to improve readability of OR's and 95%CI's. Postoperative values (T1) of the inflammatory biomarkers are used and corrected for preoperative values (T0) after 10Log transformation.

[b] Patients with inflammatory complications versus patients without complications and non-inflammatory complications.

complications among older patients is unpredictable and variable, and complications can influence short- and long-term outcomes with even death as a possible result [52]. In addition, adjuvant oncological

treatment may be omitted in case of postoperative complications, also leading to decreased survival [53,54]. In clinical practice, the inflammatory mediators IL-6 and IL-10 may provide early identification of patients with an increased risk of morbidity and thus, help to make decisions about additional monitoring and diagnostic procedures, preventive measures and potentially the early treatment of postoperative complications. Predicting risk for adverse outcomes following oncological surgery in older patients will help with the implementation of both prophylactic measures and appropriate perioperative treatment plans. Before the above can be achieved, further exploration of the perioperative inflammatory response itself is necessary as the underlying mechanism is not fully understood yet.

4.3. Evaluation of the Study

The number of patients included in the current sub-study is a strength. The current cohort is the largest in which the perioperative changes in plasma levels of inflammatory biomarkers have been explored and associated with postoperative complications in older patients with cancer. To explore the effect of the surgical procedure on plasma levels of inflammatory markers, perioperative changes in plasma were estimated by drawing blood samples immediately before and after the surgical procedure. However, an extended sampling interval might have provided more insightful data on changes of plasma levels of inflammatory biomarkers on a longer term. It is plausible that in some patients blood samples were drawn in the ascending part of the inflammatory response curves. Increasing the diagnostic window of plasma sampling might be valuable for predicting complications.

Postoperative complication severity and subsequent consequences were not taken account of in the current study. The traditional classification of complications by severity (Clavien-Dindo) might not be the most appropriate when exploring an inflammatory phenomenon and associations with the postoperative course. We aimed to elucidating the inflammatory factors that influence postoperative morbidity rather than predict complication severity. In literature inflammatory complications are more frequently used as outcome in studies evaluating the prognostic value of inflammatory biomarkers [55,56]. In addition, it is a well-known problem that complications are underreported. Underreporting usually occurs when complications are non-severe and not prospectively recorded, which might alter findings and conclusions [57]. The latter was overcome in our study by prospectively recording complications during the study period and by reviewing registrations after the study period [25].

The findings in the current study suggest that all postoperative complications have immune system involvement as inflammatory

Table 3a
Factors associated with postoperative complications, multivariable logistic regression analysis. A theory driven approach.

	Complications (yes vs no) (n = 110 vs n = 114)	Complications (yes vs no) (n = 110 vs n = 114)	Complications (yes vs no) (n = 110 vs n = 114)	Complications (yes vs no) (n = 110 vs n = 114)
	OR (CI)	OR (CI)	OR (CI)	OR (CI)
Sex				
Female	1	1	1	1
Male	**2.36 (1.23–4.52) **	**2.44 (1.23–4.85) ***	**2.42 (1.25–4.71) **	**2.30 (1.18–4.47) ***
GFI	0.96 (0.80–1.14)	0.97 (0.81–1.17)	0.96 (0.81–1.15)	0.94 (0.78–1.12)
CCI	**1.32 (1.06–1.64) ***	**1.28 (1.02–1.62) ***	**1.32 (1.06–1.66) ***	**1.32 (1.05–1.65) ***
Type of surgery				
Superficial	1	1	1	1
Intra-abdominal/thoracic	**3.49 (1.76–6.93) ***	1.44 (0.62–3.37)	**2.50 (1.17–5.33) ***	**3.33 (1.64–6.78) ***
IL-6[a]	–	**1.84 (1.32–2.57) ***	–	–
IL-10[a]	–	–	**1.73 (1.02–2.93) ***	–
CRP[a]	–	–	–	1.95 (0.62–6.14)
R²	0.20	0.29	0.22	0.23

* $p < .05$, ** $p < .01$, *** $p < .001$ (bold values are considered significant). *OR* odds ratio, *CI* 95% confidence interval, *CCI* Charlson Comorbidity Index, *GFI* Groningen Frailty Indicator, *CRP* C-reactive protein, *IL* interleukin, *TNF-α* tumour necrosis factor-α.

[a] Plasma levels of the inflammatory biomarkers were divided by a factor 100 to improve readability of OR's and 95%CI's. Postoperative values (T1) of the inflammatory biomarkers are used and corrected for preoperative values (T0) after 10Log transformation.

Table 3b
Factors associated with inflammatory complications, multivariable logistic regression analysis. A theory driven approach.

	Inflammatory complications (yes vs no) ($n = 62$ vs $n = 162$)	Inflammatory complications (yes vs no) ($n = 62$ vs $n = 162$)	Inflammatory complications (yes vs no) ($n = 62$ vs $n = 162$)	Inflammatory complications (yes vs no) ($n = 62$ vs $n = 162$)
	OR (CI)	OR (CI)	OR (CI)	OR (CI)
Sex				
Female	1	1	1	1
Male	1.95 (0.96–3.95)	1.80 (0.86–3.76)	2.02 (0.98–4.17)	1.90 (0.92–3.92)
GFI	1.02 (0.85–1.24)	1.06 (0.87–1.29)	1.05 (0.86–1.27)	1.01 (0.83–1.23)
CCI	**1.34 (1.08–1.67) ****	**1.36 (1.08–1.73) ***	**1.36 (1.08–1.70) ****	**1.34 (1.07–1.68) ***
Type of surgery				
Superficial	1	1	1	1
Intra-abdominal/thoracic	2.13 (0.99–4.60)	0.73 (0.26–2.01)	1.49 (0.63–3.55)	2.09 (0.93–4.71)
IL-6[a]	–	**2.04 (1.36–3.07) ****	–	–
IL-10[a]	–	–	1.75 (0.96–3.18)	–
CRP[a]	–	–	–	1.37 (0.44–4.25)
R^2	0.12	0.21	0.15	0.13

* $p < .05$, ** $p < .01$, *** $p < .001$ (bold values are considered significant). *OR* odds ratio, *CI* 95% confidence interval, *CCI* Charlson Comorbidity Index, *GFI* Groningen Frailty Indicator, *CRP* C-reactive protein, *IL* interleukin, *TNF-α* tumour necrosis factor-α.

[a] Plasma levels of the inflammatory biomarkers were divided by a factor 100 to improve readability of OR's and 95%CI's. Postoperative values (T1) of the inflammatory biomarkers are used and corrected for preoperative values (T0) after 10Log transformation.
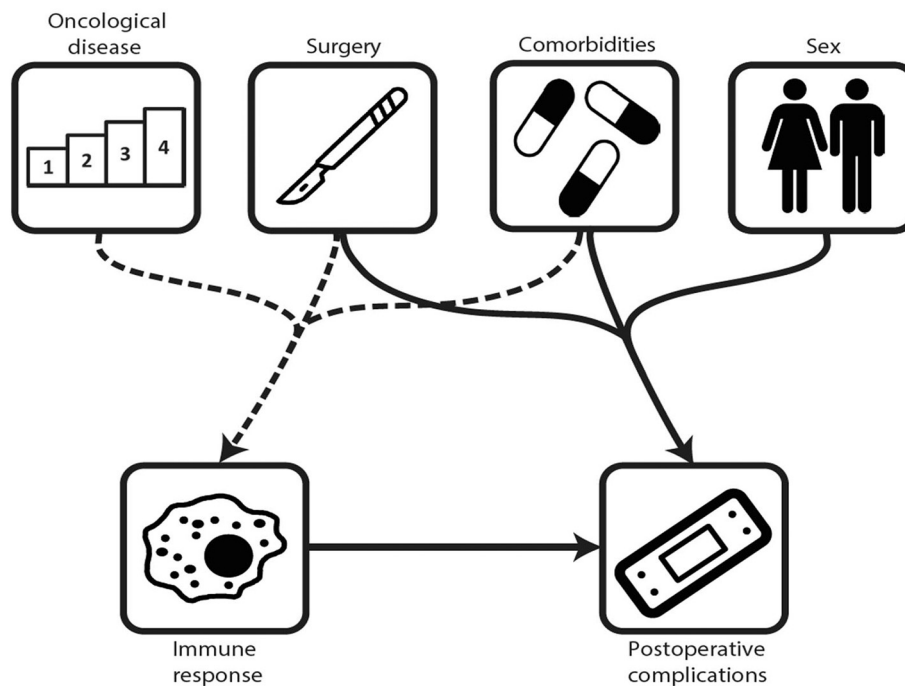

Fig. 2. The inflammatory response to surgery.

biomarkers were associated with postoperative complications overall (and not necessarily with inflammatory complications). Dividing complications in categories seemed redundant and the exact linkage between complications remains unclear. However, the results underscores the gap in knowledge considering the peroperative inflammatory response and the influence on the postoperative course.

5. Conclusions

Besides patient and surgical factors associated with adverse outcomes following oncological surgery in older patients, we also found an independent prognostic factor association with postoperative plasma levels of the inflammatory biomarkers IL-6 and IL-10. The inflammatory mediators are an interesting target for future preventive interventions which should interfere with the intricate inflammatory mechanism with the aim to improve perioperative care and outcome, and might help to improve surgical planning and decision making for older patients with cancer. Further research of the perioperative inflammatory response itself is fundamental as the underlying mechanism is not fully understood yet.

Author Contributions

MP, AR, HvdWH, JJdH ARA, GHdB, BvL - Study concepts
AR, HvdWH, JJdH, ARA, GHdB, BvL - Study design
MP, HvdWH - Data acquisition
AR, HvdWH, JJdH, ARA, GHdB, BvL - Quality control of data and algorithms
MP, AR, HvdWH, JJdH, ARA, GHdB, BvL - Data analysis and interpretation
MP, AR, HvdWH, JJdH, ARA, GHdB, BvL - Statistical analysis
MP - Manuscript preparation
MP, GHdB, BvL - Manuscript editing

AR, HvdWH, JJdH, ARA, GHdB, BvL - Manuscript review

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Declaration of Competing Interest

I confirm that all the authors have no conflicts of interest to disclose.

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