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ORIGINAL ARTICLE

Comparison of inflammatory responses following robotic and open colorectal surgery: a prospective study

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Abstract
Purpose Robotic colorectal surgery continues to rise in popularity, but there remains little evidence on the stress response following the procedure. The aim of this study was to evaluate the inflammatory response to robotic colorectal surgery and compare it with the response generated by open colorectal surgery.
Methods This was a prospective nonrandomized comparative study involving 61 patients with colorectal cancer. The evaluation of inflammatory response to either robotic or open colorectal surgery was expressed as changes in interleukin-1β, interleukin-1 receptor antagonist, interleukin-6, tumor necrosis factor-α, C-reactive protein, and procalcitonin during the first three postoperative days.
Results Of the 61 patients, 33 underwent robotic colorectal surgery while 28 had open colorectal surgery. Groups were comparable with respect to age, sex, BMI, cancer stage, and type of resection. The relative increase of interleukin-1 receptor antagonist at 8 h postoperative, compared to baseline, was higher in the open group ($P = 0.006$). The decrease of interleukin-1 receptor antagonist on postoperative days 1 and 3, compared to the maximum at 8 h, was more pronounced in the open group than in the robotic group ($P = 0.008$, $P = 0.006$, respectively), and the relative increase of interleukin-6 at 8 h after incision was higher in the open group ($P = 0.007$). The relative increase of procalcitonin on postoperative days 1 and 3 was higher in the open group than the robotic group ($P < 0.001$, $P = 0.004$, respectively).
Conclusions This study shows that when compared with open colorectal surgery, robotic colorectal surgery results in a less pronounced inflammatory response and more pronounced anti-inflammatory action.

Keywords Robotic surgery · Colorectal cancer · Stress response · Inflammatory response

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Introduction

The act of surgery initiates a significant physiologic stress reaction in the patient. This involves the release of pro-inflammatory cytokines which triggers a cascade of reactions, resulting in an acute phase response known as systemic inflammatory response syndrome (SIRS) [1, 2]. In patients with no complications, the pro-inflammatory action is quickly balanced by a compensatory anti-inflammatory response (CARS). The magnitude of SIRS is proportional to the extent of the surgical procedure, and surgical techniques that limit

tissue manipulation and destruction can reduce the SIRS and its attendant complications.

Colorectal cancer is the third most common type of cancer and the fourth leading cause of cancer deaths worldwide [3]. Curative treatment of colorectal cancer relies predominantly upon surgical resection. In Western countries, close to half of elective colorectal resections performed today are done laparoscopically [4]. Laparoscopic colorectal surgery for cancer is safe and associated with improved short-term outcomes [5, 6]. There is also evidence of an oncologic benefit that goes beyond decreased pain and a quicker recovery [7].

In recent years, robotic colorectal surgery (RCS) has gained momentum in the USA with nearly 10 % of minimally invasive rectal cancer resections now performed robotically [8]. Interestingly, however, there continues to be a lack of evidence on the stress response following RCS.

In this study, the authors evaluate the inflammatory response to robotic colorectal surgery and compare it to the response generated by open colorectal surgery (OCS).

Materials and methods

This study was designed as a prospective, comparative nonrandomized study. Between March 2013 and June 2015, 61 unselected patients with colorectal cancer were enrolled. Exclusion criteria included age <18 years, ASA >3, emergency surgery, patients with gross metastatic disease, locally advanced cancers not amenable to curative resection, and patients with tumors requiring en bloc multi-visceral resection. Patients with synchronous other cancers, severe cardiovascular or respiratory disease, severe mental disorders, or immunological diseases requiring systemic administration of corticosteroids were also excluded.

After discussing the advantages and disadvantages of each surgical approach with the operating surgeon, the patients chose either the robotic or standard open technique. The study received approval from the local ethics committee, and informed consent was given by all participating patients. The da Vinci SI surgical console (Intuitive Surgical, Sunnyvale, CA) was used for all robotic procedures.

A standard clinical pathway was applied to all patients in this study. All patients received perioperative antibiotic prophylaxis. In the first three postoperative days, parenteral opioids were used for pain control. These were gradually replaced with nonsteroidal anti-inflammatory drugs (NSAIDs). Oral liquids were permitted on postoperative day 1, and patients advanced to a liquid then solid diet by postoperative days 2 and 3, when tolerated. Nasogastric tubes were not inserted, and surgical closed drains were removed on postoperative day 1 or 2. Criteria for discharge included tolerance of soft diet and no apparent complaints or complications.

Patient demographics, co-morbidities, perioperative outcomes, postoperative complications according to the Clavien-Dindo scale, and pathology results were recorded prospectively in the database. Levels of interleukin-1β (IL-1β), interleukin-1 receptor antagonist (IL-1ra), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), C-reactive protein (CRP), and procalcitonin (PCT) were measured prior to surgery, 8 h following incision, and on postoperative days 1 and 3.

Analytical methods

Blood was drawn by venipuncture, allowed to clot for 30 min, and then centrifuged (15 min, 720×*g*). The serum was collected, divided, and kept frozen at −80 °C until examination. Levels of IL-1β, IL-1ra, IL-6, and TNF-α were measured in duplicates by means of a flow cytometry-based method that utilized magnetic microspheres conjugated with monoclonal antibodies, using the Bio-Plex 200 platform with HRF (Bio-Rad, Hercules, CA) and incorporating Luminex xMAP® technology, Bio-Plex Pro™ Human Cytokine, Chemokine, and Growth Factor Magnetic Bead-Based Assays according to the manufacturer's instructions. Standard curves were drawn using 5-PL logistic regression, and the data was analyzed using Bio-Plex Manager 6.0 software.

Procalcitonin was measured using the Vidas BRAHMS PCT automated test (bioMérieux, Marcy-l'Etoile, France) with the enzyme-linked fluorescent assay (ELFA) technique. For the purpose of statistical analysis, values below the limit of detection (0.05 ng/ml) were replaced with a value of 0.025 ng/ml. C-reactive protein was measured using the Multigent CRP Vario immunoturbidimetric test with the Architect 4100 Ci analyzer (Abbott Laboratories, Abbott Park, IL).

Statistical analysis

The normality of distribution was tested using χ^2 test with Lilliefors significance correction and the homogeneity of variations using Levene's test. Log-transformation was used when appropriate. Data were presented as median or mean with 95 % confidence interval and analyzed using Kruskal-Wallis *H* test and Mann-Whitney *U* test or one-way ANOVA and *t* test for independent samples, with Welch correction if appropriate. Repeated measures ANOVA (two-factor design) test was used to compare postsurgical dynamics in the levels of inflammatory and anti-inflammatory mediators. Estimates of sphericity were applied, including the Greenhouse-Geisser correction and Huynh-Feldt correction, corrected by Lecoultre. Two-way ANOVA was used to co-exam the effect of surgical approach and tumor location. Frequency analysis was conducted using χ^2 test or Fisher's exact test. Partial Pearson's correlation coefficients were also calculated in order

to assess the net association between cytokines and compare using z-statistics. All calculated probabilities were two tailed, and P values ≤0.05 were considered statistically significant. The statistical analysis was conducted using MedCalc Statistical Software version 16.8 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2016).

In order to better assess the dynamics in cytokine levels, as well as account for potential differences in the baseline levels between groups or the inter-assay variability of tests, relative changes were also calculated. They were expressed either as fold increase/decrease in cytokine level between points in time or as percent increase/decrease if the differences were less pronounced.

Results

Demographics and perioperative outcomes

Between March 2013 and June 2015, 61 patients were recruited. Of these, 33 qualified for, and chose, RCS. The remaining 28 patients underwent OCS. Two patients were transferred from the robotic to the open group due to intraoperative conversions. The reasons for conversion included abdominal adhesions, difficult pelvic anatomy, and iatrogenic injury of the spleen.

Demographic data for patients in the two groups were comparable (Table 1). There were no differences found between the groups in terms of tumor location or stage of cancer. The mean length of surgery was significantly increased in the RCS group ($P < 0.001$). Major postoperative complications (Clavien-Dindo III–V) were rare and observed only in the OCS group ($P = 0.113$). All complications were related to anastomotic leakage and required surgical re-intervention. There was no mortality. The adequacy of oncologic resection, expressed by the number of harvested lymph nodes, was similar in both groups (RCS = 13 [12–14.8] vs. OCS = 15 [13.6–17]) ($P = 0.154$).

IL-1β

There were significant differences among measurements taken at various points, as well as differences between the RCS and OCS groups overall (Fig. 1a). The trend analysis of perioperative dynamics of IL-1β revealed it to be linear ($P = 0.017$) in the RCS group but cubic in the OCS group ($P = 0.060$). There was a significant difference between cytokine levels preoperatively and at 8 h post incision. In the OCS group, an analysis of relative changes in the cytokine levels showed that IL-1β decreased by 10 % from 8 h post incision to 24 h post incision. In the RCS group, however, cytokine levels increased by 18 % ($P = 0.073$) during the same time frame.

To avoid potential bias due to higher number of rectal cancers in OCS group, cytokine dynamics was re-evaluated in subgroups stratified by tumor location (right sided, left sided, and rectal tumors). Additionally, the effects of different surgery types were co-examined along with tumor location as a covariate by means of two-way ANOVA.

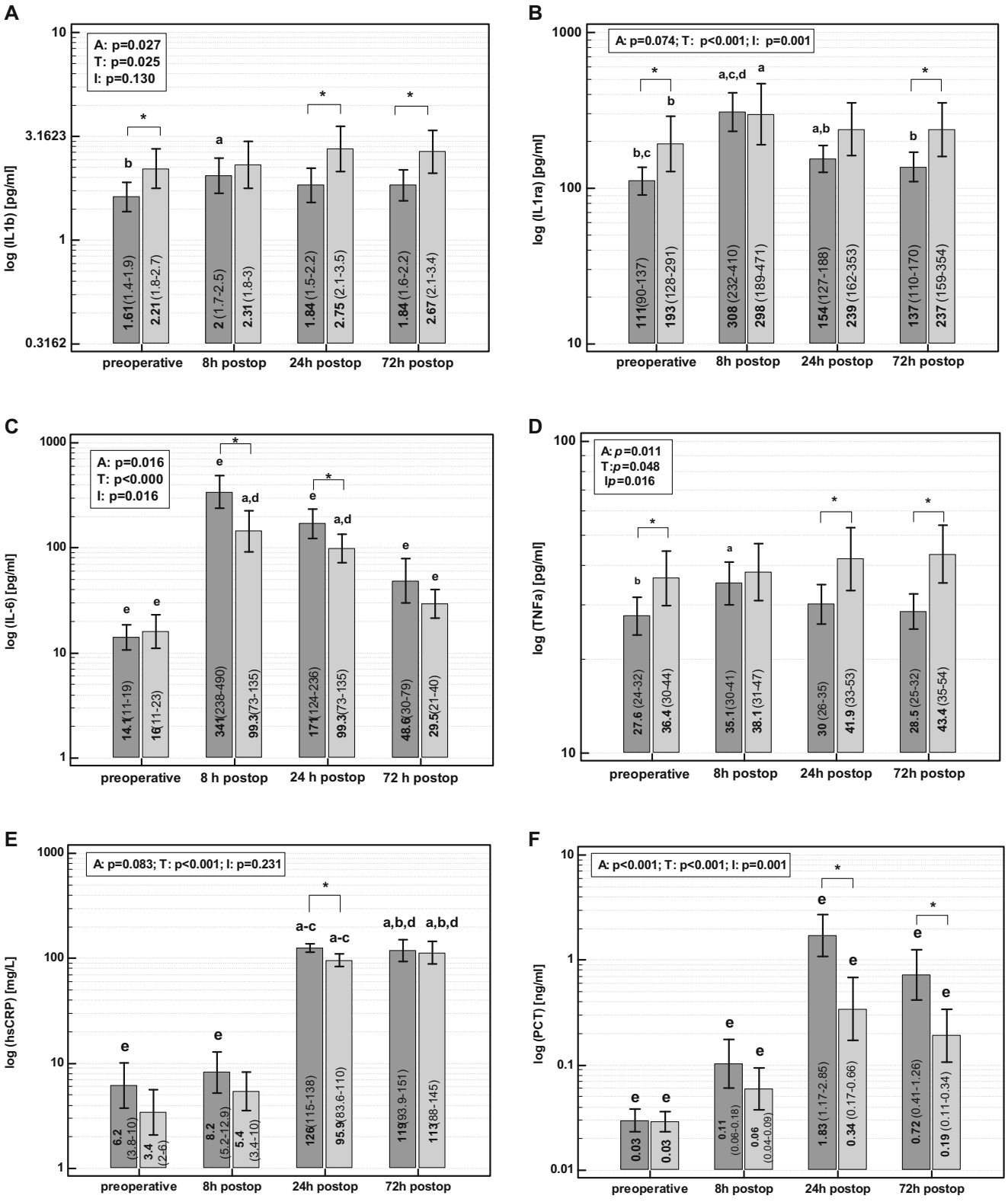
In case of IL-1β, additional analysis in subgroups did not show any significant differences with respect to surgical approach (Supplementary Figs. 1a–3a).

IL-1ra

There were significant differences in the cytokine levels and the dynamics of IL-1ra during various points in the

Table 1 Characteristics of study population

	Open surgery	Robotic surgery	P value
Number of patients	31	30	
Sex distribution (F/M)	14/17	7/23	0.127
Age (years)	68 (65–76)	67 (61.5–71.8)	0.302
ASA (1/2/3)	6/20/5	5/20/5	0.830
Stage distribution (0/I/II/III/IV)	2/2/15/9/3	2/3/11/12/2	0.839
Stage T distribution (Tis/T1/T2/T3/T4)	2/1/1/20/7	2/0/5/16/7	0.393
Stage N distribution (N0/N1/N2)	19/4/8	16/8/6	0.395
Stage M distribution (M0/M1)	28/3	28/2	0.970
Grade (G1/G2/G3/G4)	3/21/4/1	5/18/5/0	0.519
Time (min)	125 (115–150)	205 (191–240)	<0.001
Tumor location			
Left colon/right colon/rectum	11/6/14	7/12/11	0.199
Complications (Clavien III/IV)	4 (12 %)	0 (%)	0.113
Patients requiring blood transfusion	5 (16 %)	2 (6.7 %)	0.425
Length of stay, days (range)	7.5 (4–20)	5.8 (4–8)	0.023



perioperative period and also by type of surgical approach (Fig. 1b). In particular, the IL-1ra significantly increased in response to surgery and decreased on postoperative days 1 and 3 in both groups. However, there was a relative increase at 8 h compared to the preoperative cytokine levels which was significantly higher in the OCS group than in the RCS group (2.8-fold [2.1–3.7] vs. 1.6-fold [1.2–2.1]) ($P = 0.006$). In addition, the decrease at 24 h, when compared to the maximum

◀ **Fig. 1** Effect of surgical approach on perioperative dynamics of inflammatory and anti-inflammatory mediators. Data presented as geometric means accompanied by 95 % confidence interval. *Dark gray bars*–open surgery; *light gray bars*–robotic surgery. *Inserts* represent the results of two-way repeated measure ANOVA: "*A*" for a significance of difference between groups (surgical approaches), "*T*" for a significance of difference between measurements (time points at which blood was collected), and "*I*" for a significance of interaction, demonstrating whether difference between measurements is dependent on surgical approach undertaken. The analysis was followed by pairwise comparisons between groups for each time point, and significance is marked by *connector with an asterisk*. The differences between particular points in time within each group are marked by *letters* with "*a*" indicating statistical difference compared to preoperative measurement, "*b*" statistical significance compared to measurement at 8 h post incision, "*c*" statistical significance compared to measurement at 24 h post incision, "*d*" statistical difference compared to measurement at 72 h post incision, and "*e*" statistical difference compared to all other measurements

at 8 h, was more pronounced in the OCS group, where it decreased by half, while in the RCS group, it decreased by 21 % ($P = 0.008$). Similarly, the drop at 72 h, compared to 8 h, was higher in the OCS group (65 %) than in the RCS group (21 %) ($P = 0.006$).

The analysis conducted in subgroups stratified by tumor location revealed similar trends in perioperative dynamics of IL-1ra (Supplementary Figs. 1b–3b) to the trend observed in combined cohort (Fig. 1b). Regardless of tumor location, relative increase at 8 h was higher in the open than robotic group, significantly in right (2.9- vs. 1.5-fold, $P = 0.027$) and left (2.3- vs. 1.1-fold, $P = 0.021$) colonic cancers and insignificantly in rectal cancers (3- vs. 2-fold, $P = 0.259$). Also, two-way ANOVA confirmed that not tumor location ($P = 0.148$) but the surgical approach ($P = 0.005$) was responsible for relative increase in IL-1ra at 8 h post incision.

IL-6

As depicted in Fig. 1c, perioperative levels of IL-6 changed significantly with time as well as between the groups. The effect of time was impacted by the surgical approach. In both groups, patients responded to surgery with a significant increase in IL-6. After maximum elevation at 8 h post incision, IL-6 began to drop. After 72 h, however, it was still significantly higher than preoperative cytokine levels. Additionally, patients who underwent RCS experienced 2.7 times lower increase in IL-6 at 8 h post incision than those who underwent OCS (9-fold [5.1–16] vs. 24.2-fold [15.6–37.5]) ($P = 0.007$). Finally, the drop observed after 24 h was significant in the OCS group but not in the RCS group.

Similar trends were observed in patients stratified by tumor location (Supplementary Figs. 1c–3c). Relative increase at 8 h was higher in OCS than RCS group, significantly so in rectal cancers (35.9- vs. 8.9-fold, $P = 0.05$) and insignificantly in left (15.4- vs. 7.2-fold, $P = 0.077$) and right colonic (29.3- vs. 7.7-fold, $P = 0.160$) cancers. Two-way ANOVA confirmed that not tumor location ($P = 0.591$) but the surgical approach ($P = 0.015$) was responsible for observed increase in IL-6 at 8 h.

TNF-α

As with other measurements, there were significant differences observed in the TNF-α levels among various points in time as well as differences between the groups. Additionally, the dynamics of TNF-α changed with time and were dependent on type of surgical approach (Fig. 1d). Trend analysis of TNF-α perioperative dynamics showed it to be linear ($P = 0.026$) in the RCS group and cubic in the OCS group ($P = 0.012$). Analysis of relative changes in cytokine levels showed significant differences between both groups at baseline and an increase at 8 h post incision that was higher in the OCS group 127 % (110–147 %) than in the RCS group 105 % (89–125 %) ($P = 0.088$). On postoperative days 1 and 3, however, cytokine levels steadily increased in the RCS group while they decreased in the OCS group. When compared to cytokine levels at 8 h, 24-h post incision TNF-α levels constituted 86 % (76–96 %) of cytokine levels in the OCS group but 109 % (90–133 %) in the RCS group ($P = 0.034$). Even more pronounced was the difference between TNF-α at 8 and 72 h, with a drop to 81 % (69–96 %) in the OCS group and an increase to 114 % (93–139 %) of cytokine levels in the RCS group ($P = 0.009$).

Also in subgroups based on tumor location, the perioperative dynamics in TNFα were rather linear after RCS and cubic after OCS (Supplementary Figs. 1d–3d). Relative increase at 8 h tended to be more pronounced after open than robotic surgery, 122 vs. 90 %, $P = 0.160$ in left and 144 vs. 109 %, $P = 0.189$ in right colonic cancers and 146 vs. 118 %, $P = 0.320$ in rectal cancers. Compared to cytokine levels at 8 h, TNFα at 72 h decreased after OCS and increased after RCS, significantly in rectal (79.6 vs. 115 %, $P = 0.042$) and left colonic cancers (83 vs. 132 %, $P = 0.012$) and insignificantly in right colonic cancers (93 vs. 129 %, $P = 0.461$). In two-way ANOVA, not tumor location ($P = 0.762$) but the surgical approach ($P = 0.012$) significantly affected the difference between TNFα at 72 and 8 h.

Cytokine correlation pattern

At each point in time, relative changes in IL-1β and TNF-α were coordinated, regardless of the surgical approach, although the correlation seemed to be stronger in the RCS group (Table 2). Changes in the anti-inflammatory IL-1ra were positively correlated with the changes in IL-6 in the RCS group, while IL-1ra correlated rather with TNF-α in the OCS group.

Table 2 Correlation pattern between relative changes in cytokine levels following surgery and type of surgical approach

	IL-1β	IL-1ra	IL-6	TNF-α
Partial correlation[a] coefficients for relative changes in cytokine levels between 8 h and baseline ($\Delta_{8\ h/0}$)				
IL-1β	–	ns	ns	0.63, $P < 0.001$
IL-1ra	*ns*	–	ns	0.55, $P = 0.002$
IL-6	*ns*	*0.57, P = 0.002*	–	ns
TNF-α	*0.85, P < 0.0001*	*ns*	*ns*	–
Partial correlation[a] coefficients for relative changes in cytokine levels between 24 h and baseline ($\Delta_{24\ h/0}$)				
IL-1β	–	ns	ns	0.67, $P = 0.0001$
IL-1ra	*0.37, P = 0.054*	–	0.41, $P = 0.026$	0.49, $P = 0.009$
IL-6	*ns*	*0.57, P = 0.002*	–	ns
TNF-α	*0.69, P < 0.0001*	*ns*	*ns*	–
Partial correlation[a] coefficients for relative changes in cytokine levels between 72 h and baseline ($\Delta_{72\ h/0}$)				
IL-1β	–	ns	ns	0.48, $P = 0.009$[b]
IL-1ra	*0.50, P = 0.007*	–	ns	0.74, $P < 0.0001$
IL-6	*ns*	*0.63, P < 0.001*	–	−0.41, $P = 0.027$
TNF-α	*0.86, P < 0.0001*	*ns*	*ns*	–

Coefficients calculated for RCS group are given in *italics* and for OCS group in a straight script

[a] A net association, after excluding the effect of remaining variables

[b] Significantly different than respective coefficient of partial correlation in the other group (*z*-statistics)

CRP

The levels of CRP varied by time and tended to differ between the two groups (Fig. 1e). Trend analysis revealed both groups to be linear or cubic, with equal probability ($P < 0.0001$). There appeared to be significantly lower CRP levels at 24 h post incision in the RCS group as compared to the OCS group. In the analysis of relative changes, however, taking into account the CRP differences at baseline, there were no significant differences in dynamics of CRP during the perioperative period between the RCS and OCS groups.

No significant approach-related differences in hsCRP dynamics were found when tumor location was considered (Supplementary Figs. 1e–3e) except for significantly lower levels observed at 24 h after robotic surgery in patients with rectal tumors (Supplementary Fig. 3e). However, following adjustment with differences in baseline hsCRP, the observation lost statistical significance.

PCT

There were significant differences between measurements of PCT at various times as well as differences between the two groups. The dynamics of PCT changes with time were dependent upon the surgical approach (Fig. 1f). The relative increase of PCT at 8 h post incision was 3.6-fold in the OCS group and tended to be more pronounced than in the RCS group (2-fold) ($P = 0.103$). Likewise, the relative increase of PCT at 24 h was 62.1-fold in the OCS group and 11.7-fold in the RCS group, when compared to baseline levels ($P < 0.001$). Finally, at 72 h post incision, PCT adjusted to baseline levels was significantly more elevated in the OCS group (24.2-fold) than in the RCS group (6.6-fold) ($P = 0.004$).

The perioperative dynamics of PCT was similar when analyzed in subgroups stratified by tumor location with significantly higher PCT levels at 24 h after open surgery than robotic surgery in right and left colonic and rectal cancers (Supplementary Figs. 1f–3f). Also, relative increase at 24 h was significantly more pronounced in open surgery than robotic group regardless tumor location, 38.9- vs. 8.8-fold, $P = 0.044$ and 46- vs. 8.4-fold, $P = 0.038$ in right and left colonic cancers, respectively, and 113- vs. 27-fold, $P = 0.041$ in rectal cancers. In two-way ANOVA, both the surgical approach ($P = 0.001$) and tumor location ($P = 0.010$) affected relative increase at 24 h.

Discussion

Surgery, whether open, laparoscopic, or robotic, is a controlled trauma initiating a sequence of inflammatory, neuroendocrine, and metabolic changes. Laparoscopic colorectal surgery has been found to diminish the inflammatory response and blunt the immunosuppression [9, 10]. Still, while laparoscopy undoubtedly reduces the length of skin incision, the methods of tissue manipulation, division, and repair have remained somewhat crude. Conversely, the ability to enter the body through small openings, carefully divide and repair tissue, and reduce the risk of bleeding has been considerably enhanced with the advent of the surgical robot. It is therefore

expected that robotic surgery should result in even less surgical stress.

Until now, only Shibata and colleagues have studied stress response following RCS [11]. In their pioneering report, the authors compared human leukocyte antigen D-related (HLA-DR) and CRP levels. They concluded a stress response following the robotic and laparoscopic procedures to be comparable but lower than in the open procedures. Of importance, groups in their study were small and heterogeneous.

Surgical incision evokes an immediate release of numerous mediators at the local and systemic levels. The first cytokines released in the area of injury are IL-1β and TNF-α. In turn, they trigger an acute-phase cascade with a secretion of numerous pro-inflammatory mediators. Both cytokines are released immediately after the first stimuli and have a half-life of 20 and 6 min, respectively. Taking this into consideration in the current study, the first postoperative measurements at 8 h post incision likely missed the initial peak of those cytokines.

The next key mediator released in the cascade of acute response is IL-6 [12, 13], which has been shown to be strongly associated with the magnitude of operative injury. In previous reports on stress response following laparoscopic and open approaches, IL-6 was one of the most commonly measured parameters. Published results were inconsistent, however, with some authors noting concentrations of IL-6 to be higher following OCS and others finding no differences [7, 14–19] Additionally, IL-6 had not previously been examined in association with RCS. The current study is the first report demonstrating a lower increase of IL-6 among patients undergoing the robotic procedure and implying lessened SIRS following RCS. This trend is further confirmed by analysis of the PCT levels, another marker known for its correlation with the severity of SIRS [20, 21].

In the course of uneventful recovery, SIRS is quickly balanced by a compensatory anti-inflammatory response. Conversely, imbalanced pro-inflammatory action escalates SIRS and provokes multiple-organ dysfunction syndrome. One of the indicators expressing the extent of CARS is IL-1ra, which joins IL-1 receptor, blocks its downstream signaling, and limits IL-1-driven inflammation. Until now, only Schwenk et al. used IL-1ra to test CARS and found no differences following laparoscopic and open procedures [22]. In the current study, an elevation of IL-1ra was observed in both groups, although the profile of response seemed to be more favorable in the RCS group. Initially, the IL-1ra increase was less pronounced in RCS patients at 8 h post incision, but it remained elevated until postoperative day 3. In the OCS group, a rapid drop followed the initial higher cytokine peak, which implies faster termination of CARS. Interestingly, a strong correlation between IL-6 and IL-1ra was observed at every point in time following RCS, while the correlation between IL-6 and IL-1ra after OCS was less evident. Presuming that IL-6 and IL-1ra depict the extent of SIRS and CARS, respectively, this discovery indicates a poorer balance between the pro-inflammatory and anti-inflammatory responses in the OCS group.

The last decade has seen a significant amount of research around the impact of laparoscopic colorectal surgery and open colorectal surgery on the immune system. Surgery remains a mainstay of therapy for colorectal cancer; however, it also results in a transient immunosuppression with weakened tumor resistance [23]. Experimental animal studies have suggested better preservation of immunity following laparoscopic colorectal surgery, demonstrating that laparotomy compared with laparoscopy is associated with increased tumor establishment and growth [24, 25]. Unfortunately, human data supporting this hypothesis is sparse [10, 26].

In light of all of this, the results in the current study show a postoperative increase of TNF-α in the RCS group and are worth noting. Until now, only two studies analyzed TNF-α following laparoscopic and open procedures [27, 28]. In both papers, the authors considered TNF-α as purely a mediator of acute phase response and found its concentrations to be at the same level or higher, following the open surgery as compared to the laparoscopic procedure. The findings in the current study do not sync up with those findings. Instead, minute but significant differences between the RCS and OCS groups were observed, with a stable postoperative increase of TNF-α in the RCS group. It is also important to remember that TNF-α is truly a multi-functional cytokine. Thus, apart from being a classic, early mediator of inflammation, it acts on immune cells and holds strong anti-tumor activity [29]. The anti-neoplastic property of TNF-α has been documented against a wide range of tumor types and led to its use in the treatment of soft tissue sarcomas and metastatic melanomas [30, 31]. It would be of benefit to patients if the postoperative elevation of TNF-α in the RCS group echoed its strong anti-tumor activity encountered in a window of blunted host defense.

This study is one of the first reports addressing the issue of stress response following RACS and comparing it with traditional, open counterpart. Several drawbacks are present, however, including an obvious lack of randomization. Nevertheless, the analyzed groups were well balanced with respect to demographics, cancer stage, and the extent of surgery. Although tumor locations were comparable in the two groups, the number of rectal cancers in OCS group was higher. Rectal cancers are likely to require more extensive interventions leading to greater trauma, as exemplified herein by significantly more pronounced elevation of PCT in rectal cancers. Therefore, to avoid the potential bias in favor of robotic surgery, the impact of surgical approach was confirmed in the analysis in which differences in tumor location were accounted for by means of two-way ANOVA. Moreover, the data was re-analyzed in subgroups based on tumor location. All trends differentiating OCS and RCS in terms of perioperative dynamics of inflammatory mediators found in the whole

cohort were also observed after patients' stratification. However, as the statistical power of the analysis in subgroups was reduced due to substantially lower number of evaluated patients, not all of them reached statistical significance.

Another shortcoming that might be considered is discrepancy in the experience of surgeons with regard to the analyzed surgical techniques. Participating surgeons had much more experience with the conventional, open approach than with the robotic technique, which may have influenced results in favor of OCS.

In conclusion, this report shows that robotic surgery results in less pronounced inflammatory response and stronger anti-inflammatory action. In addition, subtle but significant differences in postoperative fluctuations of TNF-α were observed between the two groups, which may indicate better preservation of immune function following a robotic procedure. Certainly, the results strengthen the hypothesis that the robotic approach results in less overall disturbances of the body hemostasis, although the clinical relevance of these observations is unknown. Whether the observed changes can affect postoperative outcomes, and ideally patient survival, remains to be studied.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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