Surgical Endoscopy
https://doi.org/10.1007/s00464-023-10582-0

REVIEW ARTICLE

Impact of laparoscopic versus open surgery on humoral immunity in patients with colorectal cancer: a systematic review and meta-analysis

A. Bohne[1] · E. Grundler[1] · H. Knüttel[2] · V. Völkel[3] · A. Fürst[4]

Received: 5 August 2023 / Accepted: 4 November 2023
© The Author(s) 2023

Abstract

Background Laparoscopic surgery (LS) is hypothesized to result in milder proinflammatory reactions due to less severe operative trauma, which may contribute to the observed clinical benefits after LS. However, previous systematic reviews and meta-analyses on the impact of LS on immunocompetence are outdated, limited and heterogeneous. Therefore, the humoral response after laparoscopic and open colorectal cancer (CRC) resections was evaluated in a comprehensive systematic review and meta-analysis.

Methods Included were randomized controlled trials (RCTs) measuring parameters of humoral immunity after LS compared to open surgery (OS) in adult patients with CRC of any stage. MEDLINE, Embase, Web of Science (SCI-EXPANDED), Cochrane Library, Google Scholar, ClinicalTrials.gov and ICTRP (World Health Organization) were systematically searched. Risk of bias (RoB) was assessed using the Cochrane RoB2 tool. Weighted inverse variance meta-analysis of mean differences was performed for C-reactive protein (CRP), interleukin (IL)-6, IL-8, tumour necrosis factor (TNF)α and vascular endothelial growth factor (VEGF) using the random-effects method. Methods were prospectively registered in PROSPERO (CRD42021264324).

Results Twenty RCTs with 1131 participants were included. Narrative synthesis and meta-analysis up to 8 days after surgery was performed. Quantitative synthesis found concentrations to be significantly lower after LS at 0–2 h after surgery (IL-8), at 3–9 h (CRP, IL-6, IL-8, TNFα) and at postoperative day 1 (CRP, IL-6, IL-8, VEGF). At 3–9 h, IL-6 was notably lower in the LS group by 86.71 pg/ml (mean difference [MD] − 86.71 pg/ml [− 125.05, − 48.37], $p < 0.00001$). Combined narratively, 13 studies reported significantly lower concentrations of considered parameters in LS patients, whereas only one study reported lower inflammatory markers (for CRP and IL-6) after OS.

Conclusion The increase in postoperative concentrations of several proinflammatory parameters was significantly less pronounced after LS than after OS in this meta-analysis. Overall, the summarized evidence reinforces the view of a lower induction of inflammation due to LS.

Keywords Meta-analysis · Laparoscopy · Colorectal cancer · Inflammation · Surgical stress response · Cytokine

Colorectal cancer (CRC) is one of the leading health issues of modern times, with almost two million new cases worldwide in 2020 and a further rise expected [1]. Curative treatment still relies primarily on surgical resection, with laparoscopic and open surgery being the methods most used. While open surgery remained the "conventional" surgical approach for many decades, laparoscopic surgery has since

V. Völkel and A. Fürst have contributed equally to this work.

✉ A. Bohne
abohne857@gmail.com

[1] Universität Regensburg, Universitätsstraße 31, 93053 Regensburg, Germany

[2] Universität Regensburg, Universitätsbibliothek Regensburg, Universitätsstraße 31, 93053 Regensburg, Germany

[3] Tumorzentrum Regensburg – Zentrum für Qualitätssicherung und Versorgungsforschung, Universität Regensburg, Am Biopark 9, 93053 Regensburg, Germany

[4] Caritas Krankenhaus St. Josef Regensburg, Klinik Für Allgemein-, Viszeral-, Thoraxchirurgie und Adipositasmedizin, Landshuter Str. 65, 93053 Regensburg, Germany

Published online: 15 December 2023

been on the rise. Meta-analyses and systematic reviews could demonstrate better postoperative clinical outcomes after laparoscopic CRC resection, i.e., shorter hospital stay and reduced incidences of surgical wound infection and abdominal abscess [2, 3], while oncological outcomes were shown to be noninferior [4, 5] and probably even superior [6] to the open approach.

Every surgical intervention corresponds to a controlled trauma, leading to alterations in host immunity [7]. A proinflammatory reaction proportional to the extent of the surgical trauma is triggered [8] and subsequently followed by a much more pronounced compensatory anti-inflammatory reaction. Both states are associated with unwanted outcomes: hyperinflammation is related to tissue destruction, organ failure, a higher incidence of systemic inflammatory response syndrome (SIRS) [9, 10] and worse long-term survival [11], whereas the anti-inflammatory state makes the host more susceptible to infection [12]. The latter is very important in the context of cancer treatment, as suppressed immunity is known to promote metastasis formation and recurrence, hindering the (mostly) curative intent of surgical tumour resections [13].

It is hypothesised that alterations in host immunity are less pronounced in laparoscopically operated patients due to less severe surgical trauma. This milder proinflammatory reaction, followed by less pronounced immunosuppression, might in turn be an underlying mechanism contributing to the clinical benefits observed after laparoscopic surgery compared to open surgery. Systematic reviews and meta-analyses of randomized controlled trials (RCTs) evaluating immunocompetence after laparoscopic surgery do exist, but are restricted to studies published until 2012 [14, 15]. Faced with a limited and heterogenous set of studies and results of meta-analysis based on the data of just two studies, the authors themselves stated that conclusions were not possible on account of limited data availability [16].

Since the impact of surgery on host immunity in cancer remains a widely investigated topic and the status of laparoscopic surgery in colorectal cancer treatment is discussed to this day, the current article aims to provide an updated and rigorous review of the influence of laparoscopy on the humoral aspect of immunity and the proinflammatory reaction following surgical resection. The impact on cellular immunity is addressed elsewhere [17].

Materials and methods

The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 checklist was used when writing the report [18]. The protocol of this systematic review was registered prospectively in PROSPERO under registration number CRD42021264324, with a draft search strategy published in a public repository [19].

Eligibility criteria

Only RTCs were included in this review. The population of interest comprised patients with proven CRC of any stage. Minimally invasive (robotic and/or laparoscopic) tumour resection had to have been compared with open tumour resection in a nonemergency setting. Eligible outcomes were postoperatively measured humoral immunological parameters.

Study identification

The following bibliographic online databases and trial registries were searched last on December 10, 2021: MEDLINE (via Ovid), Embase (via Ovid), Cochrane Database of Systematic Reviews (CDSR) and the Cochrane Central Register of Controlled Trials (CENTRAL; via Cochrane Library, Wiley), Science Citation Index Expanded (via Web of Science Core Collection), Google Scholar, ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP). An initial search strategy was developed for MEDLINE and then adapted to the other databases by choosing appropriate search syntax and index terms. The search strategies aimed for high sensitivity using a broad range of synonyms and thesaurus terms. No limits such as date, language or study type were employed. The search strategy was built according to the PICO framework: population: colorectal cancer; intervention: laparoscopy; control: open surgery. Full reproducible search strategies and additional details of the searches as well as a PRISMA-S checklist [20] are contained in public repositories [21, 22]. The reference lists of relevant systematic reviews [14–16] and of the included studies were screened for further relevant studies.

Database records were imported into EndNote (version 19.3; Clarivate, London, UK). Deduplication was performed in EndNote (semiautomatic steps A–C) according to the Bramer method [23], followed by a second round employing the Systematic Review Accelerator [24]. After deduplication the records were imported into Rayyan [25] and screened for eligibility first by title and abstract, followed by a round of full-text assessment. Studies without full texts in German or English were excluded due to resource limitations. Screening was independently carried out by two authors (EG and AB), with discrepancies solved by discussion.

Data collection process

Data were collected via the "Data Collection Form–Intervention Review–RCTs Only" of the Cochrane Collaboration [26]. The data collection sheet was adapted to the review

question and included confirmation of eligibility, publication details, characteristics of the study population (age, sex, cancer stage, number of participants converted from laparoscopic to open surgery, [neo]adjuvant therapy and immunomodulatory medication), study design (allocation concealment, randomization method, number of participants included/randomized/analysed per surgical group) and surgical group characteristics (operating time, type of anaesthesia, operative methods, tumour site). In case of nonreporting of conversions, "no conversions" were assumed.

Extraction of outcome data included measuring methods, effect sizes, measures of variance and the number of participants in each group for each timepoint. Mere graphically presented data were extracted using WebPlotDigitizer version 4.6 [27]. In case of several eligible subgroups (standard or fast-track care), subgroups were pooled according to the formulas implemented in RevMan [28]. Subgroups with application of corticosteroids by default were excluded. Baseline and postoperative measurements of parameters reflecting humoral immunity up to 8 days after surgery were considered. Timeframes to group measurements were prospectively defined as 0–2 h after surgery, 3–9 h, 10–15 h, 18–30 h (equivalent to post-operative day 1 [POD1]), POD2, POD3, POD4, POD5 and POD6–8.

Data collection was carried out independently by two authors (AB and EG), with discrepancies solved by discussion. If clarifications were required, study authors were contacted once via email.

Data analysis

All included studies were considered for narrative synthesis. Graphical display of study-level data were based on relative changes in the means per surgical group from preoperative measurements. These data were either extracted directly or calculated from absolute measurements given. If several studies contributed data within one timeframe, the minimal and maximal change from baseline was chosen per surgical approach, with the resulting corridor including all other relative changes.

To perform meta-analysis, data from at least two studies meeting the following requirements within one timeframe had to be available: data had to be either reported as mean and standard deviation (SD), or estimable (from median with interquartile and/or range) according to the method reported by Wan et al. [29]. Sensitivity analyses considering only data not estimated by this method were implemented to test the robustness of results. If reported outcome dimensions deviated from common values and those reported by other studies by at least a factor of 1000, these studies' data were not included in the meta-analysis to avoid distortion of weighting if clarification from the authors could not be obtained.

All statistical analyses were performed using Review Manager (RevMan) version 5.4.1 [28]. The mean difference (MD) accompanied by the 95% confidence interval (CI) of continuous outcomes was calculated using weighted inverse variance under assumption of the DerSimonian-Laird random-effects model. A two-sided p value of < 0.05 was considered significant. The presence of heterogeneity was assessed using the Q-statistic, I^2 and τ^2. Due to the low power of tests for heterogeneity, a $p < 0.1$ was defined as significant. An I^2 of up to 30%, 60%, 80% or 100% was defined as indicating low, moderate, substantial, or considerable heterogeneity, respectively.

Assessment of methodological quality and bias

Risk of bias was assessed using the Cochrane Risk of Bias (RoB)2 tool [30]. Evaluation was performed independently by two authors (AB and EG), with discrepancies solved by discussion and consulting a senior author (VV). The RoB was assessed at the study-level with the ratings "low," "some concerns" and "high." Intention-to-treat (ITT) analysis was not rated as appropriate to assess the effect of adhering to the intervention, hence resulting in an upgrade of the RoB. The RoB assessment also included evaluation of aspects of reporting bias (bias due to selection of the reported results and selective nonreporting), which is implemented in the RoB2 tool, and of publication bias, which is implemented in the GRADE pro GDT software [31]. The latter was used to rate the quality of the evidence of the reviews' findings for better communication of confidence in the results, with overall ratings of "high," "moderate," "low" or "very low quality."

Results

Study selection

The systematic literature search in databases and registers yielded 13,714 records in total. Sources of records are indicated in the PRISMA flow diagram (Fig. 1) and the supplementary data. After deduplication, 7678 records were screened for eligibility according to title and abstract. Among these, 124 records were identified as potentially relevant. Full-text manuscripts were searched for, which was successful in 120 cases. Detailed justifications for exclusions of full texts are depicted in Fig. 1, with 20 reports remaining for inclusion. The citation search of these included studies yielded two further eligible reports. Citation searching

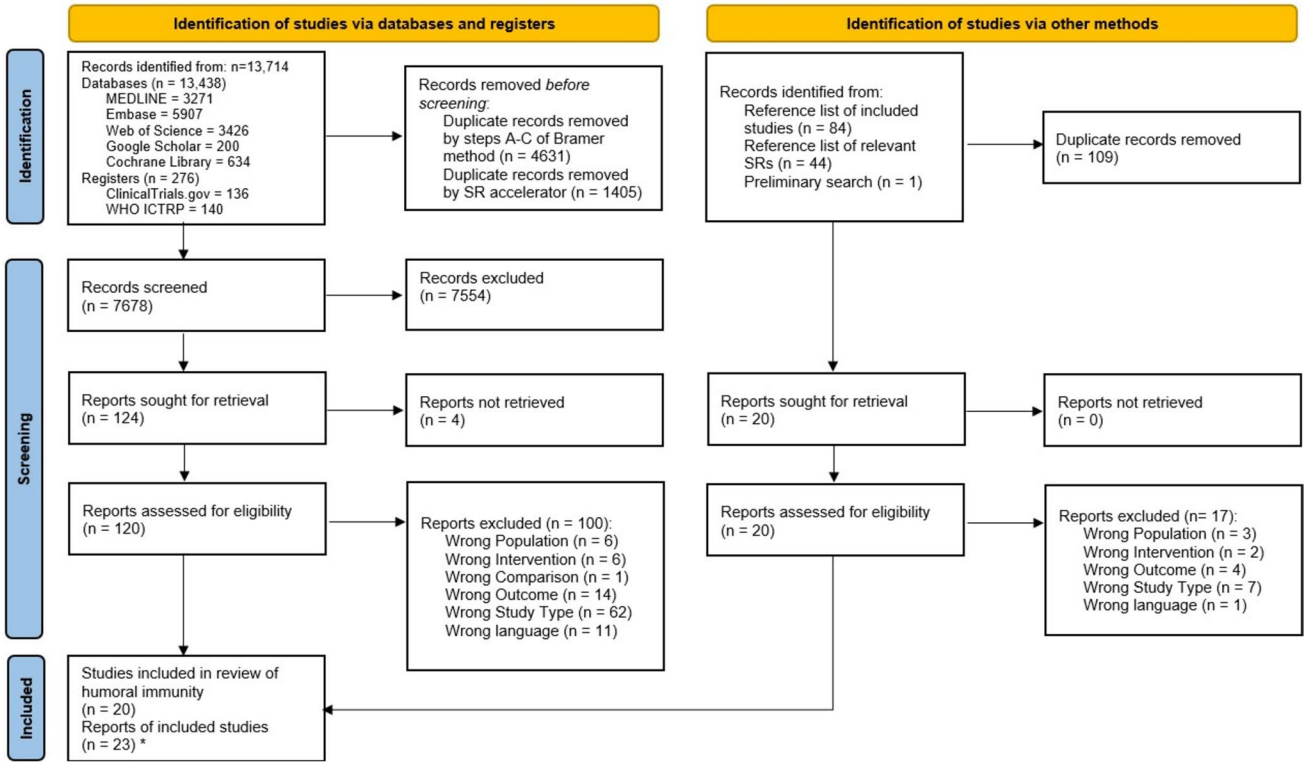

Fig. 1 PRISMA flowchart of the study selection process; from: Page et al. [18, 372:n71]. https://doi.org/10.1136/bmj.n71. *Three times two studies were based on the same study population; therefore, 23 records were included originating from 20 studies

in recent relevant meta-analyses and systematic reviews [14–16] identified by an initial scoping review following the work of Völkel et al. [32] produced no new records. The study of Zhao et al. [33] could not be included due to its full-text language. One report was directly and only identified by the initial scoping review. Because of identical study populations (judged by population characteristics, authors, year of publication), overall, 23 reports correspond to 20 studies included in this review of humoral immunity.

Study characteristics

The characteristics of included studies as well as the RoB assessment can be found in Table 1; more detailed characteristics of included studies are published in a public repository [22]. Overall, data from 1131 participants were included in this review of humoral parameters. Most commonly, results from patients with Union for International Cancer Control (UICC) tumour stage II were reported, with 182 and 171 participants in the laparoscopic (LS) and open surgery (OS) groups, respectively. No study reported significant differences regarding population characteristics or significantly differing baseline immunological parameters between LS and OS. Conversions to the open approach occurred in 13 trials, four trials reported no conversions, and the remaining three trials did not give information. Nine studies reported resections of colon and rectal cancer, eight studies performed colonic resections only and three studies carried out solely rectal resections.

The risk of bias was rated as low in five studies. In 13 studies the RoB was assessed to be of some concern and two studies were labelled with a high risk of bias. Unknown allocation concealment was the main reason to uprate the RoB arising from the randomization process. A common reason to uprate RoB due to deviations from the intended interventions were ITT analysis methods in case of conversions, affecting seven studies. The individual judgements per domain can be taken from Table S4 published at the publicly accessible repository [22].

Results of meta-analysis and systematic review

Results of the narrative syntheses of all studies can be found in the public repository as Table S2 [22]. For graphical display of postoperative development, 17 studies were eligible. Ordemann et al. [43] and Schwenk et al. [45] only reported medians with 95% CI, Stage et al. [46] only presented medians without measures of variance, thus not allowing for estimation of means, and were hence excluded from graphical display.

Thirteen studies were included in the meta-analyses. Among these, four studies reported median with range and/

Table 1 Characteristics of included studies including numbers of participants giving information as to inclusion (yes) or exclusion (no) of UICC stage IV colorectal cancer, the localizations of resections performed, overall risk of bias rating, and the outcomes assessed by study authors which are being discussed in this publication

First author	Year of publication	*n*	LS	OS	Inclusion of stage IV	Colon and/or rectal resections	Risk of bias	Outcomes evaluated
Delgado [34]	2001	97	39	58	Yes	Colorectal	Some concerns	IL6, CRP
Duque [35]	2019	37	18	19	n.a	Colorectal	Some concerns	IL6, IL8, TNFα, CRP, VEGF
Hasegawa [36]	2003	50	24	26	No	Colorectal	Some concerns	IL6, CRP
Hewitt [37]	1998	16	8	8	No	Colorectal	Some concerns	IL6
Kim [38]	2011	57	38	19	No	Colon	Low	IL6, CRP, VEGF
Kvarnström [39, 40]	2012/2013	24	12	12	n.a	Rectal	High	IL6, IL8, TNFα, CRP
Laforgia [41]	2016	14	7	7	Yes	Colorectal	Some concerns	IL6, CRP
Leung [42]	2000	34	17	17	No	Rectal	Some concerns	IL6, TNFα, CRP
Ordemann [43]	2001	40	20	20	No	Colorectal	Some concerns	IL6, TNFα
Pascual [44]	2010	120	60	60	No	Colorectal	High	IL6, VEGF
Schwenk [45]	2000	60	30	30	Yes	Colorectal	Some concerns	IL6, CRP
Stage [46]	1997	29	15	14	Yes	Colon	Low	IL6, CRP
Straatman [47]	2018	79	42	37	n.a	Colorectal	Some concerns	CRP
Tsimogiannis [48, 49]	2011/2012	40	20	20	No	Colon	Low	IL6, TNFα, CRP
Veenhof [50]	2011	40	22	18	Yes	Rectal	Some concerns	IL6, IL8, CRP
Veenhof [51]	2012	79	42	37	n.a	Colon	Some concerns	IL6, CRP
Vignali [52]	2009	26	13	13	Yes	Colon	Some concerns	IL6, IL8, TNFα, CRP
Wang [53]	2012	163	80	83	No	Colon	Low	IL6, CRP
Wu [54, 55]	2003/2004	26	12	14	No	Colon	Low	IL6, IL8, TNFα, CRP, VEGF
Zhu [56]	2017	100	50	50	No	Colon	Some concerns	TNFα, CRP

n.a. no information available, *n* total study population, *LS* study population in laparoscopic group, *OS* study population in open group

or interquartile range; hence mean and SD were estimated. Seven studies could not be considered, either due to missing units [53], a data format not allowing transformation to mean and SD [43, 45, 46], missing estimates of variance [52] or missing reporting of absolute values [50, 51]. Hence, pooling of data were possible for CRP, IL-6, IL-8, VEGF and TNFα.

C-reactive protein

Seventeen studies measured CRP concentrations in peripheral blood, with nine studies reporting significantly lower concentrations after LS up to POD5. The study by Stage et al. [46] was the only one to state lower CRP values after OS for POD1 and POD3.

An overall increase in postoperative CRP relative to preoperative values was reported by all studies (Fig. 2). Peak values were reached at POD1 and POD3 by both the OS (97.24- and 116.02-fold increase) and the LS group (48.63- and 56.00-fold increase), although all studies reported a more pronounced rise after OS. A subsequent drop in relative CRP concentrations can be observed from POD4 onwards. During the whole observation period of up to 8 days after surgery, CRP values remained above the preoperative measurements.

Meta-analysis results of CRP are shown in Fig. 3. There was no significant difference between the two surgical approaches observed during the first 0–2 h after surgery (MD − 0.65 mg/dl [− 1.44, 0.14], $p = 0.11$). However, 3–9 h after surgery, CRP concentrations were shown to be significantly lower after laparoscopy (MD − 1.67 mg/dl [− 3.25, − 0.08], $p = 0.04$). Likewise, CRP was significantly lower at POD1 after LS (MD − 3.68 mg/dl [− 5.05, − 2.32], $p < 0.00001$). Such significant differences could not be observed for the subsequent days (POD2: MD − 0.82 mg/dl [− 1.99, 0.35], $p = 0.17$; POD3: MD − 2.24 mg/dl [− 4.54, 0.06], $p = 0.06$). Heterogeneity was substantial at POD1 ($I^2 = 72\%$, $p = 0.002$) and considerable for 0–2 h ($I^2 = 91\%$, $p < 0.0001$) and 3–9 h ($I^2 = 89\%$, $p < 0.00001$).

Summarizing these findings, CRP values are probably slightly decreased after LS. Lower CRP concentrations and milder increases are outcomes considered favourable.

Interleukin 6

Narrative synthesis of 18 studies showed significantly lower concentrations of IL-6 after LS in the early postoperative period up to POD1 reported by 11 studies. After this timeframe, only Wang et al. [53] reported significantly lower IL-6 in patients after laparoscopic resection. Again, only

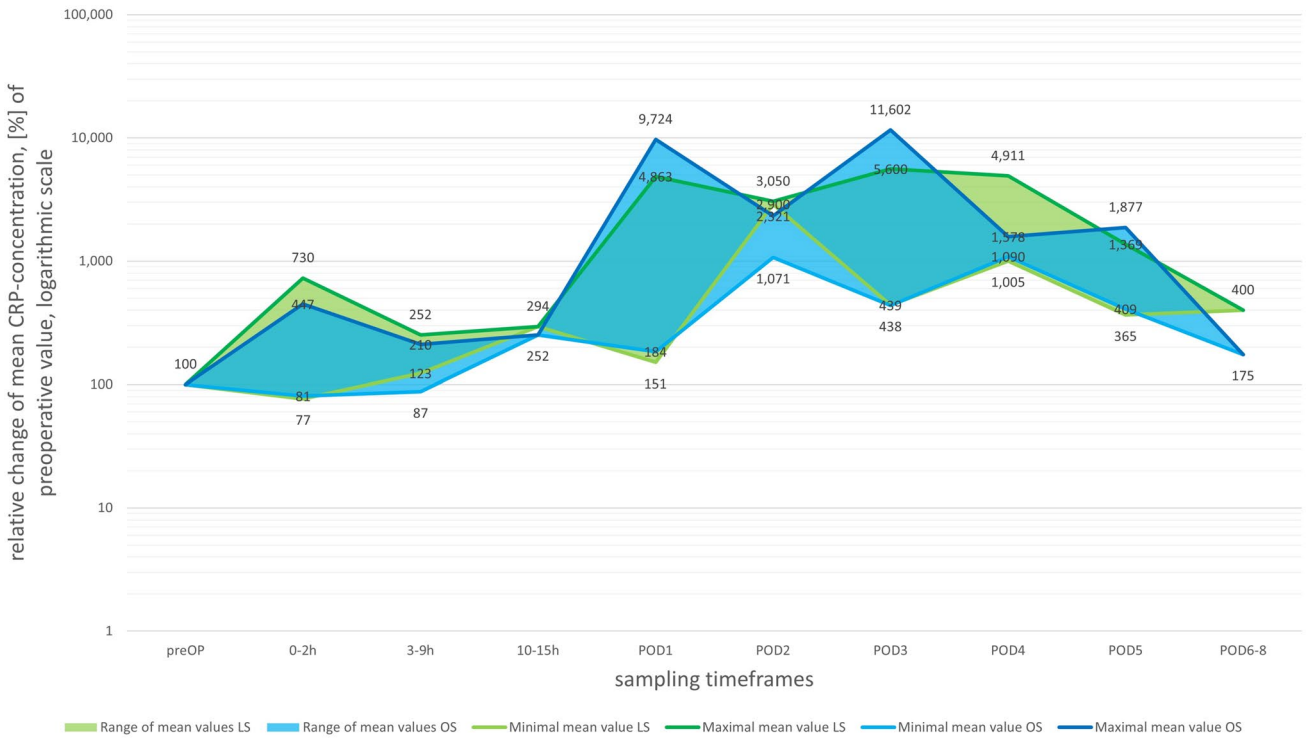

Fig. 2 Postoperative progression of relative mean CRP concentration based on preoperative values set at 100%, numbers given are minima and maxima per timepoint stratified for surgical group

Stage et al. [46] reported higher concentrations in the LS group at POD1.

Generally, studies reported rising IL-6 after both LS and OS (Fig. 4). A peak in values relative to the preoperative measurements can be observed immediately during the first 2 h after surgery (204.76-fold after LS, 84.58-fold after OS) and at POD1 (132.87-fold after LS, 111.51-fold after OS). The laparoscopic group of Laforgia et al. [41] reached concentrations comparable to preoperative values (LS POD6–8: 97%).

In meta-analysis (Fig. 5), no significant difference was observed for the first timeframe (0–2 h: MD − 28.49 pg/ml [− 74.09, 17.11], $p = 0.22$), but after 3–9 h, mean concentrations of IL-6 were significantly lower after LS by 86.71 pg/ml (MD − 86.71 pg/ml [− 125.05, − 48.37], $p < 0.00001$). Also, at POD1 (MD − 26.88 pg/ml [− 31.27, − 22.50], $p < 0.00001$) and POD2 (MD − 11.47 pg/ml [− 16.32, − 6.63], $p < 0.00001$), IL-6 was lower after LS. This difference was not present at POD6-8 according to the available data (− 0.89 pg/ml [− 6.60, 4,81], $p = 0.76$). Heterogeneity was mostly low, but considerable at 0–2 h ($I^2 = 98\%$, $p < 0.00001$) and moderate at 3–9 h ($I^2 = 44\%$, $p = 0.10$).

Overall, IL-6 values are probably lower in patients after laparoscopy compared to OS. As IL-6 is a proinflammatory cytokine, lower concentrations are favoured.

Interleukin 8

Narrative review of the results of five studies indicated significantly lower IL-8 concentrations for 0–2 h and 3–9 h in the LS group by Duque et al. [35] and Wu et al. [54, 55], but significance was not reached at later timeframes. No study found higher concentrations after LS.

The progression chart (Fig. S1, supplement) of IL-8 shows an initial postoperative rise of relative IL-8 concentrations, considerably more prominent after OS (58.95-fold; LS: twofold at 0–2 h), whereas Kvarnström et al. [39, 40] reported a drop in IL-8 values after LS in the early postoperative period (16% at 0–2 h, 50% at POD1). Return to preoperative dimensions could be observed for all surgical groups in the later postoperative period until POD6–8.

Meta-analysis (Fig. S2, supplement) demonstrated significantly lower concentrations of IL-8 after laparoscopy, with a concentration pronouncedly lower by 72.59 pg/ml after LS compared to OS at 0–2 h (0–2 h: MD − 72.59 pg/ml [− 77.53, − 67.65], $p < 0.00001$; 3–9 h: MD − 21.24 pg/ml [− 24.10, − 18.38], $p < 0.00001$; POD1: − 4.32 pg/ml [− 6.29, − 2.35], $p < 0.0001$). Heterogeneity was low throughout.

Overall, IL-8 concentrations may be lower after LS compared to OS, with lower concentrations representing a superior outcome due to the proinflammatory domain of this interleukin.

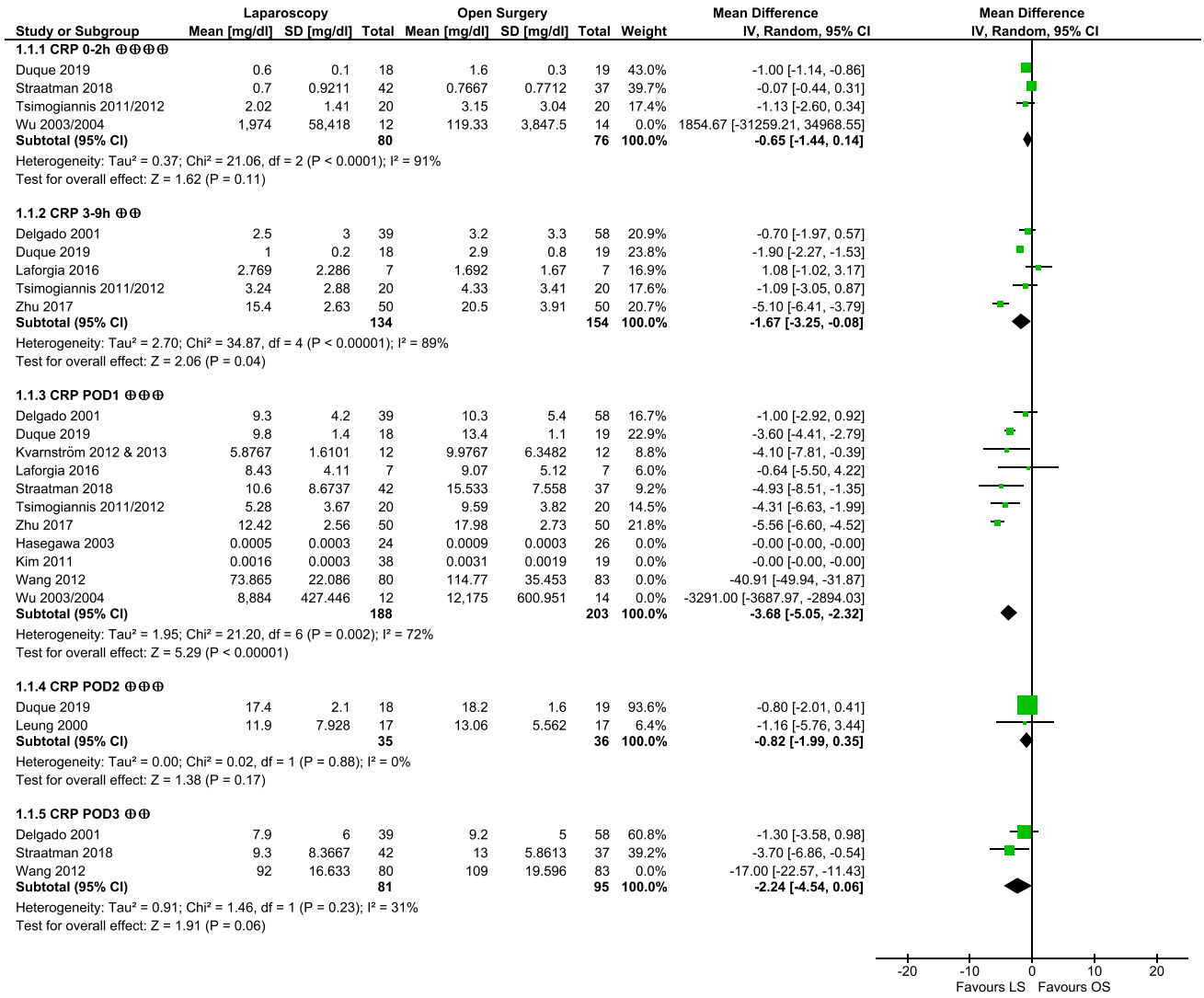

Fig. 3 Forest plot depicting meta-analysis of CRP; GRADE quality of evidence rating is indicated by ⊕ (very low), ⊕⊕ (low), ⊕⊕⊕ (moderate), ⊕⊕⊕⊕ (high); numerical data of Hasegawa et al. [36], Kim et al. [38] and Wu et al. [54, 55] reported CRP values deviating by factor 1000 from values reported by other studies and were therefore excluded from meta-analysis; numerical data of Wang et al. [53] were not included in meta-analysis due to missing reporting of units (numbers depicted in respective data tables)

Tumour necrosis factor alpha

Synthesised narratively, Ordemann et al. [43] reported significantly lower concentrations after LS for 0–2 h and 3–9 h. This was again reported by Ordemann et al. [43] and Duque et al. [35] at POD2. No study found significantly lower concentrations after OS. Wu et al. [54, 55] consistently found results below their detectable limit of 25 pg/ml, not allowing statements regarding differences in concentrations.

The postoperative changes in TNFα (Fig. S3) in the included studies were less prominent and clear: minimal and maximal levels were both reported 3–9 h after surgery by different studies (LS: 0.8-fold decrease to 1.63-fold increase; OS: 0.82-fold decrease to 1.78-fold increase). Convergence to preoperative values was observed during the later postoperative period.

Meta-analysis (Fig. S4) at 0–2 h after surgery yielded TNFα levels not significantly differing between the groups (MD − 1.25 pg/ml [− 4.24, 1.74], $p = 0.41$), nor did they differ at POD1 (MD − 3.9 pg/ml [− 9.02, 1.22], $p = 0.14$). However, 3–9 h after surgery, the mean concentration of TNFα was significantly lower after LS by 7.25 pg/ml (MD − 7.25 pg/ml [− 13.04, − 1.47] $p = 0.01$). Heterogeneity was substantial (0–2 h: $I^2 = 77\%$, $p = 0.04$) to considerable for all analyses (3–9 h: $I^2 = 95\%$, $p < 0.00001$, POD1: $I^2 = 90\%$, $p < 0.00001$).

Overall, TNFα concentrations are probably lower in patients after LS, which is a favourable outcome due to this parameter's proinflammatory nature.

Fig. 4 Postoperative relative progression of IL-6 based on preoperative values

Vascular endothelial growth factor

Summarizing the findings of the studies, Duque et al. [35] and Pascual et al. [44] found significant results for 3–9 h, POD2 and POD4, with lower concentrations of VEGF after LS. No study reported higher VEGF after LS compared to OS.

On the whole, VEGF concentrations were reported to rise postoperatively, with most pronounced serum levels at POD1 (1.79-fold after LS, 2.33-fold after OS) and POD4 (181-fold after LS and 2.29-fold after OS), although Kvarnström et al. [39, 40] stated decreasing values at 0–2 h after surgery (LS 65%, OS 95%). The VEGF concentration remained elevated in both groups during the available observation period (Fig. S5).

Meta-analysis of VEGF (Fig. S6) at 0–2 h did not result in a significant difference between the groups (MD − 186.82 pg/ml [− 418.20, 44.56], $p = 0.11$), whereas a significantly lower concentration of 303.15 pg/ml in the LS group compared to the OS group was present at POD1 (MD − 303.15 pg/ml [− 431.62, − 174.67], $p < 0.00001$). Substantial heterogeneity was present at 0–2 h ($I^2 = 66\%$, $p = 0.09$).

To summarize, concentrations of systemic VEGF are probably lower after LS. Identical to other proinflammatory cytokines, a lower VEGF concentration is favoured due to it indicating a lesser inflammatory reaction.

Reporting biases

A risk of bias due to selective nonreporting was found for CRP measurements by Kvarnström et al. [39, 40]. Although stated in the methods section for all parameters, results for two timepoints were not given. One study was seen to be at risk of bias concerning selection of the reported results:

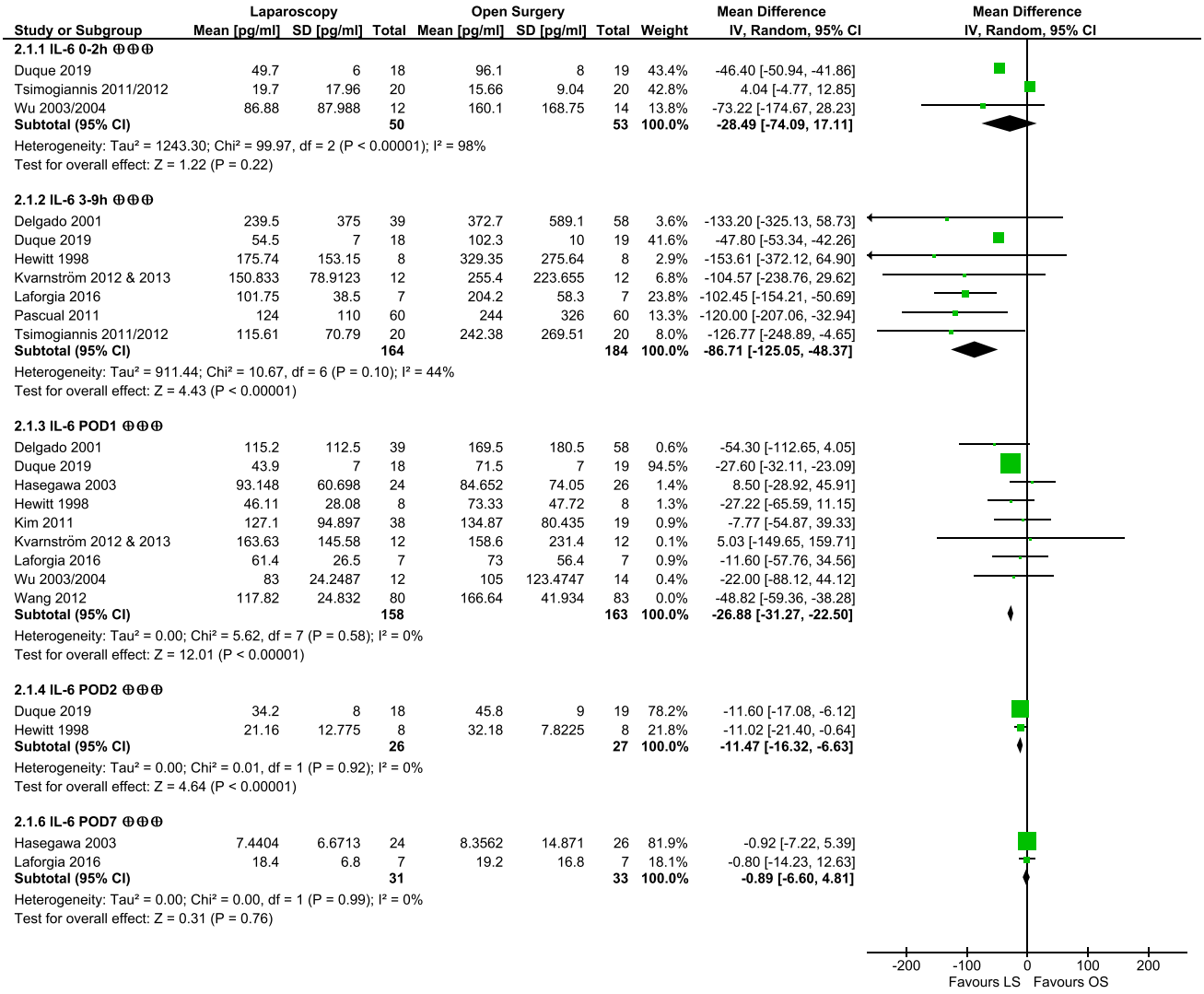

Fig. 5 Forest plot depicting meta-analysis of IL-6; GRADE quality of evidence rating is indicated by ⊕ (very low), ⊕⊕ (low), ⊕⊕⊕ (moderate), ⊕⊕⊕⊕ (high); numerical data of Wang et al. [53] were not included in meta-analysis due to missing reporting of units (numbers depicted in respective data tables)

Pascual et al. [44] reported differing timepoints of measurements in the protocol and the manuscript.

Certainty of evidence

Confidence in the estimates of effect for TNFα were moderate, being limited by imprecision due to small sample sizes or due to inconsistency because of relevant heterogeneity. The CRP effect estimates were rated to be of low to high-quality. Reasons to downrate were high risks of selection bias due to possible repeated measurements, high heterogeneity and/or limited study populations with insufficient statistical power. The quality of evidence for IL-6 was rated to be moderate for all estimates of effect. Reasons to downrate were inconsistency due to high heterogeneity, high RoB due to selective reporting or a limited overall study population contributing to the analysis. Concerning IL-8, the rating was found to be moderate or low due to limited study populations in all cases and because of a high RoB in the context of non-protocol interventions. Results for analyses of VEGF were evaluated to be of moderate quality due to imprecision.

Discussion

Generally, rising concentrations of proinflammatory mediators were observed after laparoscopic as well as open surgery, which was most pronounced in the early

postoperative period in both surgical groups. This is in concordance with previous findings from other studies [57–59].

The current meta-analysis found significant differences, with lower concentrations of proinflammatory parameters after laparoscopy. These differences were present in all parameters evaluated and seen consistently during the early postoperative period up to POD1, possibly indicating that different attenuation of immunity is most prominent in the immediate postoperative period. When narratively summarizing all given evidence, a less pronounced proinflammatory reaction is still seen: after LS, significantly lower markers of inflammation were reported by the majority of studies (13 studies finding significant differences favouring LS and six not reporting differences between surgical approaches), whereas only Stage et al. [46] stated results favouring the open approach.

Clinical trials have repeatedly shown superior short-term outcomes after laparoscopy, with fewer anastomotic leaks and infections, leading to shorter hospital stay, faster recovery and reduced perioperative morbidity and mortality [60, 61]. Elevated CRP and IL-6 indicate postsurgical infection [62, 63], while CRP concentration correlates with the incidence of anastomotic leakage [64]. In the present analysis, both parameters were significantly reduced in patients receiving laparoscopy, therefore supporting the hypothesis that a milder activation of proinflammatory processes may be the reason for the beneficial short-term outcomes seen after LS.

Besides these immediate benefits, laparoscopy has not just repeatedly been proven to be noninferior regarding oncological long-term outcomes, but recent trials even indicate superiority of LS over OS in terms of long-term survival and metastasis formation [65–68]. Although this review was limited to a timeframe of up to 8 days after surgery, the most vulnerable phase determining long-term oncological outcomes is indeed directly during and after surgery [13]. Surgical trauma triggers healing responses promoting tumour cell migration, spread and angiogenesis. Moreover, manipulation of cancerous tissue is known to cause tumour cell seeding [13, 69]. Therefore, it is very important to limit excessive postoperative concentrations of inflammatory mediators: TNFα, IL-8 and VEGF are key contributors to tumorigenesis, promoting a proinflammatory state aiding tumour growth as well as cell migration and neoangiogenesis [69–71]. Interleukins generally play a crucial role in CRC [72]: IL-6 facilitates angiogenesis, migration and proliferation [73, 74]; high serum IL-8 contributes to growth and progression of CRC [75] and is even associated with resistance to chemotherapy, an important pillar of CRC treatment besides surgery [76–78]. The current results indicate lower systemic concentrations of these parameters after LS, providing a possible explanation for the reported beneficial oncological outcomes.

Strengths and limitations

This review included data of 1131 participants from 20 RCTs on the humoral immunological impact of CRC surgery, thus representing the most comprehensive data synthesis to date. Particularly because only RCTs were included, the confidence in the estimates of effect could mostly be rated as moderate or even high. Another strength of this review lies in the rigorous search strategy applied, which reduces the risk of post-publication bias and enables a thorough overview of the topic. In contrast to previous meta-analyses, more differentiated timeframes were used for outcome grouping, while still reaching an optimal information size for several analyses.

It is important to note that mean values of CRP (3–9 h, POD1), IL-8 (POD1) and TNFα (3–9 h) showed significant differences, but these differences were not very pronounced. Although there is no common cut-off value to indicate the smallest effect size of interest and lower concentrations are generally favourable, the clinical relevance of such observed differences is unclear.

This review faces limitations resulting from included studies. Several studies had only small sample sizes. Humoral parameters as well as the sampling timepoints chosen showed high heterogeneity, rendering synthesis of results a challenging task. This resulted in some meta-analyses not reaching the optimal information size or an inability to perform meta-analysis for parameters originally planned. Study quality was satisfactory overall, although two studies [40, 44] show hints of reporting bias, which might impact on this reviews' results for CRP and IL-6. Due to the scarcity of prospective protocols corresponding to included studies, assessment of risk of bias due to selection of the reported results was limited and judgements were made based on the consistency of reporting between the methods and results sections [79].

Sensitivity analyses restricted to nonestimated data mostly yielded robust results, without changes in the level or direction of effects. However, for CRP at 0–2 h, the level of significance changed from nonsignificance to significantly lower CRP after LS (MD − 1.0 mg/dl [− 1.14, − 0.86], $p < 0.00001$). Testing for the overall effect for IL-8 at POD1 under conditions of this sensitivity analysis changed the result, leading to nonsignificance (MD − 5.73 pg/ml [− 21.3; 9.84], $p = 0.47$). Other results were not influenced.

Further high-quality studies with higher power focusing on clinically established parameters and sampling timepoints as well as provision of prospective study protocols would be desirable for future research. Also, as none of the included studies assessed the impact of robotic techniques on postoperative immunocompetence, it is the task of future research to shed further light on this topic of increasing interest.

Concluding remarks

Altogether, a less pronounced proinflammatory reaction mediated by soluble effector molecules was seen after laparoscopic surgery compared to open surgery in this meta-analysis and systematic review. Therefore, summarized evidence of this review supports the view of a lower induction of inflammation by laparoscopic surgery, probably providing an explanatory model for the observed clinically superior short- and long-term outcomes after laparoscopic surgery.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00464-023-10582-0.

Acknowledgements The authors thank Prof. Markus Feuerer for providing his immunological expertise.

Funding Open Access funding enabled and organized by Projekt DEAL. The authors have no funding to disclose.

Data availability Data supporting this article are available from a public repository ([21, 22]).

Declarations

Disclosures Annika Bohne, Elena Grundler, Helge Knüttel, Vinzenz Völkel and Alois Fürst have no conflicts of interest or financial ties to disclose.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

References

1. Morgan E, Arnold M, Gini A, Lorenzoni V, Cabasag CJ, Laversanne M, Vignat J, Ferlay J, Murphy N, Bray F (2023) Global burden of colorectal cancer in 2020 and 2040: incidence and mortality estimates from GLOBOCAN. Gut 72:338–344. https://doi.org/10.1136/gutjnl-2022-327736
2. Li YS, Meng FC, Lin JK (2020) Procedural and post-operative complications associated with laparoscopic versus open abdominal surgery for right-sided colonic cancer resection: a systematic review and meta-analysis. Medicine 99:e22431. https://doi.org/10.1097/MD.0000000000022431
3. Kulkarni N, Arulampalam T (2020) Laparoscopic surgery reduces the incidence of surgical site infections compared to the open approach for colorectal procedures: a meta-analysis. Tech Coloproctol 24:1017–1024. https://doi.org/10.1007/s10151-020-02293-8
4. Jayne DG, Thorpe HC, Copeland J, Quirke P, Brown JM, Guillou PJ (2010) Five-year follow-up of the Medical Research Council CLASICC trial of laparoscopically assisted versus open surgery for colorectal cancer. Br J Surg 97:1638–1645. https://doi.org/10.1002/bjs.7160
5. Creavin B, Kelly ME, Ryan ÉJ, Ryan OK, Winter DC (2021) Oncological outcomes of laparoscopic versus open rectal cancer resections: meta-analysis of randomized clinical trials. Br J Surg 108:469–476. https://doi.org/10.1093/bjs/znaa154
6. Kastner C, Reibetanz J, Germer C-T, Wiegering A (2021) Evidenz in der minimal-invasiven onkologischen Chirurgie des Kolons und des Rektums (Evidence in minimally invasive oncological surgery of the colon and rectum). Chirurg 92:334–343. https://doi.org/10.1007/s00104-020-01320-6
7. Schreiber RD, Old LJ, Smyth MJ (2011) Cancer immunoediting: integrating immunity's roles in cancer suppression and promotion. Science 331:1565–1570. https://doi.org/10.1126/science.1203486
8. Dąbrowska AM, Słotwiński R (2014) The immune response to surgery and infection. Cent Eur J Immunol 39:532–537. https://doi.org/10.5114/ceji.2014.47741
9. Bain CR, Myles PS, Corcoran T, Dieleman JM (2023) Postoperative systemic inflammatory dysregulation and corticosteroids: a narrative review. Anaesthesia 78:356–370. https://doi.org/10.1111/anae.15896
10. Margraf A, Ludwig N, Zarbock A, Rossaint J (2020) Systemic inflammatory response syndrome after surgery: mechanisms and protection. Anesth Analg 131:1693–1707. https://doi.org/10.1213/ANE.0000000000005175
11. Shibutani M, Nakao S, Maeda K, Nagahara H, Fukuoka T, Iseki Y, Hirakawa K, Ohira M (2020) Inflammation caused by surgical stress has a negative impact on the long-term survival outcomes in patients with colorectal cancer. Anticancer Res 40:3535–3542
12. Roxburgh CS, Horgan PG, McMillan DC (2013) The perioperative immune/inflammatory insult in cancer surgery: time for intervention? Oncoimmunology 2:e27324. https://doi.org/10.4161/onci.27324
13. Chen Z, Zhang P, Xu Y, Yan J, Liu Z, Lau WB, Lau B, Li Y, Zhao X, Wei Y, Zhou S (2019) Surgical stress and cancer progression: the twisted tango. Mol Cancer 18:132. https://doi.org/10.1186/s12943-019-1058-3
14. Karanika S, Karantanos T, Theodoropoulos GE (2013) Immune response after laparoscopic colectomy for cancer: a review. Gastroenterol Rep (Oxf) 1:85–94. https://doi.org/10.1093/gastro/got014
15. Sammour T, Kahokehr A, Chan S, Booth RJ, Hill AG (2010) The humoral response after laparoscopic versus open colorectal surgery: a meta-analysis. J Surg Res 164:28–37. https://doi.org/10.1016/j.jss.2010.05.046
16. Liu C, Liu J, Zhang S (2011) Laparoscopic versus conventional open surgery for immune function in patients with colorectal cancer. Int J Colorectal Dis 26:1375–1385. https://doi.org/10.1007/s00384-011-1281-x
17. Bohne A, Grundler E, Knüttel H, Fürst A, Völkel V (2023) Influence of laparoscopic surgery on cellular immunity in colorectal cancer: a systematic review and meta-analysis. Cancers (Basel) 15:3381. https://doi.org/10.3390/cancers15133381
18. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, Moher D (2021) The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Int J Surg 88:105906
19. Fürst A, Völkel V, Bohne A, Grundler E, Knüttel H (2021) Draft search strategy for: influence of laparoscopic versus open surgical resections on the immune system in patients with colorectal cancer: protocol for a systematic review and meta-analysis. https://epub.uni-regensburg.de/50914/

20. Rethlefsen ML, Kirtley S, Waffenschmidt S, Ayala AP, Moher D, Page MJ, Koffel JB (2021) PRISMA-S: an extension to the PRISMA statement for reporting literature searches in systematic reviews. Syst Rev 10:39. https://doi.org/10.1186/s13643-020-01542-z
21. Bohne A, Grundler E, Knüttel H, Fürst A, Völkel V (2023) Data archive (search documentation) of: impact of laparoscopic versus open surgery on immunity in patients with colorectal cancer: a systematic review and meta-analysis. https://doi.org/10.5283/epub.54402
22. Bohne A, Grundler E, Knüttel H, Fürst A, Völkel V (2023) Data archive of: impact of laparoscopic versus open surgery on humoral immunity in patients with colorectal cancer: a systematic review and meta-analysis. https://doi.org/10.5283/epub.54966
23. Bramer WM, Giustini D, de Jonge GB, Holland L, Bekhuis T (2016) De-duplication of database search results for systematic reviews in EndNote. J Med Libr Assoc 104:240–243. https://doi.org/10.3163/1536-5050.104.3.014
24. Clark J, Glasziou P, Del Mar C, Bannach-Brown A, Stehlik P, Scott AM (2020) A full systematic review was completed in 2 weeks using automation tools: a case study. J Clin Epidemiol 121:81–90. https://doi.org/10.1016/j.jclinepi.2020.01.008
25. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A (2016) Rayyan—a web and mobile app for systematic reviews. Syst Rev 5:1–10
26. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (eds) (2023) Cochrane handbook for systematic reviews of interventions, version 6.4 (updated August 2023). Cochrane. https://training.cochrane.org/handbook
27. Rohatgi A (2022) WebPlotDigitizer. https://automeris.io/WebPlotDigitizer
28. Review Manager (RevMan) (2020) Version 5.4. The cochrane collaboration
29. Wan X, Wang W, Liu J, Tong T (2014) Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol 14:135. https://doi.org/10.1186/1471-2288-14-135
30. Higgins J, Savović J, Page MJ, Sterne JAC on behalf of the RoB2 Development Group (2019) Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) Version of 22 August 2019. https://www.riskofbias.info/welcome/rob-2-0-tool/current-version-of-rob-2. Accessed 14 Dec 2022
31. McMaster University and Evidence Prime (2022) GRADEpro GDT: GRADEpro guideline development tool [software]. https://gdt.gradepro.org/
32. Völkel V, Draeger T, Gerken M, Klinkhammer-Schalke M, Benz S, Fürst A (2020) Laparoscopic surgery for colon cancer. Coloproctology 42:413–420. https://doi.org/10.1007/s00053-020-00481-6
33. Zhao G, Xiao G, Huang M, Long H (2005) Effect of laparoscopic radical operation on systemic immunity in patients with colorectal cancer. Zhonghua Wei Chang Wai Ke Za Zhi 8:407–409
34. Delgado S, Lacy AM, Filella X, Castells A, García-Valdecasas JC, Pique JM, Momblán D, Visa J (2001) Acute phase response in laparoscopy and open colectomy in colon cancer: randomized study. Dis Colon Rectum 44:638–646. https://doi.org/10.1007/BF02234558
35. Duque P, Garutti I, Terradillos E (2019) Modulation of CCL2 expression by laparoscopic versus open surgery for colorectal cancer surgery. Surg Laparosc Endosc Percutan Tech 29(2):101–108
36. Hasegawa H, Kabeshima Y, Watanabe M, Yamamoto S, Kitajima M (2003) Randomized controlled trial of laparoscopic versus open colectomy for advanced colorectal cancer. Surg Endosc 17:636–640. https://doi.org/10.1007/s00464-002-8516-4
37. Hewitt PM, Ip SM, Kwok SP, Somers SS, Li K, Leung KL, Lau WY, Li AK (1998) Laparoscopic-assisted vs. open surgery for colorectal cancer: comparative study of immune effects. Dis Colon Rectum 41:901–909. https://doi.org/10.1007/BF02235376
38. Kim JS, Hur H, Min BS, Lee KY, Chung HC, Kim NK (2011) Inflammatory and tumor stimulating responses after laparoscopic sigmoidectomy. Yonsei Med J 52:635–642. https://doi.org/10.3349/ymj.2011.52.4.635
39. Kvarnström A, Sokolov A, Swartling T, Kurlberg G, Mollnes TE, Bengtsson A (2012) Alternative pathway activation of complement in laparoscopic and open rectal surgery. Scand J Immunol 76:49–53. https://doi.org/10.1111/j.1365-3083.2012.02702.x
40. Kvarnström A, Swartling T, Kurlberg G, Bengtson J-P, Bengtsson A (2013) Pro-inflammatory cytokine release in rectal surgery: comparison between laparoscopic and open surgical techniques. Arch Immunol Ther Exp (Warsz) 61:407–411. https://doi.org/10.1007/s00005-013-0239-9
41. Laforgia R, D´Elia G, Lattarulo S (2016) Cellular and humoral inflammatory response after laparoscopic and conventional colorectal surgery: preliminary report. Ann Ital Chir 87(4):337–342
42. Leung KL, Lai PB, Ho RL, Meng WC, Yiu RY, Lee JF, Lau WY (2000) Systemic cytokine response after laparoscopic-assisted resection of rectosigmoid carcinoma: a prospective randomized trial. Ann Surg 231:506–511. https://doi.org/10.1097/00000658-200004000-00008
43. Ordemann J, Jacobi CA, Schwenk W, Stösslein R, Müller JM (2001) Cellular and humoral inflammatory response after laparoscopic and conventional colorectal resections. Surg Endosc 15:600–608. https://doi.org/10.1007/s004640090032
44. Pascual M, Alonso S, Parés D, Courtier R, Gil MJ, Grande L, Pera M (2011) Randomized clinical trial comparing inflammatory and angiogenic response after open versus laparoscopic curative resection for colonic cancer. Br J Surg 98:50–59. https://doi.org/10.1002/bjs.7258
45. Schwenk W, Jacobi C, Mansmann U, Böhm B, Müller JM (2000) Inflammatory response after laparoscopic and conventional colorectal resections—results of a prospective randomized trial. Langenbecks Arch Surg 385:2–9. https://doi.org/10.1007/s004230050002
46. Stage JG, Schulze S, Møller P, Overgaard H, Andersen M, Rebsdorf-Pedersen VB, Nielsen HJ (1997) Prospective randomized study of laparoscopic versus open colonic resection for adenocarcinoma. Br J Surg 84:391–396
47. Straatman J, Cuesta MA, Tuynman JB, Veenhof AAFA, Bemelman WA, van der Peet DL (2018) C-reactive protein in predicting major postoperative complications are there differences in open and minimally invasive colorectal surgery? Substudy from a randomized clinical trial. Surg Endosc 32:2877–2885. https://doi.org/10.1007/s00464-017-5996-9
48. Tsimogiannis KE, Telis K, Tselepis A, Pappas-Gogos GK, Tsimoyiannis EC, Basdanis G (2011) A-defensin expression of inflammatory response in open and laparoscopic colectomy for colorectal cancer. World J Surg 35:1911–1917. https://doi.org/10.1007/s00268-011-1140-5
49. Tsimogiannis KE, Tellis CC, Tselepis AD, Pappas-Gogos GK, Tsimoyiannis EC, Basdanis G (2012) Toll-like receptors in the inflammatory response during open and laparoscopic colectomy for colorectal cancer. Surg Endosc 26:330–336. https://doi.org/10.1007/s00464-011-1871-2
50. Veenhof AAFA, Sietses C, von Blomberg BME, van Hoogstraten IMW, vd Pas MHGM, Meijerink WJHJ, vd Peet DL, vd Tol MP, Bonjer HJ, Cuesta MA (2011) The surgical stress response and postoperative immune function after laparoscopic or conventional total mesorectal excision in rectal cancer: a randomized trial. Int J Colorectal Dis 26:53–59. https://doi.org/10.1007/s00384-010-1056-9
51. Veenhof AAFA, Vlug MS, van der Pas MHGM, Sietses C, van der Peet DL, de Lange-de Klerk ESM, Bonjer HJ, Bemelman

WA, Cuesta MA (2012) Surgical stress response and postoperative immune function after laparoscopy or open surgery with fast track or standard perioperative care: a randomized trial. Ann Surg 255:216–221. https://doi.org/10.1097/SLA.0b013e31824336e2
52. Vignali A, Di Palo S, Orsenigo E, Ghirardelli L, Radaelli G, Staudacher C (2009) Effect of prednisolone on local and systemic response in laparoscopic vs. open colon surgery: a randomized, double-blind, placebo-controlled trial. Dis Colon Rectum 52:1080–1088. https://doi.org/10.1007/DCR.0b013e31819ef69d
53. Wang G, Jiang Z, Zhao K, Li G, Liu F, Pan H, Li J (2012) Immunologic response after laparoscopic colon cancer operation within an enhanced recovery program. J Gastrointest Surg 16:1379–1388. https://doi.org/10.1007/s11605-012-1880-z
54. Wu FPK, Hoekman K, Sietses C, von Blomberg BME, Meijer S, Bonjer HJ, Cuesta MA (2004) Systemic and peritoneal angiogenic response after laparoscopic or conventional colon resection in cancer patients: a prospective, randomized trial. Dis Colon Rectum 47:1670–1674. https://doi.org/10.1007/s10350-004-0660-6
55. Wu FPK, Sietses C, von Blomberg BME, van Leeuwen PAM, Meijer S, Cuesta MA (2003) Systemic and peritoneal inflammatory response after laparoscopic or conventional colon resection in cancer patients: a prospective, randomized trial. Dis Colon Rectum 46:147–155. https://doi.org/10.1007/s10350-004-6516-2
56. Zhu P, Miao W, Gu F, Xing C (2017) Changes of serum and peritoneal inflammatory mediators in laparoscopic radical resection for right colon carcinoma. J Minim Access Surg. https://doi.org/10.4103/jmas.JMAS_217_17
57. Watt DG, Horgan PG, McMillan DC (2015) Routine clinical markers of the magnitude of the systemic inflammatory response after elective operation: a systematic review. Surgery 157:362–380. https://doi.org/10.1016/j.surg.2014.09.009
58. Hsu T-C, Lin C-H, Sun F-J, Chen M-J (2017) Postoperative serum levels of interleukin-6 are affected by age in patients with colorectal cancer. Int J Gerontol 11:75–79. https://doi.org/10.1016/j.ijge.2016.06.004
59. Jawa RS, Anillo S, Huntoon K, Baumann H, Kulaylat M (2011) Interleukin-6 in surgery, trauma, and critical care part II: clinical implications. J Intensive Care Med 26:73–87. https://doi.org/10.1177/0885066610384188
60. van der Pas M, Hgm HE, Cuesta MA, Fürst A, Lacy AM, Hop WC, Bonjer HJ (2013) Laparoscopic versus open surgery for rectal cancer (COLOR II): short-term outcomes of a randomised, phase 3 trial. Lancet Oncol 14:210–218. https://doi.org/10.1016/S1470-2045(13)70016-0
61. Zhang Y, Liu C, Nistala KRY, Chong CS (2022) Open versus laparoscopic Hartmann's procedure: a systematic review and meta-analysis. Int J Colorectal Dis 37:2421–2430. https://doi.org/10.1007/s00384-022-04285-6
62. Wierdak M, Pisarska M, Kuśnierz-Cabala B, Kisielewski M, Major P, Witowski JS, Ceranowicz P, Strzałka M, Budzyński A, Pędziwiatr M (2018) Use of inflammatory markers in the early detection of infectious complications after laparoscopic colorectal cancer surgery with the ERAS protocol. Wideochir Inne Tech Maloinwazyjne 13:315–325. https://doi.org/10.5114/wiitm.2018.75846
63. Wysocki M, Małczak P, Wierdak M, Walędziak M, Hady HR, Diemieszczyk I, Proczko-Stepaniak M, Szymański M, Dowgiałło-Wnukiewicz N, Szeliga J, Pędziwiatr M, Major P (2020) Utility of inflammatory markers in detection of perioperative morbidity after laparoscopic sleeve gastrectomy, laparoscopic Roux-en-Y gastric bypass, and one-anastomosis gastric bypass-multicenter study. Obes Surg 30:2971–2979. https://doi.org/10.1007/s11695-020-04636-8
64. Straatman J, Harmsen AMK, Cuesta MA, Berkhof J, Jansma EP, van der Peet DL (2015) Predictive value of C-reactive protein for major complications after major abdominal surgery: a systematic review and pooled-analysis. PLoS ONE 10:e0132995. https://doi.org/10.1371/journal.pone.0132995
65. Dehlaghi Jadid K, Cao Y, Petersson J, Angenete E, Matthiessen P (2022) Long term oncological outcomes for laparoscopic versus open surgery for rectal cancer—a population-based nationwide noninferiority study. Colorectal Dis 24:1308–1317. https://doi.org/10.1111/codi.16204
66. Schnitzbauer V, Gerken M, Benz S, Völkel V, Draeger T, Fürst A, Klinkhammer-Schalke M (2020) Laparoscopic and open surgery in rectal cancer patients in Germany: short and long-term results of a large 10-year population-based cohort. Surg Endosc 34:1132–1141. https://doi.org/10.1007/s00464-019-06861-4
67. Petersson J, Matthiessen P, Jadid KD, Bock D, Angenete E (2023) Short term results in a population based study indicate advantage for laparoscopic colon cancer surgery versus open. Sci Rep 13:4335. https://doi.org/10.1038/s41598-023-30448-8
68. Goto K, Watanabe J, Suwa Y, Nakagawa K, Suwa H, Ozawa M, Ishibe A, Ota M, Kunisaki C, Endo I (2021) A multicenter, propensity score-matched cohort study about short-term and long-term outcomes after laparoscopic versus open surgery for locally advanced rectal cancer. Int J Colorectal Dis 36:1287–1295. https://doi.org/10.1007/s00384-021-03871-4
69. Alieva M, van Rheenen J, Broekman MLD (2018) Potential impact of invasive surgical procedures on primary tumor growth and metastasis. Clin Exp Metastasis 35:319–331. https://doi.org/10.1007/s10585-018-9896-8
70. Svendsen MN, Werther K, Nielsen HJ, Kristjansen PEG (2002) VEGF and tumour angiogenesis. Impact of surgery, wound healing, inflammation and blood transfusion. Scand J Gastroenterol 37:373–379. https://doi.org/10.1080/003655202317315971
71. Muthusami S (2021) Role of inflammation in the development of colorectal cancer. Endocr Metab Immune Disord Drug Targets 21:77–90. https://doi.org/10.2174/22123873MTA5sODAnx
72. Li J, Huang L, Zhao H, Yan Y, Lu J (2020) The role of interleukins in colorectal cancer. Int J Biol Sci 16:2323–2339. https://doi.org/10.7150/ijbs.46651
73. Hu F, Song Da, Yan Y, Huang C, Shen C, Lan J, Chen Y, Liu A, Wu Q, Sun L, Xu F, Hu F, Chen L, Luo X, Feng Y, Huang S, Hu J, Wang G (2021) IL-6 regulates autophagy and chemotherapy resistance by promoting BECN1 phosphorylation. Nat Commun 12:3651. https://doi.org/10.1038/s41467-021-23923-1
74. Jones SA, Jenkins BJ (2018) Recent insights into targeting the IL-6 cytokine family in inflammatory diseases and cancer. Nat Rev Immunol 18:773–789. https://doi.org/10.1038/s41577-018-0066-7
75. Bazzichetto C, Milella M, Zampiva I, Simionato F, Amoreo CA, Buglioni S, Pacelli C, Le Pera L, Colombo T, Bria E, Zeuli M, Del Bufalo D, Sperduti I, Conciatori F (2022) Interleukin-8 in colorectal cancer: a systematic review and meta-analysis of its potential role as a prognostic biomarker. Biomedicines. https://doi.org/10.3390/biomedicines10102631
76. Shen T, Yang Z, Cheng X, Xiao Y, Yu K, Cai X, Xia C, Li Y (2017) CXCL8 induces epithelial-mesenchymal transition in colon cancer cells via the PI3K/Akt/NF-κB signaling pathway. Oncol Rep 37:2095–2100. https://doi.org/10.3892/or.2017.5453
77. Dabkeviciene D, Jonusiene V, Zitkute V, Zalyte E, Grigaitis P, Kirveliene V, Sasnauskiene A (2015) The role of interleukin-8 (CXCL8) and CXCR2 in acquired chemoresistance of human colorectal carcinoma cells HCT116. Med Oncol 32:258. https://doi.org/10.1007/s12032-015-0703-y
78. Du J, He Y, Li P, Wu W, Chen Y, Ruan H (2018) IL-8 regulates the doxorubicin resistance of colorectal cancer cells via modulation of multidrug resistance 1 (MDR1). Cancer Chemother Pharmacol 81:1111–1119. https://doi.org/10.1007/s00280-018-3584-x
79. Higgins JPT, Savović J, Page MJ, Elbers RG, Sterne JAC (2021) Chapter 8: assessing risk of bias in a randomized trial. In: Higgins

JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (eds) Cochrane handbook for systematic reviews of interventions, version 6.4 (updated February 2023) Cochrane. https://www.training.cochrane.org/handbook

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.