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# Evaluation of surgical stress after colorectal interventions: a multicenter randomized clinical trial of robotic versus laparoscopic surgery

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**A major factor in the development of morbidity after surgery is the surgical stress response. The aim of this interventional multicenter randomized open label, parallel group trial is to evaluate the possible lower inflammatory stress response induced by robot-assisted versus laparoscopic surgery for colorectal resections. A total of 593 patients diagnosed with colorectal cancer planned for elective, curative surgery was screened for eligibility. 314 patients planned for right colectomy, left colectomy or rectal resection were randomly assigned 1:1 to robotic ($n=161$) or laparoscopic group ($n=153$). The primary endpoint was the 24-hours postoperative Δ% change of IL-6 serum levels. Subgroup analyses included the assessment of IL-6 Δ% changes stratified according to age, obesity, comorbidities, tumor staging and resection type have been also performed. In conclusion robotic surgery was associated to a lower surgical stress after colorectal surgery and this finding may help in decision-making regarding when to proceed to robotic approach for colorectal cancer, especially in selected high risk clinical settings.**

**Keywords** Surgical stress, Mininvasive surgery, Robotic surgery, Laparoscopic surgery, Colorectal surgery, Colorectal cancer

A major factor in the development of morbidity after surgery is the surgical stress response. Few is known about the potential advantages of robotic approach. The aim of this interventional multicenter randomized open label, parallel group trial is to evaluate the possible lower inflammatory stress response induced by robot-assisted versus laparoscopic surgery for colorectal resections.

Benefits of minimally invasive surgery for treatment of colorectal cancer have been proved. The underlying reason for these short-term advantages of laparoscopy may be related to a decreased systemic inflammatory response[1–7].

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The acute-phase response consists of a series of hormonal, metabolic and immunologic changes in response to surgery, trauma or sepsis[8].The major mediators of the acute-phase response in humans are TNF-α, IL-1β, and IL-6. The levels of the cytokines during colorectal surgery and in the early post-operative period have been found to be related to the magnitude of surgery and the presence of complications[9–12]. Therefore, they have been used as surrogate biochemical markers of surgical tissue trauma[13–15].

In this setting, little is known about the impact of robotic surgery on systemic inflammatory response.

The rationale to hypothesize lower surgical stress in robotic over laparoscopic surgery lays in the theoretical advantages in terms of surgical technique.

The aim of ESSIMIC (Evaluation of Surgical Stress and Immune response after Minimally Invasive Colorectal surgery) randomized clinical trial (Clinicaltrial.gov identifier NCT02871960) was to provide evidence of a lower inflammatory stress response induced by robot-assisted versus laparoscopic surgery for colorectal resection.

## Materials and methods

A total of 593 patients diagnosed with colorectal cancer planned for elective, curative surgery was screened for eligibility. 314 patients planned for right colectomy, left colectomy or rectal resection were randomly assigned 1:1 to robotic ($n = 161$) or laparoscopic group ($n = 153$).

Main outcome measures: The primary endpoint was the 24-hours postoperative Δ% change of IL-6 serum levels. Subgroup analyses included the assessment of IL-6 Δ% changes stratified according to age, obesity, comorbidities, tumor staging and resection type have been also performed.

### Study design

This is an interventional multicenter randomized open label, parallel group trial designed to compare stress-related outcomes of patients who underwent laparoscopic versus robotic surgery for colorectal cancer.

All participating surgeons, from 7 Italian centers, had to provide evidence of at least 100 colorectal cancer surgeries before taking part into the trial, at least 30 of which had to be robotic and at least 30 had to be conventional laparoscopic procedures. An independent central evaluation of surgical technique and operative skills have been also performed. This has been guaranteed by video review of at least 1 anonymous unedited surgical intervention for each surgical procedure included in the study from randomly selected laparoscopic and robotic cases (Global Operative Assessment of laparoscopic skills GOALS)[16].

The experimental protocol was approved by "Federico II" University of Naples Ethics Committee. The clinical trial registration number is 108/16/ES01 and the date of first registration is 27/11/2016. The reference number is 1901/16.

All methods were performed in accordance with the ethical guidelines of the 1975 Declaration of Helsinki. Informed consent was obtained from all enrolled patients.

### Participants

All consecutive patients from January 2017 to December 2019 with a diagnosis of primary cancer of colon or rectum planned for elective colorectal cancer surgery were screened for inclusion. Among this interval of time, each center enrolled their patients within a 6 months period.

Inclusion criteria were diagnosis of primary cancer of colon or rectum planned for elective colorectal cancer surgery, age > 18 years and written informed consent provided.

Exclusion criteria were locally advanced cancers not amenable to curative surgery or requiring en-bloc multivisceral resection, severe systemic disease that contraindicated minimally invasive surgery and valid informed consent denied. Conversion to open surgery, intraoperative complications and post-operative complications within 30 days from surgical intervention, classified as ≥I at Clavien-Dindo Classification[17], were also considered exclusion criteria. Atypical resections (splenic flexure resection or mid transverse colon resection) and abdominoperineal resections have been excluded in order to have homogeneous surgical procedures groups (right colon, left colon and rectal resection).

### Randomization

Enrolled patients have been randomly allocated on a 1:1 ratio to undergo robotic (experimental arm) or laparoscopic (control arm) surgical approach. Randomization, performed using a computer-based randomization system, has been balanced for gender, age, body mass index, Charlson Comorbidity Index (CCI), type of resection and tumor staging.

### Procedures

All surgical interventions have been standardized. An absolute requirement was that the procedures had to be totally minimally invasive and under robotic surgery the robot had to be used for all surgical steps.

Right colectomy. The terminal ileum and the ascending colon were dissected through the embryological avascular plane between the mesocolon and Gerota's fascia preserving the retroperitoneal essential structures. The dissection continued along the duodenum and head of the pancreas performing a central vascular ligation transecting the colic vessels at the root of the superior mesenteric vein (SMV) and superior mesenteric artery (SMA) and then the dissection continued to the right colic vessels, the gastrocolic trunk of Henle and the middle colic vessels. Colon was transected with a resection margin of at least 5 cm. Intracorporeal linear stapled side-to-side anastomosis was performed. Specimen was extracted through a 5–7 cm Pfannenstiel incision.

Left colectomy. Mobilization of the left colon was conducted dissecting the embryological avascular plane. Central vascular ligation (CVL) was performed ligating the inferior mesenteric artery (IMA) at its root. The inferior mesenteric vein (IMV) was ligated at the lower border of the pancreas. Splenic flexure mobilization was performed dissecting the root of the transverse mesocolon from the lower border of the pancreas entering the

lesser sac. The posterior attachments of the distal transverse colon and the descending colon were divided. The left lateral paracolic attachments, splenocolic ligament and phrenocolic ligament were lysed. The splenic flexure was fully mobilized with the separation of the omentum from the colon. The distal division of the colon was performed intracorporeally with a resection margin of at least 5 cm using a linear stapler. A 5–7 cm Pfannenstiel incision was carried out to perform the proximal section extracorporeally after dividing the mesocolon up to the chosen site. Anastomosis has been performed with a standard Knight-Griffen technique.

Anterior rectal resection. Total Mesorectal Excision has been added to the steps of left colectomy. Posterior mesorectal plane was identified at the level of the promontory and the initial "holy plane" was dissected. TME was conducted laterally, preserving nerves and the left ureter, up to the peritoneal reflection and down to the pelvic floor where the mesorectal fat usually ends. After the identification of the distal extent of resection, rectal wall was dissected circumferentially and the distal division of the colon was performed.

## Outcomes

The primary endpoint was the difference between baseline and 24-hours postoperative serum levels of IL-6 evaluated as Δ% changes. Δ% changes in serum levels of other inflammatory mediators (IL-1β, IL-10, IL-13, TNFα) 24 and 72 h after laparoscopic and robotic procedures were also analyzed as secondary outcomes.

Δ% changes of serum IL-6 levels have been evaluated to better define the impact of surgical procedure on inflammatory response after surgery[8,12,13,18–21,21–23].

Δ% changes of serum IL-6 levels at 24 h has been selected as primary outcome being it the most used cytokine in current literature to define inflammatory response to surgical trauma[9,12–14] and being the maximum cytokines' increase within the first 24 h after surgery[19,21].

Prespecified subgroup analyses included the assessment of IL-6 Δ% changes stratified according to age, obesity, comorbidities, tumor staging and resection type.

Elderly patients have been defined as age ≥ 65 years, obesity has been considered for BMI ≥ 30 ($Kg/m^2$), comorbidities have been evaluated by Charlson Comorbidity Index identifying three groups on the basis of low (2 to 5 points), middle (6 to 10 points) or high severity (11 to 14 points), tumor staging has been stratified according to AJCC 8th edition criteria[24] identifying two groups (0 to II stage and III-IV stage) and resection type has been divided into right colectomy, left colectomy and rectal resection with Total Mesorectal Excision (TME).

To design a study with a ≥ 50% difference in IL-6 serum levels between robotic and laparoscopic surgery, a sample of 142 patients was necessary to obtain a power of 80% and a level of significance of 5%. To account for possible dropouts or technical failures, we planned to enroll ≈ 150 subjects per study arm.

## Sample processing and cytokines assay

The systemic inflammatory response, evaluated in terms of altered secretion of pro- (IL-1β, IL-6, TNFα) and anti-inflammatory (IL-10 and IL-13) mediators, was investigated before surgery (T0), 24 h and 72 h postoperatively (T24 and T72).

Blood samples in serum separator tubes from each subject enrolled in the study pre- (T0) and post-operative (T24 and T72) were centrifuged and stored at – 80 °C. Serum samples were then screened for the determination of Interleukins IL-1β, IL-6, IL-10, IL- 13, and Tumor Necrosis Factor-α (TNF-α), using the Bio-Plex Pro Human Cytokine Screening Panel (Bio-Rad, Hercules, CA, USA) according to the manufacturer's protocol. Briefly, serum samples were centrifuged at 1000 g for 15 min and 25 µl were diluted 1:4 with sample diluent. Standards and control samples were reconstituted by adding 250 µl of standard diluent to each tube, vortexed for 5 s, and incubated on ice for 30 min. The 10x beads were prepared by a 1x dilution, vortexed for 30 s and 50 µl of 1x beads were added to each well of the assay plate. The plate containing the beads was washed two times on a magnetic plate with 100 µl of wash buffer. 50 µl of standards, blank, controls, and samples were added to each well of the plate and then incubated on a shaker at 850 rpm for 30 min at room temperature. The plate was washed three times on a magnetic plate with 100 µl of wash buffer. The 10x Detection antibodies for IL-1β, IL-6, IL-10, IL-13, and TNFα were prepared by 1x dilution with antibody diluent and 25 µl of antibodies mix was added to each well. Then, the plate was incubated on a shaker at 850 rpm for 30 min at room temperature. The plate was washed three times on a magnetic plate with 100 µl of wash buffer and then 100x Streptavidin- Phycoerythrin (SA-PE) was prepared by 1x dilution in assay buffer. 50 µl of SA-PE were added to each well and the plate was incubated on a shaker at 850 rpm for 10 min at room temperature. The plate was washed three times on a magnetic plate with 100 µl of wash buffer and beads were resuspended in 125 µl of assay buffer. Finally, the plate was incubated on a shaker at 850 for 30 s, and samples were acquired by using the Bio-Plex Luminex System.

## Statistical analysis

Analysis has been performed on an intention-to-treat basis. All results are presented as two-tailed values with statistical significance defined as p-values < 0.05. Statistical analysis was performed using SPSS 28 (SPSS Inc., Chicago, IL, USA).

Continuous variables were presented as mean ± standard deviation (SD) and compared using Student's t-test or the Mann–Whitney *U* test. Nominal variables were described using counts and percentages and compared using χ2 test or Fisher's exact test, when appropriate. Normality of data was tested using the Shapiro-Wilk test, homogeneity of variances was tested using the Levene test.

Logistic regression with a step wise approach has been performed to adjust the results for gender, age, obesity, Charlson Comorbidity Index, tumor stage and surgical resection. Subgroup analyses have been also performed to investigate the effect of robotic and laparoscopic surgery on specific targeted patients and tumors.

As to study sample size, based on personal exploratory results suggesting a ≥ 50% difference in IL-6 serum levels between robotic and laparoscopic surgery, 142 patients need to be enrolled in each treatment arm to

obtain a power of 80% and a level of significance of 5%. To account for possible dropouts or technical failures, we planned to enroll ≈ 150 subjects per study arm.

## Results

A total of 593 patients with a diagnosis of primary cancer of colon or rectum planned for elective colorectal cancer surgery were assessed for eligibility from January 2017 to December 2019. After excluding 11 patients who did not give the consent to be enrolled in the clinical trial and 62 patients who did not fulfil the inclusion criteria, 520 patients were randomized: 260 to laparoscopic surgery and 260 to robotic surgery. Additionally, 47 patients were excluded because of atypical resection or abdominoperineal resection.

Among the 473 patients who underwent right colectomy, left colectomy or rectal resection with TME, 31 have been excluded for intra-post-operative complications or conversion to open surgery and 128 have been excluded for post operative complications.

Of the 314 included in the final analysis (Fig. 1), 153 received conventional laparoscopic surgery and 161 robotic assisted surgery. The treatment groups were well balanced with respect to clinical and demographic characteristics and operative procedures (Table 1).

About operative time, no statistically significant results were found with 190.26 ± 58.20 in the robotic group and 199.79 ± 59.97 in the laparoscopic group ($p = 0.603$). About blood loss, no intraoperative transfusion was required because blood loss was minimal.

### Surgical stress

All baseline serum levels of cytokines were comparable in the two surgical arms. In details IL-1β levels were 2,61 ± 2,27 and 2,61 ± 1,73 ($p = 0,683$), IL-6 levels were 12,32 ± 12,85 and 13,48 ± 23,76 ($p = 0,828$), TNF-α levels were 69,66 ± 30,14 and 68,63 ± 49,01 ($p = 0,092$), IL-10 levels were 14,91 ± 5,99 and 13,47 ± 7,02 ($p = 0,066$), IL-13 levels were 6,23 ± 7,03 and 6,24 ± 5,00 ($p = 0,114$) respectively in the robotic and laparoscopic arm (Table 2).

At 24-hours post-operative assessment, Δ% change in IL-6 serum levels was lower for the robotic arm as compared to laparoscopic arm (478,41 ± 739,25 vs. 730,24 ± 1096,42; $p = 0,003$). This result has been confirmed by the multivariate analysis in which the surgical technique was an independent predictor of post-operative Δ% change in IL-6 serum levels ($\beta = 0.131$, $p = 0.021$). Of interest, obesity has been identified as a further independent predictor of surgical stress ($\beta = 0.130$. $p = 0,020$). Similarly, 72-hours Δ% change of IL-6 serum level was lower in the robotic arm (136,82 ± 174,5 vs. 276,25 ± 573,50; $p = 0,032$) (Fig. 2) (Table 2).

Δ% changes of IL-1β, TNF-α, IL-10 and IL-13 serum levels were also analyzed at 24 and 72 h after surgery. Δ% change of IL-10 serum levels at 24 h was lower in the robotic arm (24,19 ± 36,28 in robotic arm vs. 49,0 ± 68,27 in laparoscopic arm; $p = 0,006$), Δ% of serum levels of TNF-α at 24 h was similarly lower in the robotic arm (15,57 ± 49,44 vs. 47,58 ± 124,50 in robotic and laparoscopic arm respectively; $p = 0,024$), Δ% of IL-10 serum levels at 72 h was lower as well in the robotic arm (10,60 ± 28,47 in robotic arm vs. 37,23 ± 94,93 in laparoscopic arm; $p = 0,041$) and Δ% of TNF-α serum levels at 72 h was also lower in the robotic arm (11,81 ± 59,31 vs. 29,85 ± 84,88 in robotic and laparoscopic arm respectively. $p = 0,019$), as shown in Fig. 3 (Table 2).

### Subgroup analyses

Regarding the subgroup analyses performed on elderly/non elderly patients, obese/non obese patients, on low/moderate/severe CCI, on AJCC stages and on type of surgical resection (right/left/rectal resection), robotic surgery was associated with significantly lower Δ% changes of IL6 in obese patients and in subjects undergoing rectal resection (Fig. 4).

In the subgroup of sixty-eight obese patients (21,7%) robotic surgery has been performed in 39 cases (57,3%) obtaining a Δ% of IL6 serum levels at 24 h of 472,48 ± 318,36 as compared to 1455,04 ± 1860,69 in those undergoing laparoscopic surgery ($p = 0,004$).

In the subgroup of ninety-three rectal resections (29,6%) robotic surgery has been performed in 52 cases (55,9%) with a Δ% of IL6 serum levels at 24 h of 475,14 ± 383,62 as compared to 846,25 ± 911,66 in those undergoing laparoscopic surgery ($p = 0,002$). About preoperative treatment in rectal cancer cases no statistically significant results were found with 17 patients in the robotic group and 16 patients in the laparoscopic group who underwent a preoperative treatment ($p = 0.663$).

Of interest both in the subgroup of obese patients and in the subgroup of rectal resection baseline characteristics were well balanced between robotic and laparoscopic surgical arm (eTable 1 and eTable 2).

## Discussion

Robotic Surgery is able to provide a better response to surgical stress if compared to laparoscopic surgery, as reflected by the Δ% of IL6 serum levels that was lowest in the robotic colorectal procedures (Δ% > 50%; $p = 0,003$).

A randomized clinical trial has been ad hoc designed to explore whether robotic has advantages over laparoscopic surgery in reducing surgical stress response after surgery which causes alterations in the host immune function with activation of the complement cascade and releasing of pro- and anti-inflammatory interleukins[12,22,23].

TNF-α, IL-1β and IL-6 have been found to correlate with the magnitude of the surgery and the presence of complications. Thus, they have been recognized as sensitive markers of tissue damage after surgery[8,13]..

Laparoscopic surgery is associated with lower levels of IL-6, IL-1β and other proinflammatory cytokines if compared to open surgery[19,20,25,28,28,29].

Conversely, up to date, no one have questioned about the potential role of robotic surgery in obtaining a further reduction of surgical stress response over laparoscopic surgery.

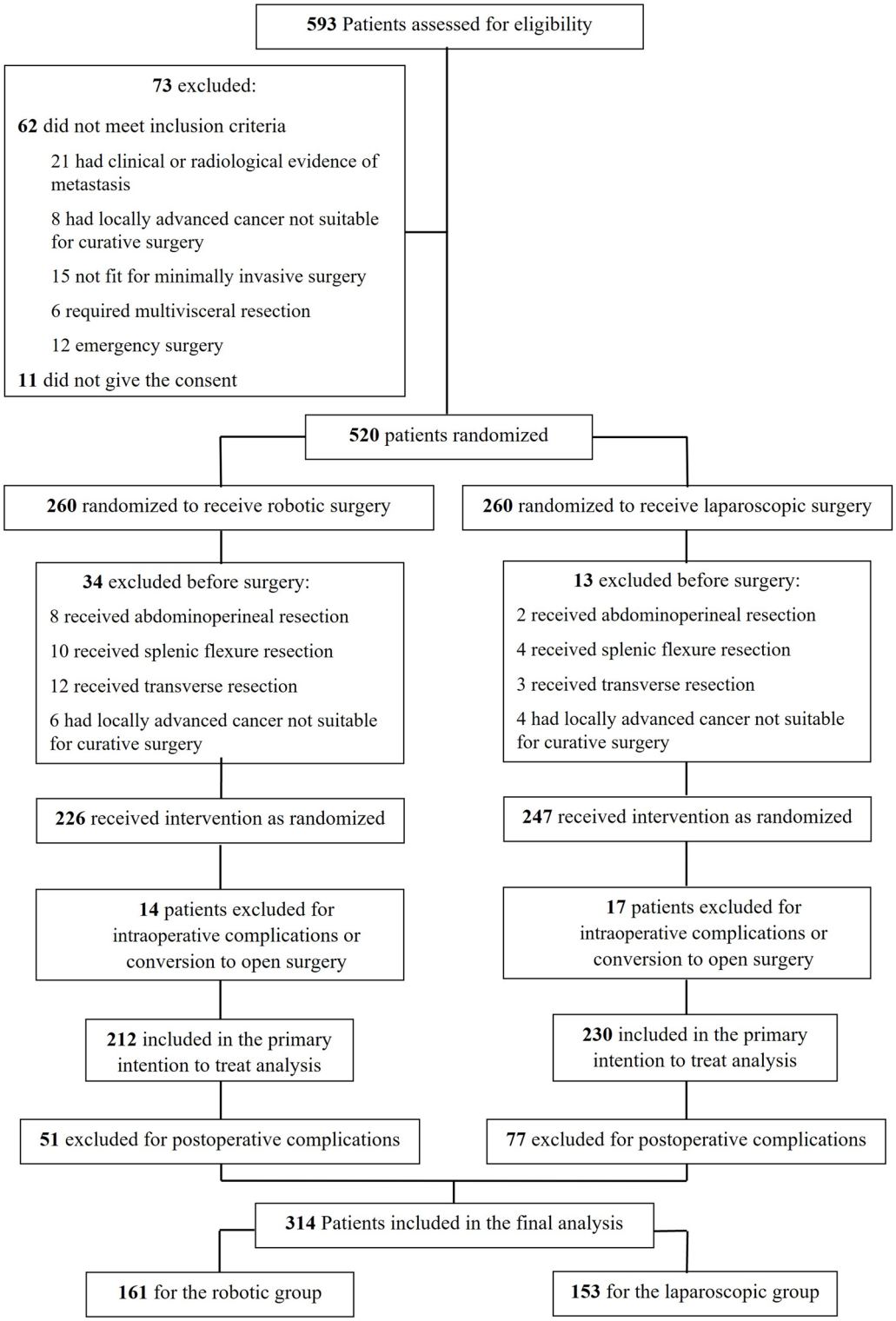


**Fig. 1**. Consort flowchart.

The rationale to hypothesize less surgical stress in robotic surgery lays in the theoretical advantages in terms of surgical technique.

Robotic instruments have multiple degrees of freedom for movement, leading to flexibility similar to or even better than a surgeon's hands. Enlarged three-dimensional vision can also offer a more detailed view of the surgical field and the three operating arms are all controlled by the surgeon, which can replace the role of the assistant in laparoscopic surgery. These technical advantages could make robotic surgery more accurate and convenient to reduce surgical trauma and the related stress response.

| | Robotic ($n=161$) | Laparoscopic ($n=153$) | $p$ |
|---|---|---|---|
| Male ($n$) (%) | 94 (58,4%) | 88 (57,5%) | 0,876 |
| Age (years) (mean ± SD) | 66,75 ± 10,24 | 67,37 ± 11,17 | 0,611 |
| BMI (kg/m$^2$) (mean ± SD) | 26,39 ± 4,3 | 26,00 ± 4,09 | 0,414 |
| ASA score (n) (%) | | | 0,919 |
| I | 5 (3,1%) | 7 (4,6%) | |
| II | 86 (53,4%) | 81 (52,9%) | |
| III | 64 (39,8%) | 60 (39,2%) | |
| IV | 6 (3,7%) | 5 (3,3%) | |
| Charlson Comorbidity Index (n) (%) | | | 0,258 |
| Low severity (2 to 5 points) | 94 (58,4%) | 85 (55,5%) | |
| Middle severity (6 to 10 points) | 62 (38,5%) | 57 (37,3%) | |
| High severity (11 to 14 points) | 5 (3,1%) | 11 (7,2%) | |
| AJCC (n) (%) | | | 0,552 |
| 0 - II | 109 (67,7%) | 98 (64%) | |
| III – IV | 52 (32,3%) | 55 (36%) | |
| Type of intervention (n) (%) | | | 0,511 |
| Right colectomy | 59 (36,7%) | 64 (41,8%) | |
| Left colectomy | 50 (31,0%) | 48 (31,4%) | |
| Anterior rectal resection | 52 (32,3%) | 41 (26,8%) | |

**Table 1**. clinical and demographic characteristics and operative procedures of the two groups.

| | | Robotic ($n=161$) | Laparoscopic ($n=153$) | $p$ |
|---|---|---|---|---|
| | IL-6 | | | |
| T0 | (mean ± SD) | 12,32 ± 12,85 | 13,48 ± 23,76 | 0,828 |
| T24 | (mean ± SD) | 478,41 ± 739,25 | 730,24 ± 1096,42 | 0,003 |
| T72 | (mean ± SD) | 136,82 ± 174,5 | 276,25 ± 573,50 | 0,032 |
| | IL-10 | | | |
| T0 | (mean ± SD) | 14,91 ± 5,99 | 13,47 ± 7,02 | 0,066 |
| T24 | (mean ± SD) | 24,19 ± 36,28 | 49,0 ± 68,27 | 0,006 |
| T72 | (mean ± SD) | 10,60 ± 28,47 | 37,23 ± 94,93 | 0,041 |
| | TNFα | | | |
| T0 | (mean ± SD) | 69,66 ± 30,14 | 68,63 ± 49,01 | 0,092 |
| T24 | (mean ± SD) | 15,57 ± 49,44 | 47,58 ± 124,50 | 0,024 |
| T72 | (mean ± SD) | 11,81 ± 59,31 | 29,85 ± 84,88 | 0,019 |

**Table 2**. Stress Response after Surgery.

Response provided by our trial confirm this hypothesis of a less surgical stress after robotic approach if compared with conventional laparoscopic surgery, as reflected by the Δ% of IL6 serum levels at 24 h that was lowest in the robotic arm (478,41 ± 739,25 vs. 730,24 ± 1096,42 in robotic and laparoscopic arm respectively; $p=0,003$).

Confirmation of this result could permit to identify an objective clinical advantage of robotic surgery in the surgical treatment of colorectal cancer helping colorectal surgeons in the choice to include or not robotics in the needed armamentarium[29].

Regarding colorectal surgery, first reports of robot assisted interventions were described by Weber et al[30].

No strong results certifying the advantages of robotic surgery have been produced at the moment in current literature.

A meta-analysis has been designed to point out the state of art of robotic versus laparoscopic colorectal surgery identifying an advantage of robotic surgery in terms of anastomotic leakage rate, overall complication rate, conversion to open surgery and time to regular diet[31]. However no convincing conclusion can be stated on these results being literature on the topic too preliminary and the evidence very low, most of the studies included were of an observational design and risk of bias assessment of serious concern. The overall level of clinical evidence was low. Additionally, it was challenging to match the patient characteristics in all the studies and some degree of heterogeneity between the two groups remained[32].

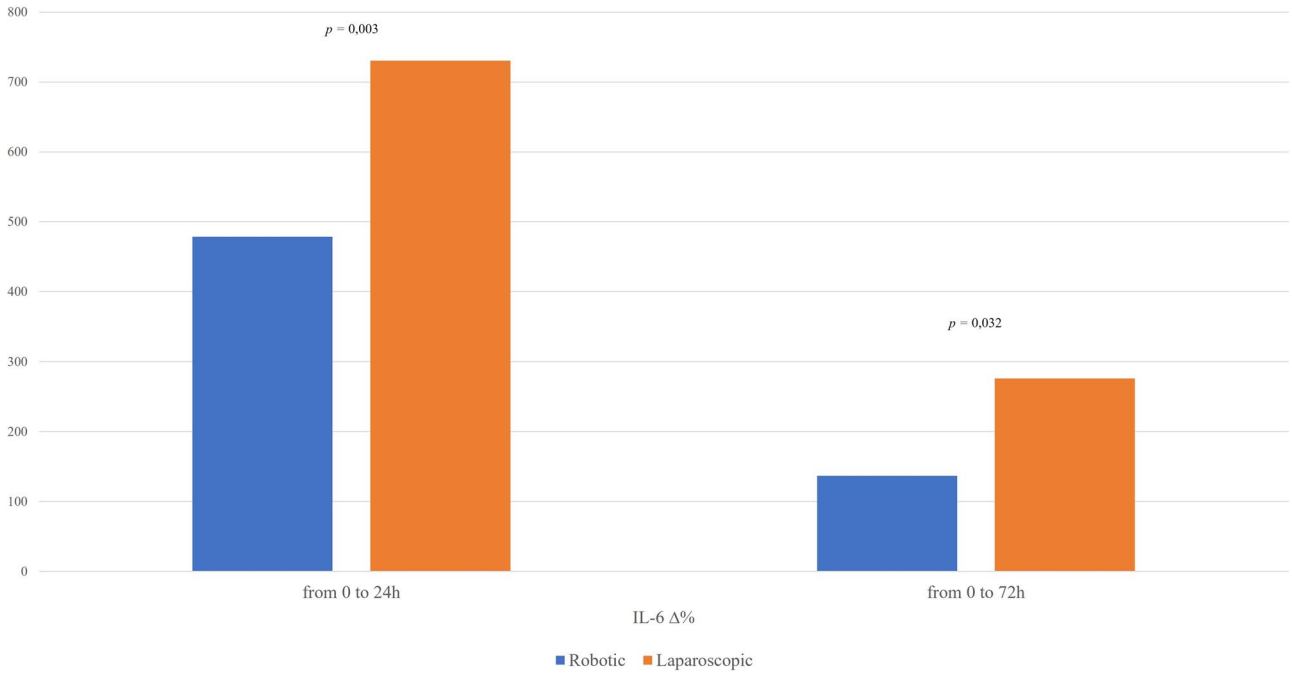


**Fig. 2**. Δ% change in IL-6 serum levels.

Two RCT on rectal cancer and one on right colon cancer could be identified in our best knowledge.

The REAL trial[33] suggested that for middle and low rectal cancer, robotic surgery resulted in better oncological quality of resection than conventional laparoscopic surgery with better postoperative recovery. However, ROLARR trial[34] found that among patients with rectal adenocarcinoma, robotic-assisted laparoscopic surgery, as compared with conventional laparoscopic surgery, did not significantly reduce the risk of conversion to open laparotomy. Similarly, the one trial on colonic surgery by JS Park et al.[35] concluded that Robotic-assisted laparoscopic right colectomy was feasible but provided no benefit to justify the greater cost.

Thus, a call to give objective evidence was needed to justify implementation of robotic in the field of colorectal surgery. In this setting the provided advantages of robotic surgery could be considered an issued point to justify preference to a robotic approach in colorectal surgery.

Performing subgroup analyses in all kinds of patients and tumor characteristics we can identify obese patients and rectal tumor as the best setting in which robotic surgery was able to minimize the surgical stress response.

This study has several limitations. No blinding to treatment allocation was incorporated into this trial but the primary outcome was unaffected by this. The choice to include only patients with an uneventful clinical course limited the generalizability of our results even if excluding all surgical complications give us the possibility to attribute to the surgical technique a specific role on the impact of surgery on stress related inflammatory response. Variability among surgeons' ability cannot be excluded in all multicenter surgical studies even if we included only expert surgeons both in laparoscopic and robotic surgery. Heterogeneity among included patients' characteristics and surgical differences could limit again generalizability of our results. However, allocation in the two treatment arms has been balanced for all patients and surgical conditions and a multivariate analysis has been performed to confirm the results and to excluding others confounding factors.

Although further studies are needed to provide insights on this topic, we can conclude that robotic surgery was associated to a lower surgical stress after colorectal surgery and this finding may help in decision-making regarding when to proceed to robotic approach for colorectal cancer, especially in obese and rectal cancer.

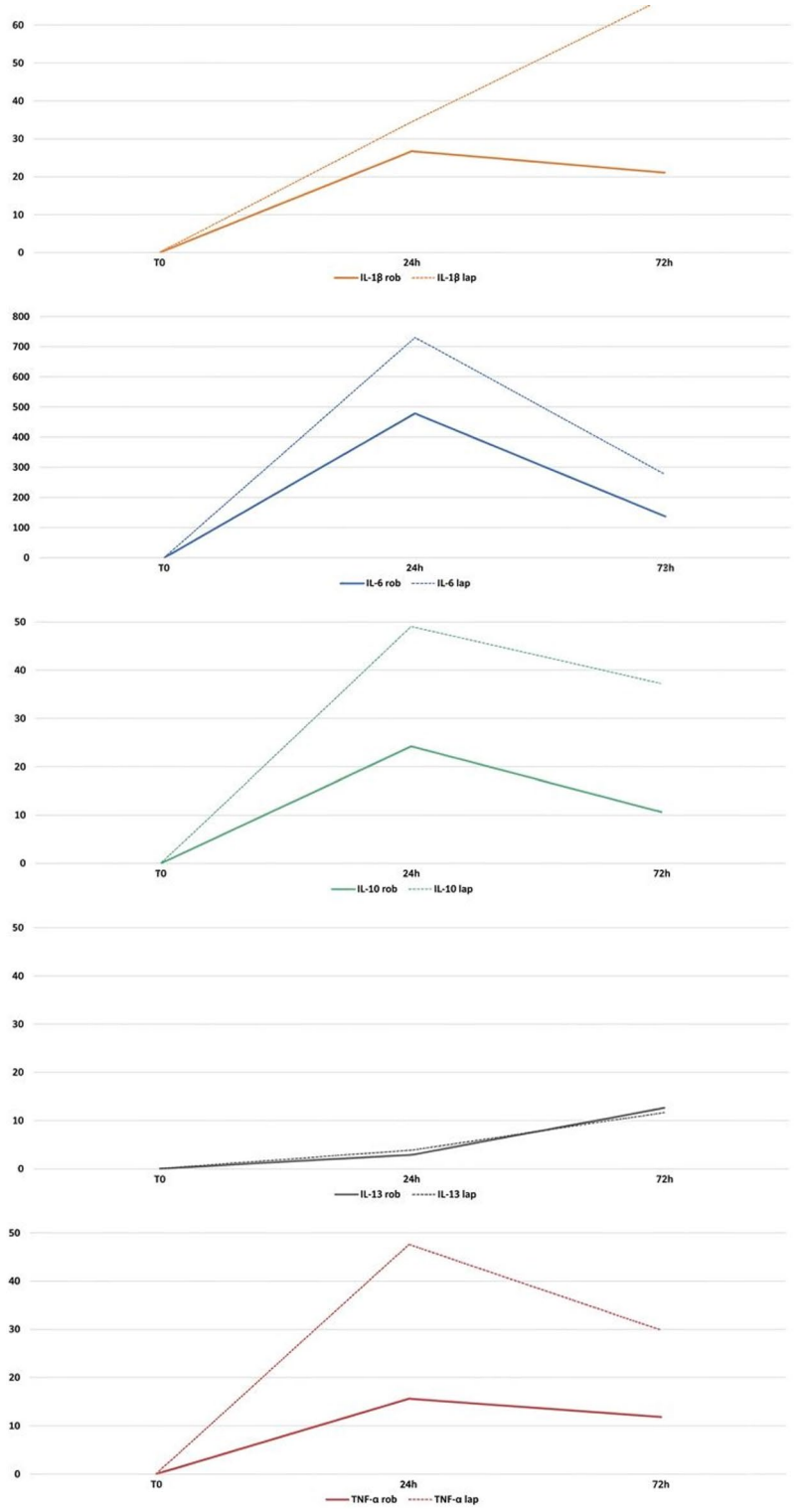


**Fig. 3**. Δ% changes of IL-1β, TNF-α, IL-10 and IL-13 serum levels.

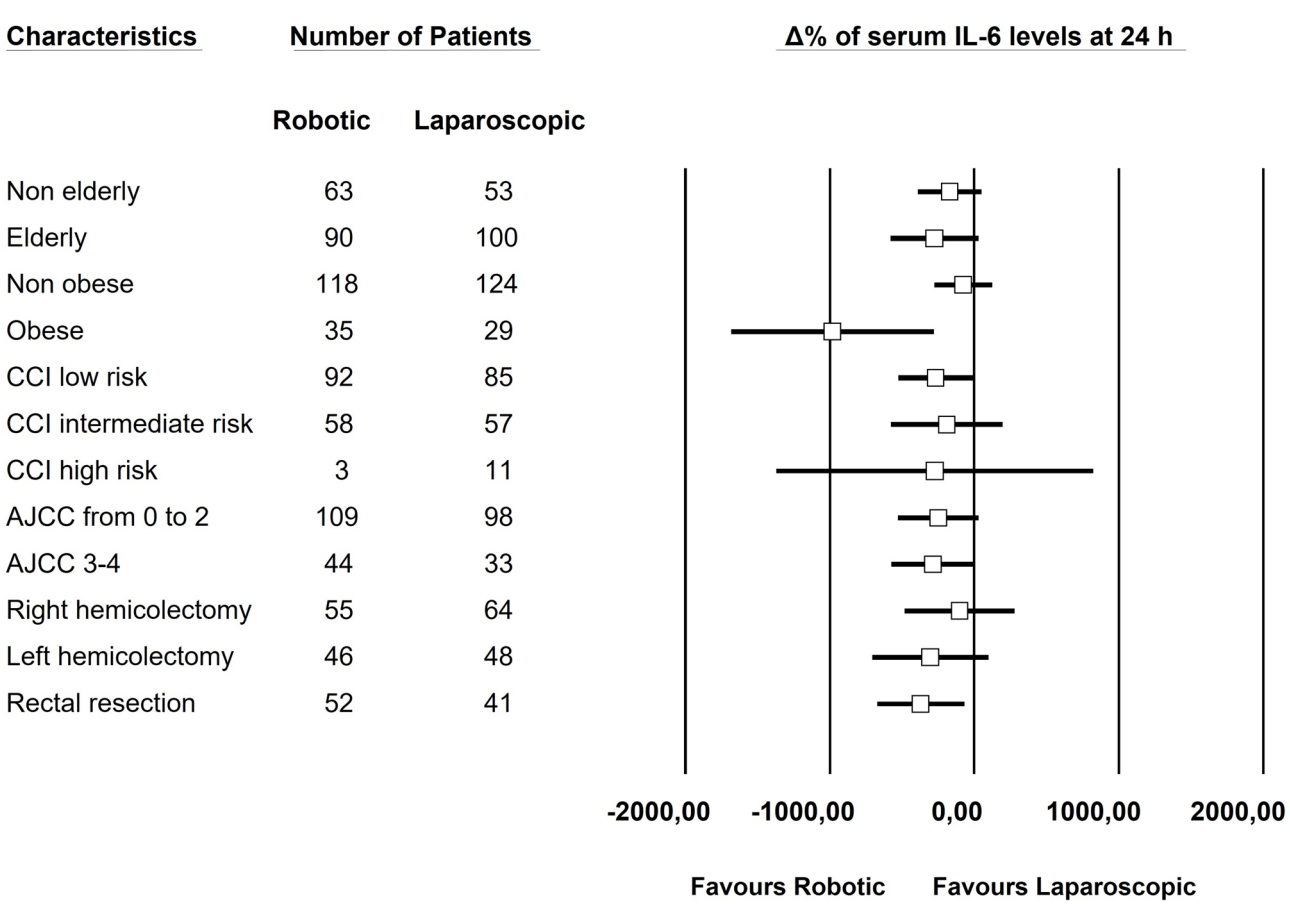


**Fig. 4**. Δ% change in IL-6 serum levels in the subgroup analyses performed on elderly/non elderly patients, obese/non obese patients, on low/moderate/severe CCI, on AJCC stages and on type of surgical resection (right/left/rectal resection).

## Data availability

Deidentified participant data collected for the study and data dictionary are available on request from the corresponding author (M.M.) upon reasonable request.

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## Author contributions

M.M., designed and directed the project; M.C., F.D.E.D.P., G.A.R., and A.D. processed the serum samples and performed the cytokines essay; A. D'A., P. A., S. B., I. C., M. C., G. C., M. D., P. D., U. R. F., M. G., M. O., U. P., F. P., L. P., W. P., R. R., D. R., G. A. R., F. R., A.S. and G. D. D. P. collected the data and contributed to the design and implementation of the research; S.V., M.M. and M.N.D.D.M. performed the statistical analysis; S. V., A. D'A., P. A. and M. M. analyzed data; M.M. wrote the paper in consultation with S.V. and M.M.; G.D.D.P. supervised the project; all authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.


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## Declarations

## Competing interests

The authors declare no competing interests.

## Additional information

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