

Systematic Review

Intraoperative surgical stress markers in open and laparoscopic surgery – a systematic review

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ABSTRACT

INTRODUCTION. Surgical stress response (SSR) reflects physiological reactions to surgical trauma. No standardised method exists to measure SSR intraoperatively, but intraoperative parameters may serve as surrogate markers. This systematic review investigated associations between intraoperative SSR and 1) changes in intraoperative parameters and 2) post-operative outcomes, including length of hospital stay and 30-day complications.

METHODS. This review followed the Cochrane Handbook for Reviews of Interventions and the PRISMA guidelines. A systematic search was performed in PubMed, the Cochrane Library and Google Scholar. Risk of bias was independently assessed by two authors using the Newcastle-Ottawa Score for non-randomised studies and the Cochrane RoB tool for randomised controlled trials.

RESULTS. Three studies (n = 102) comparing laparoscopic and open surgery met the inclusion criteria. Two studies assessed inflammatory markers, showing higher IL-6 levels in open surgery. One study evaluated haemodynamic parameters, finding no blood pressure differences but reporting greater blood loss in open than laparoscopic surgery. Length of hospital stay was inconsistently reported. Two studies reported post-operative complications without employing a standardised classification (e.g. the Clavien-Dindo), limiting comparability.

CONCLUSIONS. Intraoperative IL-6 levels were higher in open than laparoscopic surgery in two studies. However, small, heterogeneous studies prevent conclusions regarding optimal SSR measurement. Whether intraoperative markers predict post-operative complications or other clinical outcomes remains uncertain, and this question warrants further investigation.

KEY POINTS

- Surgical stress response (SSR) causes physiological changes in response to surgical trauma and may influence post-operative recovery.
- Inflammatory markers, particularly IL-6, may reflect the magnitude of SSR.
- Further studies are needed to determine whether intraoperative markers of SSR can predict post-operative complications and other clinical outcomes.

The surgical stress response (SSR) represents a pattern of physiological and pathophysiological changes that occur in response to surgical trauma. This reflects the body's attempts to keep physiological homeostasis [1].

The magnitude, invasiveness and duration of surgery are central in determining the degree of the body's

integrated stress response [1, 2]. The SRR increases with the invasiveness of surgical procedures [3, 4]. SSR is triggered by the nociceptive response induced by tissue damage. The damage triggers metabolic, inflammatory and neuroendocrine responses via the spinothalamic tract [4]. These responses include sympathetic activation and increased cortisol secretion and proinflammatory cytokine release [4]. Anaesthesia can modulate these responses by blocking nociceptive receptors and their corresponding neural pathways [4]. Thus, anaesthesia plays a crucial role in mitigating SRR [4].

Currently, no standardised objective method exists to measure SSR during a surgical procedure. However, one approach may be to use intraoperative parameters as surrogate markers. These parameters are objective, as they are affected by the nociceptive response triggered by surgery and reflect the body's instantaneous response to surgical trauma.

This systematic review aimed to identify intraoperative parameters reflecting SSR. This is important, as it will enable anesthesiologists to better monitor and address patients' SSR. Furthermore, this review aimed to investigate whether these parameters may be associated with post-operative outcomes.

Methods

Study aim

This systematic review aimed to investigate the association between the degree of intraoperative SSR and 1) changes in various intraoperative parameters and 2) the effect of SSR on post-operative outcomes, such as length of hospital stay (LOS) and post-operative complications within the first 30 days.

Exposure

Type of surgical procedure, including details about invasiveness, complexity and extent of dissection. Surgical procedures were limited to abdominal surgery where access to the abdominal cavity was laparoscopic, open or robotic. This was a pragmatic choice to obtain a homogeneous group of surgical procedures with a more or less similar SSR profile.

Outcome

The primary outcome was changes in intraoperative parameters defined as “*physiological indicators, such as blood pressure, heart rate, oxygen saturation and temperature*”. These parameters are usually monitored during surgical procedures to ensure patient safety and optimal outcomes [5]. Other parameters included blood gas analysis, central venous pressure, pulse oximetry (SpO₂), end-tidal O₂ and CO₂, tidal volume (set and measured), peak and pause pressure, respiratory rate (set and measured), minute ventilation, serial dead space, effective alveolar ventilation, oxygen consumption, CO₂ production, respiratory exchange ratio, energy expenditure, rapid shallow breathing index, ventilator mode, ventilator settings (O₂, pressure/volume, frequency and positive end-expiratory pressure (PEEP)).

The secondary outcome was the LOS and the occurrence of post-operative complications in patients, defined according to the Clavien-Dindo Classification as “*deviations from the normal post-operative course, categorised based on the required treatment, ranging from minor to life-threatening conditions*” [6].

Study design

This systematic review was conducted according to the recommendations in the Cochrane Handbook for Reviews of Interventions and reported according to the guidelines established by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses. Ethics approval was not required for this type of study. This review was registered in PROSPERO (CRD420251040608).

Search strategy

Two independent authors (AJ and JJH) conducted a systematic, organised literature search querying three databases: PubMed, Cochrane Library and Google Scholar. The following search thread was used:

(((((comparison) OR (comparing) OR (versus) OR (vs)))) AND (((("Laparoscopy"[Mesh]) OR (open surgery) OR (robotic assisted)))) AND (((("Monitoring, Intraoperative"[Mesh]) OR (Intraoperative parameters) OR (Inflammation) OR (inflammatory response))))

The final date of the search was 24 February 2025.

Eligibility criteria

Original studies, including cohort studies and RCTs, were included. Studies were eligible if they involved adult participants (≥ 18 years old) who had undergone abdominal surgery. Studies comparing two or more types of surgical approaches (laparoscopy, open and robotic surgery) were included. Elective and curative surgical procedures were considered eligible. Articles published between 2005 and 2025 were included to ensure that recent advancements in surgical techniques and intraoperative monitoring were captured [7]. Only studies written in English were included.

Meta-analyses, systematic reviews, animal studies, narrative reviews, case reports, correspondences, personal opinions, conference abstracts and other non-original publications were excluded. Finally, studies involving emergency and/or palliative surgical procedures were also excluded from this review.

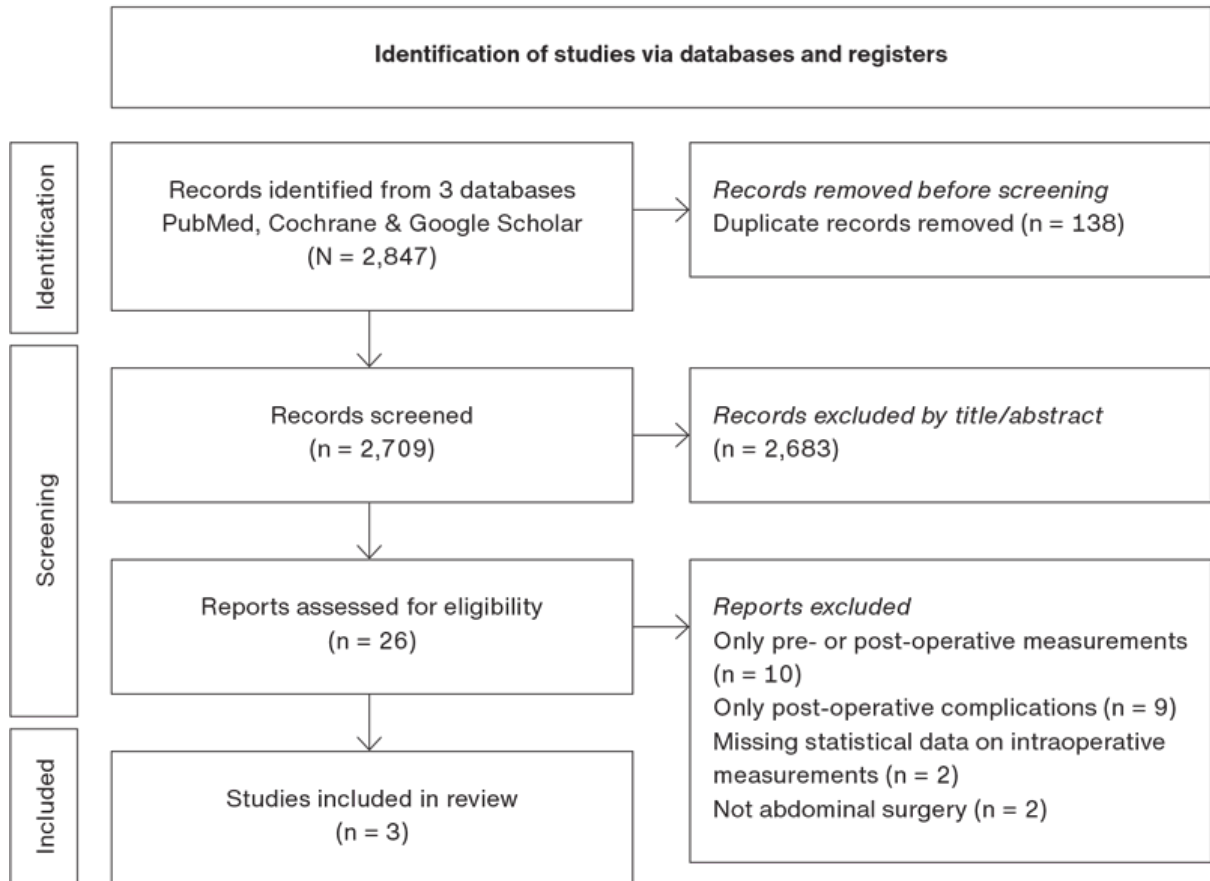
Selection process

Articles that met the inclusion and exclusion criteria were assessed by two independent authors (AJ and JJH), and any disagreement was resolved by discussion and involvement of a third author (AE).

Two independent authors (AJ and JJH) used data extraction forms to extract study data, and disagreement was resolved by discussion and involvement of a third author (AE). The authors extracted data regarding the first author, year of publication, country, study design, mean patient age, sex, number of patients/subjects and biomarker SSR measurement, timing of the measurements and post-operative complications.

The selection process for the PubMed search is summarised in the PRISMA flowchart shown in **Figure 1**. We searched PubMed, Cochrane and Google Scholar using the search thread provided above, applying filters for language, species, article type, publication date and study population age, which yielded 2,847 articles. After removing duplicates, 2,709 articles remained. Following title and abstract screening, 26 articles were selected for full-text review. Among these, three articles met the eligibility criteria and were included in this systematic review.

FIGURE 1 PRISMA diagram outlining the selection process.



Assessment of risk of bias in the included studies

The risk of bias was independently assessed by two authors (AJ and AE). The Newcastle-Ottawa Score (NOS) was used to assess the risk of bias in cohort and case-control studies. In RCTs, the Cochrane RoB tool for risk assessment was used. The results of the risk of bias assessment for each article are presented in [Table 1](#). A detailed evaluation of each study is provided in [Supplementary Table 1 and Table 2](#).

TABLE 1 Overview of the studies included.

Reference	Type of surgery	Risk of bias assessment	Surgical procedure	Underlying disease	Sample size, n	Intraoperative parameters	Post-operative complications
Wang et al., 2010 [8]	Prospective non-randomised comparative study	Low bias	Radical cystectomy	Bladder cancer	38	Inflammatory IL-6, INF- γ , incidence and duration of SIRS	The laparoscopic surgery group 3 patients: 1 ileus, 1 pneumonia, 1 pelvic abscess The open surgery group 10 patients: 7 cases of ileus, 2 wound infections, 1 wound dehiscence
Kvarnström et al., 2013 [9]	RCT	Some concerns for bias	Anterior rectal resection or abdomino-perineal resection	Rectal cancer	24	Inflammatory IL-1 α , IL-6, IL-8, IL-10, TNF- α , white blood cells, ICAM-1, VCAM-1	Not reported
Tiberio et al., 2008 [10]	RCT	Low bias	Adrenalectomy	Pheochromocytoma	22	Haemodynamic SBP, hypertensive peak, hypotensive crises, blood loss	No post-operative complications occurred in either group

ICAM = intercellular adhesion molecule; INF = interferon; SBP = systolic blood pressure; SIRS = systemic inflammatory response syndrome; VCAM = vascular cell adhesion molecule.

Statistical analysis

No statistical analysis was performed due to the limited number of studies within subgroups and substantial

heterogeneity within the groups. This decision was made to avoid drawing misleading conclusions based on insufficient or heterogeneous data. For further details, please refer to the Discussion section.

Results

In total, three studies met the inclusion criteria. These studies investigated intraoperative changes in physiological parameters among 102 patients, comparing laparoscopic and open surgical techniques. The intraoperative parameters assessed included haemodynamic markers in one study and inflammatory markers in two studies. Post-operative complications were reported in two of the included studies, although they did not use a standardised classification system such as the Clavien-Dindo Classification. The characteristics of the studies are summarised in Table 1.

Further analysis is divided into two subgroups based on the intraoperative parameters assessed: haemodynamic and inflammatory. Each subgroup is reviewed separately below.

Studies on surgical stress response inflammatory markers

Two studies examined intraoperative changes in inflammatory markers between laparoscopic and open surgical procedures. Both studies assessed cytokine levels, particularly IL-6, as a marker of inflammatory response.

Wang et al. [8] presented a prospective non-randomised study that investigated inflammatory responses in 38 patients undergoing radical cystectomy for non-metastatic bladder cancer, either laparoscopically or by open surgery. IL-6 and interferon (INF)- γ were measured intraoperatively.

The results showed that IL-6 levels increased during surgery in both groups, consistent with a stress response. However, IL-6 concentrations were significantly higher in the open surgery group, with median (and IQR) levels at 10.39 pg/ml (3.74-14.78 pg/ml) in the laparoscopic group and at 13.75 pg/ml (3.29-22.61 pg/ml) in the open group. The IQRs of both groups were relatively wide, and the ranges overlapped. Therefore, despite a statistically significant difference between the groups, the overlap in IQRs makes it difficult to translate this result into a clear clinical difference. No significant differences in INF- γ levels were found between the groups.

Kvarnström et al. [9] was a randomised controlled trial including 24 patients undergoing either anterior rectal resection or abdomino-perineal resection for rectal cancer. The study measured several cytokines at two intraoperative time points: T1 (180 minutes) and T2 (360 minutes) after surgery began. Markers included pro-inflammatory cytokines (IL1 α , IL6, IL8, TNF α), the anti-inflammatory cytokine IL10, white blood cell (WBC) count, intercellular adhesion molecule (ICAM)1 and vascular cell adhesion molecule (VCAM)1. CRP was also measured at 24 hours and 3-5 days post-operatively and was therefore considered post-operative rather than intraoperative and therefore not included in this review.

IL-6 levels were significantly lower in the laparoscopic group than in the open group at both T1 and T2. Median (IQR) levels in the laparoscopic group were 45.6 pg/ml (29.3-69.1 pg/ml) and 146.4 pg/ml (106.0-200.1 pg/ml) at T1 and T2, respectively, compared with corresponding values of 276.8 pg/ml (176.2-409.2 pg/ml) and 208.5 pg/ml (145.5-412.2 pg/ml) in the open group. Additionally, IL-10 levels were significantly lower in the laparoscopic group than in the open group at T1. Other cytokines and inflammatory markers showed no significant differences between surgical approaches.

Both studies demonstrated that IL-6 levels were significantly higher in open surgery than in laparoscopy, suggesting a greater inflammatory response. However, the absolute IL-6 levels were markedly higher in Kvarnström et al. than in Wang et al., and the magnitude of the between-group differences also varied. The second study also showed differences in IL-10, an anti-inflammatory cytokine, though other inflammatory

markers were not significantly associated with surgical technique.

Studies on surgical stress response haemodynamic markers

Only one study assessed haemodynamic changes intraoperatively.

Tiberio et al. [10] was a randomised controlled trial investigating 22 patients undergoing adrenalectomy for pheochromocytoma. Haemodynamic parameters included the occurrence of hypertensive peaks (defined as a > 25% increase in mean systolic blood pressure (SBP) and intraoperative blood loss.

No significant differences in hypertensive peaks or mean SBP were observed between the laparoscopic and open groups. However, blood loss was significantly greater in the open surgery group ($p < 0.05$).

Studies linking surgical stress response with length of hospital stay and post-operative complications

In addition to intraoperative parameters, all three studies investigated length of stay (LOS) within their study populations. Tiberio et al. reported a significantly shorter LOS in the laparoscopic group than in the open surgery group, despite observing no significant differences in intraoperative haemodynamic parameters. In contrast, Wang et al. and Kvarnström et al., who found significant differences in IL-6 levels, reported no significant differences in LOS between the two groups.

Post-operative complications were reported in two of the studies included. In Wang et al. [8], three and ten patients in the laparoscopic and open groups, respectively, experienced post-operative complications, whereas in Tiberio et al. [10], no post-operative complications were observed in either group. However, none of these studies used a standardised classification such as the Clavien-Dindo for post-operative complications.

Discussion

This systematic review showed that measurement of SSR is an under-investigated area of research despite its potential to shed light on the impact of intraoperative events on post-operative outcomes. The literature was composed of a small series of studies.

However, a recent study investigated haemodynamic indicators of intraoperative physiological measurements (e.g., energy expenditure), but did not compare different surgical techniques as a measure of stress [11].

Most studies focus on preoperative or post-operative stress markers, whereas few capture real-time intraoperative data [12, 13].

In the two studies on the SSR inflammatory marker, a statistical analysis was not feasible due to substantial heterogeneity. The studies varied in disease types, surgical procedures and reporting. According to the literature, both disease characteristics and surgical technique are significant confounders that can influence SSR magnitude [14].

To allow for valid cross-study comparisons, it is essential to adjust for such variables. Further heterogeneity was caused by differences in measurement, timing and methods. For example, Kvarnström et al. collected blood samples at 180 and 360 minutes after the start of surgery [9], whereas Wang et al. failed to report exact sampling times [8], complicating direct comparison. This may also partly explain the large differences in measured IL-6 values between the two studies, as cytokine release during surgery can depend on factors such as type of surgery, timing of measurement and patient population.

SSR can be influenced by preoperative confounders such as comorbidities and baseline patient status [14]. For instance, Wang et al. adjusted for ASA classification [8], but it remains unclear whether the other studies [9, 10] accounted for such variables. Other important covariates include disease burden and tumour characteristics

[14]. Tiberio et al. adjusted for tumour size [10], and Wang et al. for tumour stage [8], but it is not evident whether Kvarnström et al. controlled for these factors [9], raising the risk of residual confounding.

In addition, although both included studies showed higher IL-6 levels in open surgery, the clinical relevance of this finding remains uncertain. This is because no established threshold values can distinguish a physiological from a pathological stress response in individual patients. Furthermore, these markers are not available bedside, which limits their applicability in clinical practice.

It should also be noted that caution is required when interpreting the haemodynamic findings from Tiberio et al., as the hypertensive peaks and SBP may be influenced by the underlying disease, pheochromocytoma. This means that changes in these parameters do not necessarily reflect the SSR alone.

For secondary outcomes, the findings regarding LOS were inconsistent. Whereas Tiberio et al. reported a shorter LOS in the laparoscopic group, Wang et al. and Kvarnström et al. found no significant differences despite variations in inflammatory markers. Furthermore, none of the included studies used a standardised classification system such as the Clavien-Dindo for reporting of post-operative complications, which limits comparison and interpretation of associations with intraoperative parameters.

This systematic review has some limitations due to the methodological weaknesses of the included studies. Inadequate sample size, limited adjustment for confounders and poor outcome reporting were among the factors producing this weakness. Future studies must include larger samples, better adjustment for confounders that affect SSR and better reporting of the post-operative outcomes.

Conclusions

Intraoperative IL-6 levels were higher during open than during laparoscopic surgery in the two studies assessing inflammatory markers. However, the small number and the heterogeneity of studies prevent conclusions regarding the most appropriate method for measuring intraoperative SSR. Whether intraoperative markers, including IL-6, can predict post-operative complications or other clinical outcomes remains uncertain and warrants further investigation.

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Supplementary material https://content.ugeskriftet.dk/sites/default/files/2026-09/a03260213_supplementary.pdf

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