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DOI:

[10.1111/cen.13820](https://doi.org/10.1111/cen.13820)

License:

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Document Version

Peer reviewed version

Citation for published version (Harvard):

Prete, A, Yan, Q, Al-Tarrah, K, Akturk, H, Prokop, L, Alahdab, F, Foster, MA, Lord, J, Karavitaki, N, Wass, J, Murad, M, Arlt, W & Bancos, I 2018, 'The cortisol stress response induced by surgery: a systematic review and meta-analysis', *Clinical Endocrinology*, pp. 554-567. <https://doi.org/10.1111/cen.13820>

[Link to publication on Research at Birmingham portal](#)

Publisher Rights Statement:

This is the peer reviewed version of the following article: Prete, A. , Yan, Q. , AlTarrah, K. , Akturk, H. K., Prokop, L. J., Alahdab, F. , Foster, M. A., Lord, J. M., Karavitaki, N. , Wass, J. A., Murad, M. H., Arlt, W. and Bancos, I. (2018), The cortisol stress response induced by surgery: a systematic review and metaanalysis. *Clin Endocrinol. Accepted Author Manuscript.* . doi:10.1111/cen.13820, which has been published in final form at 10.1111/cen.13820. This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Self-Archiving

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The cortisol stress response induced by surgery: a systematic review and meta-analysis.

Journal:	<i>Clinical Endocrinology</i>
Manuscript ID	CEN-2018-000638.R1
Manuscript Type:	5 Unsolicited Review
Date Submitted by the Author:	12-Jul-2018
Complete List of Authors:	<p>Prete, Alessandro; University of Birmingham, Institute of Metabolism and Systems Research; Birmingham Health Partners, Centre for Endocrinology, Diabetes and Metabolism Yan, Qi; Mayo Clinic, Department of Surgery Al-Tarrah, Khaled; University of Birmingham, Institute of Inflammation and Ageing Akturk, Halis; University of Colorado School of Medicine, Barbara Davis Center for Diabetes Prokop, Larry; Mayo Clinic, Mayo Clinic Libraries Alahdab, Fares; Mayo Clinic, Evidence-based Practice Center Foster, Mark A.; University of Birmingham, Institute of Inflammation and Ageing; Queen Elizabeth Hospital Birmingham & Royal Centre for Defence Medicine, NIHR Surgical Reconstruction and Microbiology Research Centre Lord, Janet M; University of Birmingham, Institute of Inflammation and Ageing Karavitaki, Niki ; University of Birmingham, Institute of Metabolism and Systems Research; Birmingham Health Partners, Centre for Endocrinology, Diabetes and Metabolism Wass, John A.H.; University of Oxford, Oxford Centre for Diabetes, Endocrinology and Metabolism, Churchill Hospital Murad, Mohammad; Mayo Clinic, Evidence-based Practice Center Arlt, Wiebke; University of Birmingham, Institute of Metabolism and Systems Research; Birmingham Health Partners, Centre for Endocrinology, Diabetes and Metabolism Bancos, Irina; Mayo Clinic, Division of Endocrinology, Metabolism and Nutrition, Department of Internal Medicine</p>
Key Words:	Cortisol < Hormones/related: < Adrenal, Surgery, Stress, Pituitary-Adrenal System, Adrenal insufficiency < Conditions: < Adrenal

The cortisol stress response induced by surgery: a systematic review and meta-analysis

Running title: The cortisol response to surgery.

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Word count: 3,808 words.

SUMMARY

Objective: Surgery is a stressor that can be categorized by duration and severity, and induces a systemic stress response that includes increased adrenal cortisol production. However, the precise impact of surgical stress on the cortisol response remains to be defined.

Design: We performed a systematic review and meta-analysis to assess the cortisol stress response induced by surgery and to stratify this response according to different parameters.

Methods: We conducted a comprehensive search in several databases from 1990 to 2016. Pairs of reviewers independently selected studies, extracted data and evaluated the risk of bias. Cortisol concentrations were standardized, pooled in meta-analysis and plotted over time.

Results: We included 71 studies reporting peri-operative serum cortisol measurements in 2,953 patients. The cortisol response differed substantially between moderately/highly invasive and minimally invasive surgical procedures. Minimally invasive procedures did not show a peri-operative cortisol peak, whereas more invasive surgeries caused a cortisol surge that was more pronounced in older subjects, women and patients undergoing open surgery and general anaesthesia. The duration of the procedure and the use of etomidate for induction of anaesthesia did not affect the cortisol response.

Conclusions: The peri-operative cortisol stress response is dynamic and influenced by patient-specific, surgical and anaesthetic features. However, the available evidence is derived from highly heterogeneous studies, with only two of 71 studies measuring cortisol by mass spectrometry, which currently prevents a precise and reproducible definition of this response.

Key words: Cortisol; Surgery; Stress; Pituitary-Adrenal System; Adrenal Insufficiency; Hydrocortisone; Adrenal cortex.

INTRODUCTION

The controlled trauma of a surgical insult activates adaptive changes in the neuro-hormonal system and the inflammation response.¹ The primary mechanism responsible for cortisol hypersecretion in response to stress is executed by the afferent nerve signals derived from the surgical site, which in turn stimulate the hypothalamus to release corticotropin-releasing hormone and arginine vasopressin.² These two peptides then stimulate secretion of adrenocorticotrophic hormone from the anterior pituitary, which stimulates cortisol secretion by the adrenal cortex. Surgery can be considered a standardized model for assessing the cortisol response to stress and relevant modifying factors.

Understanding the expected magnitude of cortisol production during surgical stress is very relevant, especially for patients with adrenal insufficiency who require a dose increase in exogenous cortisol replacement during stress. Primary and secondary adrenal insufficiency affects up to 424/1,000,000 people and comes with the need for lifelong glucocorticoid replacement.³ Furthermore, according to a recent meta-analysis,⁴ 2.4-21.5% of patients receiving chronic treatment with supraphysiological exogenous steroids, e.g. for chronic obstructive pulmonary disease, develop tertiary adrenal insufficiency after glucocorticoid discontinuation. In all these patients, surgical stress required an increase in glucocorticoid replacement dose to avoid a life-threatening adrenal crisis.

Recommendations regarding the dose, administration route, timing, tapering and duration of glucocorticoid therapy vary substantially.⁵ Moreover, the recommended doses of perioperative steroid dosing is based on the long-held notion that the activation of the hypothalamic-pituitary-adrenal (HPA) axis, including the adrenal cortisol output in response to surgery, is directly proportionate to the severity of the surgical stress.⁶⁻⁸ However, most of the data underpinning this assumption derive from works published before 1990 and are based on limited case series. Surgical and anaesthetic techniques, as well as the rigour of

1
2
3 cortisol assays have changed significantly since then, in particular following the now more
4
5 widespread introduction of the current diagnostic reference standard mass spectrometry.
6

7 Therefore, our objective was to perform a systematic review and meta-analysis of
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9 published studies investigating the cortisol response to surgery in order to estimate the
10
11 expected range of perioperative cortisol concentrations and to identify factors that potentially
12
13 affect this response.
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16 17 18 **METHODS AND EVIDENCE ACQUISITION**

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20 This systematic review and meta-analysis was performed based on an *a priori*
21
22 protocol. The methods and results of the review are reported according to the PRISMA
23
24 statement (preferred reporting items for systematic reviews and meta-analyses).⁹
25

26 27 **Inclusion and exclusion criteria**

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29 We included original studies published after 1990 that enrolled adult humans
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31 undergoing any type of surgical procedure (under local or general anaesthesia), with a sample
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33 size of at least 5, and which reported at least one measurement of serum cortisol by any
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35 method during surgery and within 10 days from surgery. Studies published before 1990 were
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37 not considered representative of the recent advances in surgical and anaesthetic techniques, as
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39 well as of current methods for cortisol estimation used in clinical practice. Studies reporting
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41 cortisol measurements only after the administration of exogenous glucocorticoids or
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43 corticotropic agents (i.e. tetracosactide) were excluded. Surgical procedures involving the
44
45 brain were also excluded to remove the potential confounding factor of surgically-induced
46
47 central adrenal insufficiency.¹⁰
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50 51 **Data sources and search strategy**

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53 A comprehensive search of several databases was conducted for records published
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55 between 1990 and May 26th, 2016. The databases included Medline In-Process & Other
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3 Non-Indexed Citations, MEDLINE, EMBASE, Cochrane Central Register of Controlled
4 Trials, and Cochrane Database of Systematic Reviews. The search strategy was designed and
5 conducted by an experienced librarian (LJP) with input from the corresponding author (IB).
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7 Controlled vocabulary supplemented with keywords was used to search for articles of
8
9 interest. The full search strategy is available in **Supplementary Table 1**.
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13 **Study selection**

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15 Initial screening of the identified studies was performed by four independent
16 reviewers (AP, KA, HKA and IB). Titles and abstracts of the identified studies were screened
17 in duplicate, taking into consideration the predefined inclusion criteria. Many of the identified
18 studies retrieved by our search were not relevant or not original and were excluded at this
19 phase. The full-text screening was then performed in duplicate to assess eligibility for final
20 inclusion and discrepancies were resolved through discussion and consensus. The reference
21 lists of the original studies and narrative reviews were searched for any additional relevant
22 studies that were not identified by our literature search. The list and characteristics of the
23 included studies is reported in **Table 1**.
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35 **Data extraction and variable and outcome definitions**

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37 Data extraction of the eligible studies was carried out independently and in duplicate
38 (AP, KA, HKA and IB) using the DistillerSR online platform, Evidence Partners.¹¹ Any
39 disagreements or discrepancies in extracted data were resolved by consensus.
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44 The data initially extracted included the last name of the first author and year of
45 publication, the country where the study was conducted, demographics of participants, patient
46 inclusion and exclusion criteria, and study design. The reviewers then extracted the cortisol
47 measurements from all the eligible studies, dividing them by the time since the baseline
48 assessment (prior to surgery). When exact figures were not reported in the text, cortisol
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3 measurements and descriptive statistics were extracted from graphs. All cortisol
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5 measurements were converted to SI units (nmol/L).
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7 Finally, we considered various parameters potentially affecting cortisol concentrations
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9 during and after surgery (age, gender, grade and duration of surgical procedure, type of
10
11 anaesthesia use and type of serum total cortisol assay) and extracted these data from the
12
13 studies for which this information was available with the plan to perform subgroup analyses.
14

15 The surgical procedures were classified according to the modified Johns Hopkins
16
17 surgical criteria, which define three grades of invasiveness (**Supplementary Table 2**):
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19 minimally invasive (grade I), moderately invasive (grade II), and highly invasive (grade
20
21 III).¹² **Supplementary Table 3** reports the parameters that have been extracted and used to
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23 generate specific subsets of patients, as well as the number of cohorts and sample sizes used
24
25 for meta-analysis of the cortisol measurements. The latter are reported according to the time
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27 of measurement, ranging from baseline to the 7th post-operative day (POD-7).
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30 31 **Methodological quality and risk of bias assessment**

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33 Critical appraisal of the included studies was assessed independently and in duplicate
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35 (AP, KA, HKA and IB). Therefore, we derived the following parameter from an existing
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37 guide on appraising uncontrolled studies¹³: (i) inclusion criteria; (ii) exclusion criteria; (iii)
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39 cortisol assay; (iv) timing of cortisol measurements; (v) reporting of cortisol measurements;
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41 (vi) time points of cortisol measurements. Any disagreements or differences in the quality
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43 assessments were resolved by consensus.
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46 47 **Statistical analysis**

48 We conducted a meta-analysis using the random-effects model to pool estimates from
49
50 the included studies. A random-effects model was used, rather than a fixed-effects model, in
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52 order to account for heterogeneity between-study and within-study variability. We used the I^2
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54 statistic to estimate the percentage of total between-study variation due to heterogeneity
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3 rather than chance (ranging from 0 to 100%). I^2 values of 25, 50 and 75% are considered to
4 represent low, moderate and high heterogeneity, respectively. Statistical analyses were
5 conducted using OpenMeta[Analyst].¹⁴⁻¹⁶ The outcome of interest was total serum cortisol
6 concentration, a continuous outcome that was extracted from the studies as means and
7 standard deviations when possible. If the standard deviations were not reported, we converted
8 the standard errors or interquartile ranges to standard deviations. Medians were used in place
9 of means when the means were not reported and the sample size was 25 or more. The area
10 under the curve (AUC) was calculated using the trapezoidal rule. AUCs have been then
11 divided by 24-h intervals and compared either to the pre-operative cortisol measurements or
12 to a standard AUC 0-24-h for cortisol derived from the literature (data from cortisol profiling
13 of 33 healthy adults sampled over 24 hours every 20 minutes).^{17,18} Most studies in this
14 systematic review reported multiple cortisol measurements during the day of surgery (i.e. the
15 first 24 hours after the baseline assessment). From the 1st post-operative day (POD-1)
16 onwards only single measurements every 24 hours were reported. To compare post-surgical
17 cortisol secretion to the day of surgery cortisol secretion, we calculated the cortisol AUCs of
18 each 24-h-interval.
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40 RESULTS

41 Characteristics of included studies

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43 The search yielded 7,634 references for the abstract screening of which 71 studies¹⁹⁻⁸⁹
44 were included in the analysis (**Table 1**). The PRISMA flow diagram (**Figure 1**) details the
45 number of records identified, included and excluded, and the reasons for exclusions. Eligible
46 studies included are predominantly prospective (n=34 interventional and n=36 observational),
47 while one study is of retrospective-prospective nature. Most of the studies are from European
48 (n=39) and Asian-Pacific centres (n=22) while ten studies originated from American centres.
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3 A total of 2,953 patients (mean age 54 years, 50.2% women) undergoing surgery
4 (n=223 grade I minimally invasive surgery, n=1,568 grade II moderately invasive surgery,
5 and n=1,162 grade III highly invasive surgery, **Table 1**) were included. The mean duration of
6 surgery was 154 min (range 24-495) min as reported by 42/71 studies.
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11 Peri-operative cortisol measurements were extracted from the studies and included
12 baseline assessment (prior to surgery) up to 7th post-operative day (POD-7). As described in
13 **Supplementary Table 3**, the number of observations up to POD-2 was high (>9,000 single
14 cortisol measurements). However, the number of patient cohorts with available cortisol
15 measurement between POD-3 and POD-7 available for analysis dropped considerably (<600
16 single cortisol measurements).
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24 Most of the studies were judged to be of good quality (**Supplementary Table 4**); low
25 quality scores were mainly due to absent or inadequate description of inclusion and exclusion
26 criteria (especially the latter). Overall, the included studies clearly reported the methodology
27 and the timing of cortisol measurements. For those studies reporting more than one patient
28 cohort, the reviewers were almost always able to discriminate the cortisol measurements
29 among the different cohorts and perform sub-group analyses (**Supplementary Tables 3 and**
30 **5**).
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40 **Grade of surgery and peri- and post-operative cortisol concentrations**

41 Four studies (n=194 patients) reported data for grade I (minimally invasive)
42 procedures, while the cortisol response during grade II and grade III surgeries has been
43 investigated in 41 (n=1,494 patients) and 22 studies (n=1,095 patients), respectively. Four
44 studies (n=170 patients) reported cortisol measurements from mixed cohorts, ranging across
45 the three grades of surgery (**Table 1 and Supplementary Table 3**). Whilst grade II surgical
46 procedures were heterogeneous in terms of the type of surgery and surgical techniques, most
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3 of the studies on grade III procedures (16 out of 24) focused on cardiac surgery, mainly
4 coronary artery bypass grafting (CABG), **Table 1**.

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7 Cortisol measurements from patients undergoing grade I surgery have been performed
8 only over a period of up to 24 hours after surgery, while patients undergoing grade II and III
9 surgeries have been evaluated for cortisol up to POD-7 (**Table 2 and Supplementary Table**
10 **3**). In order to increase the number of observations, we have also merged data from grade II
11 and III procedures and these results are reported in **Table 2** and **Figure 2B+F**.

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18 In our systematic review, we found that grade of surgery significantly affected
19 cortisol secretion. Patients undergoing grade I surgery did not show an intraoperative cortisol
20 peak, and even demonstrated lower intraoperative cortisol measurements when compared to
21 baseline; post-surgical cortisol concentrations were again similar to baseline when measured
22 within 6 hours after the procedure (**Figure 2C**). Nevertheless, when compared to published
23 data on healthy, unstressed adults,^{17,18} the mean cortisol output over the first 24 hours after
24 grade I surgical procedure is approximately doubled. On the other hand, patients undergoing
25 grade II and III surgery had 1.9-fold and 1.7-fold, respectively, higher cortisol output within
26 the first 24-h period than patients with grade I surgery, and 4-fold and 3.5-fold higher cortisol
27 output than healthy, unstressed individuals. Total serum cortisol peaked around the time of
28 extubation (grade II procedures) and between 6 and 18h after the end of surgery (grade III
29 procedures) (**Figure 2A**). Moreover, in both grade II and III surgeries, mean cortisol values
30 remained elevated in comparison to the baseline measurements up to POD-7 (**Figure 2D-F**).

41 42 43 **Demographics and peri- and post-operative cortisol concentrations**

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48 After stratifying the combined cohorts of grade II and III procedures according to age
49 (cut-off 60 years), we observed that older patients demonstrated higher cortisol
50 concentrations (**Figure 3A**). In comparison to cohorts with female predominance (79% on
51 average), in studies with >50% male patients (78% on average) the cortisol output was lower
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3 the first 24-h from surgery but higher on POD1 (**Figure 3B**). The AUCs for total cortisol
4 measurements, stratified by age and gender, are reported in **Supplementary Table 5**.

7 **Duration of surgery and peri- and post-operative cortisol concentrations**

9
10 When dividing the cohorts according not only to the grade but also the mean duration
11 of surgery (≤ 180 or >180 min, 884 patients vs. 875 patients, respectively), we found that
12 duration of surgery did not substantially affect the cortisol response within 48 hours of
13 surgery (**Figure 3C+D**). The AUCs for total cortisol measurements are reported in
14 **Supplementary Table 5**.

19 **Surgical and anaesthetic techniques and peri- and post-operative cortisol concentrations**

21
22 A laparoscopic surgical approach (n=446 patients) was associated with a slightly
23 lower cortisol response during and after surgery as compared to open surgery (n=654
24 patients) (**Figure 4A**). Conversely, studies with $>50\%$ of patients treated preoperatively with
25 the anaesthetic agent etomidate, a known inhibitor of CYP11B1 and hence cortisol
26 synthesis,^{90,91} have not demonstrated significant differences in cortisol response (n=502
27 patients vs. n=1,444 patients who did not receive etomidate) (**Figure 4B**). Three studies
28 (n=134 patients) compared general anaesthesia to regional (spinal or epidural) anaesthesia;
29 the latter group had a 17% lower AUC for total cortisol over the first 24 hours after the
30 initiation of surgery (**Figure 4C**). The AUCs for total cortisol measurements, stratified by
31 surgical and anaesthetic techniques, are reported in **Supplementary Table 5**.

44 **Effect of cortisol assay on peri- and post-operative cortisol concentrations**

46
47 As expected, the types of cortisol assays used in the studies varied, with 63 studies
48 using immunoassays, two liquid chromatography-tandem mass spectrometry (LC-MS/MS),
49 two spectrophotometry and one double isotope dilution (**Table 1**). Three studies did not
50 report the assay used. Perioperative total cortisol concentrations measured by immunoassay
51 were higher when compared to cortisol measurements by LC-MS/MS – **Figure 4D**. While we
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3 found no significant differences based on the type of immunoassay used, total cortisol
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5 measurements with ELISA demonstrated the highest measurements up to POD-1. The AUCs
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7 for total cortisol measurements stratified by the assay are reported in **Supplementary Table**
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9 **5**. None of the included studies utilised LC-MS/MS to measure total cortisol between
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11 baseline (prior to the initiation of surgery) and POD-1; thus, the AUCs for the first 24-h could
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13 not be compared between immunoassays and LC-MS/MS.
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18 **DISCUSSION**

19
20 Surgery causes a controlled systemic stress response that encompasses a wide range
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22 of endocrine, immune and cardiovascular effects.² In this systematic review and meta-
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24 analysis, we focused on the surgery-induced HPA axis activation with an objective to
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26 estimate cortisol output and their dependence on several defined parameters.
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29 We found that the cortisol response to surgical stress varies significantly in patients
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31 undergoing minimally invasive surgeries (grade I) in comparison to patients undergoing
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33 moderate and highly invasive surgeries (grade II and III). On the day of surgery, the cortisol
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35 output increases by 2-fold (grade I), 4-fold (grade II) and 3.5-fold (grade III) in comparison
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37 to a reference population of healthy individuals.
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40 Interestingly, we found that grade I procedures do not cause a peri-operative cortisol
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42 peak. Moreover, cortisol actually decreases in comparison to pre-surgical measurements,
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44 possibly explained by the fact that the (minor) stress stimulus is counteracted by other
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46 factors, such as anaesthesia and sedation. It is important to keep in mind that only 6 studies
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48 on 223 patients reported on cortisol measurements after minor surgeries, and strong
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50 conclusions are not possible.
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53 We found that the cortisol response does not differ substantially between moderately
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55 (grade II) and highly invasive (grade III) surgeries with serum cortisol peaking between the
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3 time of extubation and 18h after surgery, and increased cortisol concentrations noted up to 1
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5 week after surgery. Studies included in the current systematic review were highly
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7 heterogeneous in terms of patient selection, surgical and anaesthetic techniques, peri-
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9 operative care and methodological aspects – all these factors can affect the cortisol stress
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11 response to surgery (**Supplementary Table 6**).⁹²⁻⁹⁸ Recently, Khoo B., et al.⁹⁹ reported on
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13 the peri-operative cortisol response after stratifying surgical procedures according to the
14
15 POSSUM scoring system¹⁰⁰ and observed a positive correlation of cortisol peak to the
16
17 invasiveness of the surgical procedure.⁹⁹ We believe that several elements can account for the
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19 differences compared to the results of our systematic review, including (i) a different
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21 classification system, (ii) difference in demographics, and (iii) the difference in procedures.
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25 Studies published before 1990 suggested that serum cortisol during major surgery
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27 rises rapidly but usually returns to baseline values within 24-48-h.⁷ Our data, on the contrary,
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29 show that mean cortisol can remain higher than baseline measurements for a longer duration,
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31 up to POD-7. For example, the study by Naito Y., et al. (included in this systematic-review
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33 and meta-analysis) measured cortisol at 1-h intervals in patients undergoing elective upper
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35 abdominal surgery up to POD-7 and showed that cortisol levels remained elevated for more
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37 than 3 days after surgery, with a loss of the circadian rhythm.²³ However, it is important to
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39 highlight that our results regarding the cortisol response after POD-3 derive only from a
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41 limited number of studies with small sample sizes.
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45 Our data show that older subjects tend to have a higher peri-operative cortisol
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47 response. This can partly be explained by the fact that these patients (i) can have multiple
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49 comorbidities and a poorer pre-operative performance status, (ii) have a higher risk of post-
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51 operative complications and (iii) often require non-elective surgery. In addition, some age-
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53 related physiological changes of the HPA axis should be taken into account. In fact, older,
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55 non-stressed patients show a flattened circadian cortisol rhythm, and are likely to have higher
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3 cortisol values in comparison to younger controls.¹⁰¹ A further confounding factor is that
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5 cortisol measurements might underestimate the actual cortisol production in older patients. In
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7 fact, some authors observed a reduction of cortisol-binding globulin (CBG) with age,
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9 especially in males,¹⁰² although this has not been confirmed by others.¹⁰³ Further studies are
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11 needed to investigate which mechanisms actually affect the age-related cortisol response
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13 induced by surgery. In fact, the number of older patients undergoing surgical procedures is
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15 increasing over recent decades, and higher post-operative cortisol values in the older patient
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17 population with an increased risk of complications (e.g. cognitive dysfunction).^{65,83} This may
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19 also have a bearing when considering glucocorticoid stress supplementation in older
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21 hypoadrenal patients undergoing surgery.
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25 Laparoscopic surgery triggers a less robust acute phase and immune response in
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27 comparison to open procedures, and is also associated with a reduction of post-operative pain
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29 and hospital stay.¹⁰⁴⁻¹⁰⁷ Our data on the cortisol response from abdominal and pelvic
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31 laparoscopic procedures are in line with these observations, although large-scale, prospective
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33 studies are lacking. Similarly, our results regarding the effects of etomidate on the post-
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35 operative cortisol response are based on a quite disproportionate comparison of only 8 studies
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37 in comparison to 38 studies without etomidate. Moreover, the regimens and doses of
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39 etomidate used throughout the studies varied considerably, and inhibition of the major
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41 cortisol biosynthesis enzyme CYP11B1 by cortisol will invariably result in accumulation of
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43 11-deoxycortisol, which can cross-react with cortisol immunoassays, leading to 'falsely'
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45 elevated cortisol values.¹⁰⁸ These factors may explain why we did not observe the well-
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47 known inhibitory effect of etomidate on cortisol production.¹⁰⁹ Our data obtained from 3
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49 prospective randomized studies, show that regional anaesthetic techniques are associated with
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51 a 17% lower cortisol response than that of general anaesthesia over the first 24-h. Epidural
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53 anaesthesia techniques (especially when performed below the umbilicus) can lead to blunted
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3 cortisol responses after surgery, in comparison to general anaesthesia. This effect seems more
4 prominent when epidural anaesthetics are used instead of epidural opioids, probably because
5 the first affect both sensory and sympathetic afferent stimuli, whereas opioids act on
6 nociceptive pathways only.¹¹⁰
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11 A limitation of this systematic review and meta-analysis is that serum cortisol has
12 been measured with different assays. Immunoassays are known to have different degrees of
13 cross-reactivity to endogenous and exogenous steroids other than cortisol,^{108,111,112} and this
14 cross-reactivity can be exacerbated during stress, as the HPA axis activation leads to
15 increased output of cortisol and its precursors.¹¹³ Moreover, inter-assay and inter-laboratory
16 variability of serum cortisol measurements in patients with septic shock can be substantial for
17 both immunoassays and LC-MS/MS-based techniques.¹¹⁴ If we refer to cortisol
18 measurements through LC-MS/MS as the 'gold standard', our results confirm that
19 immunoassays lead to an over-estimation of cortisol after surgery. However, data from LC-
20 MS/MS are very limited (only 2 studies from the same study group) and no cortisol
21 measurements are available during or immediately after surgery, when the cortisol response
22 is at its highest and the disagreement between LC-MS/MS and immunoassays is expected to
23 be more apparent.¹¹⁵
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40 Another limitation is that we could only compile data on total cortisol. In healthy subjects,
41 95% of serum cortisol is protein-bound, primarily to CBG and secondarily to albumin.¹¹⁶
42 Five percent of serum cortisol is free (not protein-bound) and this is its bioactive form.¹¹⁷
43 Several authors have observed a drop of CBG after surgery (up to 23-44% compared to
44 baseline).^{57,71,99} This drop correlates with the severity of surgery,⁹⁹ and can be interpreted as
45 an adaptive mechanism to increase the delivery of bioactive cortisol to target tissues.¹¹⁸ The
46 direct measurement of free cortisol is cumbersome and not routinely available in clinical
47 settings, moreover, formulas to indirectly calculate unbound cortisol from total cortisol and
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3 CBG values have been proven to be inaccurate after surgery, because of the effects of post-
4 operative hypoalbuminaemia and haemodilution.^{8,46,119} Notably, the drop of albumin can be
5 substantial after CABG.⁷¹ The unavailability of free cortisol measurements in the included
6 studies could have affected some of our observations. First, we did not observe a stratification
7 of the total cortisol stress response between grade II and III surgical procedures – the high
8 prevalence of CABG among grade III surgery (and thus the confounding effect of
9 haemodilution, hypoalbuminaemia and CBG drop) may partially explain this. Moreover,
10 studies including predominantly male patients mainly report total cortisol measurements from
11 grade III procedures (CABG in most of the cases), and this may account for the differences
12 that we observed among men and women.
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24 **There is general agreement that the daily dose of glucocorticoids needs to be**
25 **increased in patients with adrenal insufficiency undergoing surgery to prevent adrenal**
26 **crisis, and that hydrocortisone is the treatment of choice.^{5,120} Nonetheless, no**
27 **randomized controlled studies have assessed the precise glucocorticoid dose**
28 **requirements in these patients and no consensus exists regarding the optimal**
29 **management of perioperative glucocorticoid therapy. The perioperative glucocorticoid**
30 **requirements detailed in the recent Endocrine Society guideline on diagnosis and**
31 **treatment of primary adrenal insufficiency rely only on the severity of the surgical**
32 **stress.¹²⁰ The guideline recommends hydrocortisone 25-75mg/24h in adults for 1 to 2**
33 **days after minor to moderate surgery and intravenous bolus of 100mg hydrocortisone**
34 **followed by continuous infusion of 200mg/24h on the day of major surgery, to be**
35 **tapered rapidly switching to oral regimen depending on clinical state.¹²⁰ The results of**
36 **this systematic review and meta-analysis suggest that other factors should be taken into**
37 **account in addition to the magnitude of the surgical stress when deciding for the**
38 **perioperative steroid coverage. According to the serum cortisol response, older subjects,**
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3 **women and patients undergoing open surgery and general anaesthesia may require**
4 **higher doses of hydrocortisone. Moreover, extra steroid coverage might be required at**
5 **least up to one week following moderately to highly invasive procedures.**
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10 11 **CONCLUSIONS**

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13 This systematic review and meta-analysis of the modern literature of cortisol response
14 during surgery demonstrated significant differences of cortisol response in relation to the
15 grade of surgery, with significantly higher cortisol response to grade II and III than to grade I
16 surgery. We found that increased cortisol secretion continues up to the post-operative day 7
17 after surgery and is affected by age, sex and invasiveness of the surgical or anaesthetic
18 technique. Current evidence stems from highly heterogeneous studies of mostly moderate
19 quality. Of note, only two of 71 included studies have used LC-MS/MS, which, however, is
20 now considered state-of-the-art for the measurement of cortisol.¹²¹ Large prospective studies,
21 entailing rigorous patient selection, stratification, and standardized outcome measurement by
22 LC-MS/MS are needed to clarify how the adrenal gland responds to surgery and which
23 factors shape this response. Such data would help to inform and tailor the current guidelines
24 on glucocorticoid stress dose cover in hypoadrenal patients undergoing surgery.
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41 **DECLARATION OF CONFLICT OF INTEREST**

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43 The authors have stated explicitly that there are no conflicts of interest in connection with this
44 article.
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REFERENCES

1. Finnerty CC, Mabvuure NT, Ali A, Kozar RA, Herndon DN. The surgically induced stress response. *JPEN J Parenter Enteral Nutr.* Sep 2013;37(5 Suppl):21S-29S.
2. Desborough JP. The stress response to trauma and surgery. *Br J Anaesth.* Jul 2000;85(1):109-117.
3. Charmandari E, Nicolaides NC, Chrousos GP. Adrenal insufficiency. *Lancet.* Jun 21 2014;383(9935):2152-2167.
4. Broersen LH, Pereira AM, Jorgensen JO, Dekkers OM. Adrenal Insufficiency in Corticosteroids Use: Systematic Review and Meta-Analysis. *J Clin Endocrinol Metab.* Jun 2015;100(6):2171-2180.
5. Liu MM, Reidy AB, Saatee S, Collard CD. Perioperative Steroid Management: Approaches Based on Current Evidence. *Anesthesiology.* Jul 2017;127(1):166-172.
6. Chernow B, Alexander HR, Smallridge RC, et al. Hormonal responses to graded surgical stress. *Arch Intern Med.* Jul 1987;147(7):1273-1278.
7. Lamberts SW, Bruining HA, de Jong FH. Corticosteroid therapy in severe illness. *N Engl J Med.* Oct 30 1997;337(18):1285-1292.
8. Arafah BM. Hypothalamic pituitary adrenal function during critical illness: limitations of current assessment methods. *J Clin Endocrinol Metab.* Oct 2006;91(10):3725-3745.
9. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol.* Oct 2009;62(10):1006-1012.
10. Arlt W. The approach to the adult with newly diagnosed adrenal insufficiency. *J Clin Endocrinol Metab.* Apr 2009;94(4):1059-1067.

- 1
2
3 11. DistillerSR online platform, Evidence Partners [website].
4
5 <https://www.evidencepartners.com/products/distillersr-systematic-review-software/>.
6
7 Accessed June 22, 2018.
8
- 9 12. Donati A, Ruzzi M, Adrario E, et al. A new and feasible model for predicting
10 operative risk. *Br J Anaesth*. Sep 2004;93(3):393-399.
11
- 12 13. Murad MH, Sultan S, Haffar S, Bazerbachi F. Methodological quality and synthesis
13 of case series and case reports. *BMJ evidence-based medicine*. Apr 2018;23(2):60-63.
14
- 15 14. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. Sep
16 1986;7(3):177-188.
17
- 18 15. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*.
19 Jun 15 2002;21(11):1539-1558.
20
- 21 16. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-
22 analyses. *BMJ*. Sep 06 2003;327(7414):557-560.
23
- 24 17. Debono M, Ghobadi C, Rostami-Hodjegan A, et al. Modified-release hydrocortisone
25 to provide circadian cortisol profiles. *J Clin Endocrinol Metab*. May
26 2009;94(5):1548-1554.
27
- 28 18. Darzy KH, Shalet SM. Absence of adrenocorticotropin (ACTH) neurosecretory
29 dysfunction but increased cortisol concentrations and production rates in ACTH-
30 replete adult cancer survivors after cranial irradiation for nonpituitary brain tumors. *J*
31 *Clin Endocrinol Metab*. Sep 2005;90(9):5217-5225.
32
- 33 19. Høgevoid HE, Mundal HH, Norman N, Reikerås O. Platelet release reaction and
34 plasma catecholamines during total hip replacement. No effects of high doses of
35 corticosteroids. *Thromb Res*. Jan 01 1990;57(1):21-29.
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 20. Bartalena L, Martino E, Brandi LS, et al. Lack of nocturnal serum thyrotropin surge
4 after surgery. *The Journal of clinical endocrinology and metabolism*. Jan
5 1990;70(1):293-296.
6
7
8
9 21. Hosokawa T, Hori Y, Hashimoto T, Nakagawa H, Miyazaki M. Interaction between
10 immunological change and serum cortisol concentration in patients undergoing major
11 and minor surgery. *Endocrine response to anesthesia and intensive care: proceedings*
12 *of the 4th International Symposium on Endocrinology in Anesthesia and Surgery,*
13 *Osaka, 14-15 September 1989*. Vol 893: Elsevier Science Publishers B. V.
14 (Biomedical Division); 1990:157-163.
15
16
17
18
19
20
21
22 22. Bickel U, Wiegand-Löhnert C, Fleischmann JW, et al. Different modulation of the
23 perioperative stress hormone response under neurolept-anaesthesia or enflurane for
24 cholecystectomy. *Horm Metab Res*. Apr 1991;23(4):178-184.
25
26
27
28
29 23. Naito Y, Fukata J, Tamai S, et al. Biphasic changes in hypothalamo-pituitary-adrenal
30 function during the early recovery period after major abdominal surgery. *J Clin*
31 *Endocrinol Metab*. Jul 1991;73(1):111-117.
32
33
34
35 24. Juma AH, Ardawi MS, Baksh TM, Serafi AA. Alterations in thyroid hormones,
36 cortisol, and catecholamine concentration in patients after orthopedic surgery. *J Surg*
37 *Res*. Feb 1991;50(2):129-134.
38
39
40
41
42 25. Harris MJ, Baker RT, McRoberts JW, Mohler JL. The adrenal response to trauma,
43 operation and cosyntropin stimulation. *Surg Gynecol Obstet*. Jun 1990;170(6):513-
44 516.
45
46
47
48 26. Donald RA, Perry EG, Wittert GA, et al. The plasma ACTH, AVP, CRH and
49 catecholamine responses to conventional and laparoscopic cholecystectomy. *Clin*
50 *Endocrinol (Oxf)*. Jun 1993;38(6):609-615.
51
52
53
54
55
56
57
58
59
60

- 1
2
3 27. McMahon AJ, O'Dwyer PJ, Cruikshank AM, et al. Comparison of metabolic
4 responses to laparoscopic and minilaparotomy cholecystectomy. *Br J Surg*. Oct
5 1993;80(10):1255-1258.
6
7
- 8
9 28. Deuss U, Dietrich J, Kaulen D, et al. The stress response to laparoscopic
10 cholecystectomy: investigation of endocrine parameters. *Endoscopy*. Feb
11 1994;26(2):235-238.
12
13
- 14
15 29. Crozier TA, Müller JE, Quittkat D, Sydow M, Wuttke W, Kettler D. Effect of
16 anaesthesia on the cytokine responses to abdominal surgery. *Br J Anaesth*. Mar
17 1994;72(3):280-285.
18
19
- 20
21 30. Jakeways MS, Mitchell V, Hashim IA, et al. Metabolic and inflammatory responses
22 after open or laparoscopic cholecystectomy. *Br J Surg*. Jan 1994;81(1):127-131.
23
24
- 25
26 31. Dionigi R, Dominioni L, Benevento A, et al. Effects of surgical trauma of
27 laparoscopic vs. open cholecystectomy. *Hepatogastroenterology*. Oct
28 1994;41(5):471-476.
29
30
- 31
32 32. Frank SM, Higgins MS, Breslow MJ, et al. The catecholamine, cortisol, and
33 hemodynamic responses to mild perioperative hypothermia. A randomized clinical
34 trial. *Anesthesiology*. Jan 1995;82(1):83-93.
35
36
- 37
38 33. Ellström M, Bengtsson A, Tylman M, Haeger M, Olsson JH, Hahlin M. Evaluation of
39 tissue trauma after laparoscopic and abdominal hysterectomy: measurements of
40 neutrophil activation and release of interleukin-6, cortisol, and C-reactive protein. *J*
41 *Am Coll Surg*. May 1996;182(5):423-430.
42
43
- 44
45 34. Jameson P, Desborough JP, Bryant AE, Hall GM. The effect of cortisol suppression
46 on interleukin-6 and white blood cell responses to surgery. *Acta Anaesthesiol Scand*.
47 Feb 1997;41(2):304-308.
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 35. Karayiannakis AJ, Makri GG, Mantzioka A, Karousos D, Karatzas G. Systemic stress
4 response after laparoscopic or open cholecystectomy: a randomized trial. *Br J Surg.*
5 Apr 1997;84(4):467-471.
6
7
8
9 36. Roth-Isigkeit AK, Schmucker P. Postoperative dissociation of blood levels of cortisol
10 and adrenocorticotropin after coronary artery bypass grafting surgery. *Steroids.* Nov
11 1997;62(11):695-699.
12
13
14
15 37. Stratton RJ, Dewit O, Crowe E, Jennings G, Villar RN, Elia M. Plasma leptin, energy
16 intake and hunger following total hip replacement surgery. *Clin Sci (Lond).* Aug
17 1997;93(2):113-117.
18
19
20
21
22 38. Plunkett JJ, Reeves JD, Ngo L, et al. Urine and plasma catecholamine and cortisol
23 concentrations after myocardial revascularization. Modulation by continuous
24 sedation. Multicenter Study of Perioperative Ischemia (McSPI) Research Group, and
25 the Ischemia Research and Education Foundation (IREF). *Anesthesiology.* Apr
26 1997;86(4):785-796.
27
28
29
30
31
32
33 39. Eriksson-Mjöberg M, Olund A, Carlström K. Hormonal patterns in postmenopausal
34 women during gynecological surgery. *Gynecol Obstet Invest.* 1997;43(1):41-46.
35
36
37 40. Bellón JM, Manzano L, Larrad A, Honduvilla GN, Bujan J, Alvarez-Mon M.
38 Endocrine and immune response to injury after open and laparoscopic
39 cholecystectomy. *Int Surg.* Jan-Mar 1998;83(1):24-27.
40
41
42
43
44 41. Engin A, Bozkurt BS, Ersoy E, Oguz M, Gökçora N. Stress hyperglycemia in
45 minimally invasive surgery. *Surg Laparosc Endosc.* Dec 1998;8(6):435-437.
46
47
48 42. Yamauchi H, Kobayashi E, Yoshida T, et al. Changes in immune-endocrine response
49 after surgery. *Cytokine.* Jul 1998;10(7):549-554.
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 43. Delogu G, Famularo G, Luzzi S, et al. General anesthesia mode does not influence
4
5 endocrine or immunologic profile after open or laparoscopic cholecystectomy. *Surg*
6
7 *Laparosc Endosc Percutan Tech.* Oct 1999;9(5):326-332.
8
- 9 44. Friedrich M, Rixecker D, Friedrich G. Evaluation of stress-related hormones after
10
11 surgery. *Clin Exp Obstet Gynecol.* 1999;26(2):71-75.
12
- 13 45. Vogeser M, Felbinger TW, Röhl W, Jacob K. Cortisol metabolism in the postoperative
14
15 period after cardiac surgery. *Exp Clin Endocrinol Diabetes.* 1999;107(8):539-546.
16
17
- 18 46. Roth-Isigkeit AK, Dibbelt L, Schmucker P. Blood levels of corticosteroid-binding
19
20 globulin, total cortisol and unbound cortisol in patients undergoing coronary artery
21
22 bypass grafting surgery with cardiopulmonary bypass. *Steroids.* Sep 2000;65(9):513-
23
24 520.
25
- 26 47. Schricker T, Carli F, Schreiber M, et al. Propofol/sufentanil anesthesia suppresses the
27
28 metabolic and endocrine response during, not after, lower abdominal surgery. *Anesth*
29
30 *Analg.* Feb 2000;90(2):450-455.
31
32
- 33 48. Cho YM, Kim SY, Cho BY, Lee HK, Yang HK, Lee KU. Dissociation between
34
35 plasma adrenocorticotropin and serum cortisol level during the early postoperative
36
37 period after gastrectomy. *Horm Res.* 2000;53(5):246-250.
38
- 39 49. Ogata M, Okamoto K, Kohriyama K, Kawasaki T, Itoh H, Shigematsu A. Role of
40
41 interleukin-10 on hyporesponsiveness of endotoxin during surgery. *Crit Care Med.*
42
43 Sep 2000;28(9):3166-3170.
44
45
- 46 50. Mahla E, Tiesenhausen K, Rehak P, Fruhwald S, Pürstner P, Metzler H. Perioperative
47
48 myocardial cell injury: the relationship between troponin T and cortisol. *J Clin*
49
50 *Anesth.* May 2000;12(3):208-212.
51
52
53
54
55
56
57
58
59
60

- 1
2
3 51. Nguyen NT, Goldman CD, Ho HS, Gosselin RC, Singh A, Wolfe BM. Systemic
4 stress response after laparoscopic and open gastric bypass. *J Am Coll Surg*. May
5 2002;194(5):557-566; discussion 566-557.
6
7
8
9 52. Ozarda İlçöl Y, Ozyurt G, Kilicturgay S, Uncu G, Ulus IH. The decline in serum
10 choline concentration in humans during and after surgery is associated with the
11 elevation of cortisol, adrenocorticotrophic hormone, prolactin and beta-endorphin
12 concentrations. *Neurosci Lett*. May 10 2002;324(1):41-44.
13
14
15
16
17 53. Holub Z, Jabor A, Šprongl L, Kliment L, Fischlová D, Urbánek Š. Surgically induced
18 hormonal, metabolic and inflammatory changes in laparoscopic hysterectomy: a
19 comparison with abdominal hysterectomy. *Gynaecological Endoscopy*. 2002;11:299-
20 304.
21
22
23
24
25
26 54. Marana E, Annetta MG, Meo F, et al. Sevoflurane improves the neuroendocrine stress
27 response during laparoscopic pelvic surgery. *Can J Anaesth*. Apr 2003;50(4):348-354.
28
29
30
31 55. Vogeser M, Groetzner J, Küpper C, Briegel J. Free serum cortisol during the
32 postoperative acute phase response determined by equilibrium dialysis liquid
33 chromatography-tandem mass spectrometry. *Clin Chem Lab Med*. Feb
34 2003;41(2):146-151.
35
36
37
38
39 56. Vogeser M, Groetzner J, Küpper C, Briegel J. The serum cortisol:cortisone ratio in
40 the postoperative acute-phase response. *Horm Res*. 2003;59(6):293-296.
41
42
43
44 57. le Roux CW, Chapman GA, Kong WM, Dhillon WS, Jones J, Alaghband-Zadeh J.
45 Free cortisol index is better than serum total cortisol in determining hypothalamic-
46 pituitary-adrenal status in patients undergoing surgery. *The Journal of clinical*
47 *endocrinology and metabolism*. May 2003;88(5):2045-2048.
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 58. Lattermann R, Carli F, Wykes L, Schricker T. Perioperative glucose infusion and the
4 catabolic response to surgery: the effect of epidural block. *Anesth Analg*. Feb
5 2003;96(2):555-562, table of contents.
6
7
8
9 59. Shahbazi S, Talei A, Besharati A, Shamsnia SJ. Comparison of serum cortisol level in
10 open heart surgery--morphine versus sufentanil. *Middle East J Anaesthesiol*. Jun
11 2004;17(5):969-974.
12
13
14
15 60. Maciejczyk-Pencula M, Polak G, Kotarski J. Serum cortisol and acute phase protein
16 concentrations after hysterectomy with and without peritoneal sutures. *Eur J Obstet*
17 *Gynecol Reprod Biol*. Apr 15 2004;113(2):240-244.
18
19
20
21
22 61. Haque Z, Rahman M, Siddique MA, et al. Metabolic and stress responses of the body
23 to trauma: produced by the laparoscopic and open cholecystectomy. *Mymensingh Med*
24 *J*. Jan 2004;13(1):48-52.
25
26
27
28 62. Ledowski T, Bein B, Hanss R, et al. Neuroendocrine stress response and heart rate
29 variability: a comparison of total intravenous versus balanced anesthesia. *Anesth*
30 *Analg*. Dec 2005;101(6):1700-1705.
31
32
33
34
35 63. Crema E, Ribeiro EN, Hial AM, Alves Júnior JT, Pastore R, Silva AA. Evaluation of
36 the response of cortisol, corticotropin and blood platelets kinetics after laparoscopic
37 and open cholecystectomy. *Acta Cir Bras*. Sep-Oct 2005;20(5):364-367.
38
39
40
41 64. Yeager MP, Rassias AJ, Fillinger MP, et al. Cortisol antiinflammatory effects are
42 maximal at postoperative plasma concentrations. *Crit Care Med*. Jul
43 2005;33(7):1507-1512.
44
45
46
47 65. Kudoh A, Takase H, Katagai H, Takazawa T. Postoperative interleukin-6 and cortisol
48 concentrations in elderly patients with postoperative confusion.
49 *Neuroimmunomodulation*. 2005;12(1):60-66.
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 66. Nicholson G, Woodfine J, Bryant AE, et al. The hormonal and inflammatory
4 responses to pelvic reconstructive surgery following major trauma. *Injury*. Feb
5 2005;36(2):303-309.
6
7
8
9 67. Rahr HB, Bendix J, Ahlburg P, Gjedsted J, Funch-Jensen P, Tonnesen E.
10 Coagulation, inflammatory, and stress responses in a randomized comparison of open
11 and laparoscopic repair of recurrent inguinal hernia. *Surg Endosc*. Mar
12 2006;20(3):468-472.
13
14
15
16
17 68. Buyukkocak U, Daphan C, Caglayan O, et al. Effects of different anesthetic
18 techniques on serum leptin, C-reactive protein, and cortisol concentrations in
19 anorectal surgery. *Croat Med J*. Dec 2006;47(6):862-868.
20
21
22
23
24 69. Kashiwabara M, Miyashita M, Nomura T, et al. Surgical trauma-induced adrenal
25 insufficiency is associated with postoperative inflammatory responses. *J Nippon Med*
26 *Sch*. Aug 2007;74(4):274-283.
27
28
29
30
31 70. Baričević I, Jones DR, Đorđević B, Malenković V, Nedić O. Differential influence of
32 open surgery and sepsis on the circulating insulin-like growth factors and their
33 binding proteins as representative metabolic markers. *Clin Biochem*. Oct
34 2007;40(15):1122-1128.
35
36
37
38
39 71. Christ-Crain M, Jutla S, Widmer I, et al. Measurement of serum free cortisol shows
40 discordant responsivity to stress and dynamic evaluation. *The Journal of clinical*
41 *endocrinology and metabolism*. May 2007;92(5):1729-1735.
42
43
44
45
46 72. Rapp-Kesek D, Stridsberg M, Andersson LG, Berne C, Karlsson T. Insulin resistance
47 after cardiopulmonary bypass in the elderly patient. *Scand Cardiovasc J*. Apr
48 2007;41(2):102-108.
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 73. Spratt DI, Kramer RS, Morton JR, Lucas FL, Becker K, Longcope C.
4
5 Characterization of a prospective human model for study of the reproductive hormone
6
7 responses to major illness. *Am J Physiol Endocrinol Metab.* Jul 2008;295(1):E63-69.
8
- 9 74. Mujagić Z, Čičko E, Vegar-Brozović V, Prašo M. Serum levels of cortisol and
10
11 prolactin in patients treated under total intravenous anesthesia with propofol-fentanyl
12
13 and under balanced anesthesia with isoflurane-fentanyl. *Cent Eur J Med.*
14
15 2008;3(4):459-463.
16
- 17 75. Bender Ö, Balci FL, Yüney E, Sağlam F, Özdenkaya Y, Sari YS. Systemic
18
19 inflammatory response after Kugel versus laparoscopic groin hernia repair: a
20
21 prospective randomized trial. *Surg Endosc.* Dec 2009;23(12):2657-2661.
22
23
- 24 76. Kim TK, Yoon JR. Comparison of the neuroendocrine and inflammatory responses
25
26 after laparoscopic and abdominal hysterectomy. *Korean J Anesthesiol.* Oct
27
28 2010;59(4):265-269.
29
- 30 77. Mu DL, Wang DX, Li LH, et al. High serum cortisol level is associated with
31
32 increased risk of delirium after coronary artery bypass graft surgery: a prospective
33
34 cohort study. *Crit Care.* 2010;14(6):R238.
35
36
- 37 78. Engin AB, Engin A, Sepici-Dincel A. Influence of surgical trauma on neopterin
38
39 concentrations in gastric carcinoma patients. *Tumori.* Jul-Aug 2010;96(4):589-593.
40
- 41 79. Celic-Spuzic E. Effect of anesthesia on the changes in the hormones levels during and
42
43 after transvesical prostatectomy. *Med Arh.* 2011;65(6):348-353.
44
45
- 46 80. Mello RC, Sad EF, Andrade BC, et al. Serum and salivary cortisol in the diagnosis of
47
48 adrenal insufficiency and as a predictor of the outcome in patients with severe sepsis.
49
50 *Arq Bras Endocrinol Metabol.* Oct 2011;55(7):455-459.
51
52
53
54
55
56
57
58
59
60

- 1
2
3 81. Debono M, Sheppard L, Irving S, et al. Assessing adrenal status in patients before and
4 immediately after coronary artery bypass graft surgery. *Eur J Endocrinol*. Mar
5 2011;164(3):413-419.
6
7
8
9 82. Adas G, Kemik A, Adas M, et al. Metabolic and inflammatory responses after ERCP.
10 *Int J Biomed Sci*. Dec 2013;9(4):237-242.
11
12
13 83. Mu DL, Li LH, Wang DX, et al. High postoperative serum cortisol level is associated
14 with increased risk of cognitive dysfunction early after coronary artery bypass graft
15 surgery: a prospective cohort study. *PLoS One*. 2013;8(10):e77637.
16
17
18
19 84. Ferreira CG, Tenório SB. Subarachnoid clonidine and trauma response in cardiac
20 surgery with cardiopulmonary bypass. *Rev Bras Anesthesiol*. Nov-Dec 2014;64(6):395-
21 399.
22
23
24
25 85. Kahveci K, Ornek D, Doger C, et al. The effect of anesthesia type on stress hormone
26 response: comparison of general versus epidural anesthesia. *Niger J Clin Pract*. Jul-
27 Aug 2014;17(4):523-527.
28
29
30
31
32 86. Maas KW, Biere SS, van Hoogstraten IM, van der Peet DL, Cuesta MA.
33 Immunological changes after minimally invasive or conventional esophageal
34 resection for cancer: a randomized trial. *World J Surg*. Jan 2014;38(1):131-137.
35
36
37
38 87. Gu CY, Zhang J, Qian YN, Tang QF. Effects of epidural anesthesia and postoperative
39 epidural analgesia on immune function in esophageal carcinoma patients undergoing
40 thoracic surgery. *Mol Clin Oncol*. Jan 2015;3(1):190-196.
41
42
43
44 88. Lebherz C, Kahles F, Piotrowski K, et al. Interleukin-6 predicts inflammation-induced
45 increase of Glucagon-like peptide-1 in humans in response to cardiac surgery with
46 association to parameters of glucose metabolism. *Cardiovasc Diabetol*. Feb 03
47 2016;15:21.
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 89. Możański M, Tomaszewski D, Rybicki Z, Bejm J, Balkota M. Etomidate, but not
4 thiopental, decreases serum cortisol concentration in morbidly obese patients. A
5 randomized controlled trial. *Anaesthesiol Intensive Ther.* 2016;48(1):7-12.
6
7
8
9 90. Allolio B, Stuttmann R, Fischer H, Leonhard W, Winkelmann W. Long-term
10 etomidate and adrenocortical suppression. *Lancet.* Sep 10 1983;2(8350):626.
11
12
13 91. Fellows IW, Byrne AJ, Allison SP. Adrenocortical suppression with etomidate.
14 *Lancet.* Jul 2 1983;2(8340):54-55.
15
16
17 92. Bent JM, Paterson JL, Mashiter K, Hall GM. Effects of high-dose fentanyl
18 anaesthesia on the established metabolic and endocrine response to surgery.
19 *Anaesthesia.* Jan 1984;39(1):19-23.
20
21
22 93. Crozier TA, Beck D, Schlaeger M, Wuttke W, Kettler D. Endocrinological changes
23 following etomidate, midazolam, or methohexital for minor surgery. *Anesthesiology.*
24 May 1987;66(5):628-635.
25
26
27 94. Giesecke K, Hamberger B, Jarnberg PO, Klingstedt C, Persson B. High- and low-dose
28 fentanyl anaesthesia: hormonal and metabolic responses during cholecystectomy. *Br J*
29 *Anaesth.* Nov 1988;61(5):575-582.
30
31
32 95. Hall GM, Young C, Holdcroft A, Alaghband-Zadeh J. Substrate mobilisation during
33 surgery. A comparison between halothane and fentanyl anaesthesia. *Anaesthesia.*
34 Nov-Dec 1978;33(10):924-930.
35
36
37 96. Ilies C, Gruenewald M, Ludwigs J, et al. Evaluation of the surgical stress index during
38 spinal and general anaesthesia. *Br J Anaesth.* Oct 2010;105(4):533-537.
39
40
41 97. Lacoumenta S, Yeo TH, Burrin JM, Bloom SR, Paterson JL, Hall GM. Fentanyl and
42 the beta-endorphin, ACTH and glucoregulatory hormonal response to surgery. *Br J*
43 *Anaesth.* Jun 1987;59(6):713-720.
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 98. Nicholson G, Burrin JM, Hall GM. Peri-operative steroid supplementation.
4 *Anaesthesia*. Nov 1998;53(11):1091-1104.
5
6
7 99. Khoo B, Boshier PR, Freethy A, et al. Redefining the stress cortisol response to
8 surgery. *Clin Endocrinol (Oxf)*. Jul 31 2017.
9
10
11 100. Copeland GP. The POSSUM system of surgical audit. *Arch Surg*. Jan
12 2002;137(1):15-19.
13
14
15 101. Ferrari E, Cravello L, Muzzoni B, et al. Age-related changes of the hypothalamic-
16 pituitary-adrenal axis: pathophysiological correlates. *Eur J Endocrinol*. Apr
17 2001;144(4):319-329.
18
19
20 102. Kudielka BM, Buske-Kirschbaum A, Hellhammer DH, Kirschbaum C. HPA axis
21 responses to laboratory psychosocial stress in healthy elderly adults, younger adults,
22 and children: impact of age and gender. *Psychoneuroendocrinology*. Jan
23 2004;29(1):83-98.
24
25
26 103. Pavlov EP, Harman SM, Chrousos GP, Loriaux DL, Blackman MR. Responses of
27 plasma adrenocorticotropin, cortisol, and dehydroepiandrosterone to ovine
28 corticotropin-releasing hormone in healthy aging men. *J Clin Endocrinol Metab*. Apr
29 1986;62(4):767-772.
30
31
32 104. Buunen M, Gholghesaei M, Veldkamp R, Meijer DW, Bonjer HJ, Bouvy ND. Stress
33 response to laparoscopic surgery: a review. *Surg Endosc*. Jul 2004;18(7):1022-1028.
34
35
36 105. Sylla P, Kirman I, Whelan RL. Immunological advantages of advanced laparoscopy.
37 *Surg Clin North Am*. Feb 2005;85(1):1-18, vii.
38
39
40 106. Farrar MW, Hall GM. Neuroendocrine and inflammatory aspects of surgery: do they
41 affect outcome? *Eur J Anaesthesiol*. Nov 1998;15(6):736-739.
42
43
44 107. Hendolin HI, Paakonen ME, Alhava EM, Tarvainen R, Kempainen T, Lahtinen P.
45 Laparoscopic or open cholecystectomy: a prospective randomised trial to compare
46
47
48
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2
3 postoperative pain, pulmonary function, and stress response. *Eur J Surg*. May
4 2000;166(5):394-399.
5
6
7 108. Roberts RF, Roberts WL. Performance characteristics of five automated serum
8 cortisol immunoassays. *Clinical biochemistry*. Jun 2004;37(6):489-493.
9
10
11 109. Preda VA, Sen J, Karavitaki N, Grossman AB. Etomidate in the management of
12 hypercortisolaemia in Cushing's syndrome: a review. *Eur J Endocrinol*. Aug
13 2012;167(2):137-143.
14
15
16 110. Liu S, Carpenter RL, Neal JM. Epidural anesthesia and analgesia. Their role in
17 postoperative outcome. *Anesthesiology*. Jun 1995;82(6):1474-1506.
18
19
20
21 111. Diamandis EP. Immunoassay interference: a relatively rare but still important
22 problem. *Clinical biochemistry*. May 2004;37(5):331-332.
23
24
25 112. Minutti CZ, Lacey JM, Magera MJ, et al. Steroid profiling by tandem mass
26 spectrometry improves the positive predictive value of newborn screening for
27 congenital adrenal hyperplasia. *J Clin Endocrinol Metab*. Aug 2004;89(8):3687-3693.
28
29
30
31 113. Cohen J, Ward G, Prins J, Jones M, Venkatesh B. Variability of cortisol assays can
32 confound the diagnosis of adrenal insufficiency in the critically ill population.
33 *Intensive Care Med*. Nov 2006;32(11):1901-1905.
34
35
36
37 114. Briegel J, Sprung CL, Annane D, et al. Multicenter comparison of cortisol as
38 measured by different methods in samples of patients with septic shock. *Intensive*
39 *Care Med*. Dec 2009;35(12):2151-2156.
40
41
42
43 115. Tractenberg RE, Jonklaas J, Soldin SJ. Agreement of immunoassay and tandem mass
44 spectrometry in the analysis of cortisol and free t4: interpretation and implications for
45 clinicians. *Int J Anal Chem*. 2010;2010.
46
47
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49
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53
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2
3 116. Dunn JF, Nisula BC, Rodbard D. Transport of steroid hormones: binding of 21
4 endogenous steroids to both testosterone-binding globulin and corticosteroid-binding
5 globulin in human plasma. *J Clin Endocrinol Metab.* Jul 1981;53(1):58-68.
6
7
8
9 117. Venkatesh B, Cohen J, Cooper M. Ten false beliefs about cortisol in critically ill
10 patients. *Intensive Care Med.* Oct 2015;41(10):1817-1819.
11
12
13 118. Pugeat M, Bonneton A, Perrot D, et al. Decreased immunoreactivity and binding
14 activity of corticosteroid-binding globulin in serum in septic shock. *Clin Chem.* Aug
15 1989;35(8):1675-1679.
16
17
18
19 119. Hamrahian AH, Oseni TS, Arafah BM. Measurements of serum free cortisol in
20 critically ill patients. *N Engl J Med.* Apr 15 2004;350(16):1629-1638.
21
22
23
24 120. Bornstein SR, Allolio B, Arlt W, et al. Diagnosis and Treatment of Primary Adrenal
25 Insufficiency: An Endocrine Society Clinical Practice Guideline. *The Journal of*
26 *clinical endocrinology and metabolism.* Feb 2016;101(2):364-389.
27
28
29
30 121. Hawley JM, Owen LJ, Lockhart SJ, et al. Serum Cortisol: An Up-To-Date
31 Assessment of Routine Assay Performance. *Clin Chem.* Sep 2016;62(9):1220-1229.
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FIGURE LEGENDS

Figure 1 – PRISMA flow diagram.

Figure 2 – Total serum cortisol concentrations according to the grade of surgery. All values are expressed in nmol/L and are reported as means \pm 95% CI, obtained after meta-analysis of all included studies. The first value in each panel corresponds to baseline cortisol measurements before initiation of surgery. The cortisol measurement at time 0 corresponds to the initiation of surgery (Knife-To-Skin, KTS). **Panel A)** Comparison between the three grades of surgery over the first 24-h – the numbers 1 to 7 indicate the specific time points at which cortisol has been measured (1: baseline; 2: KTS; 3: during surgery; 4: end of surgery; 5: first 6h after surgery; 6: between 6 and 18h after surgery; 7: 24-h after surgery). **Panel B)** Cortisol response over the first 24-h, after combining the data of surgery grade II and III (n=67 studies). **Panel C)** Surgery grade I (n=4 studies). **Panel D)** Surgery grade II (n=41 studies). **Panel E)** Surgery grade III (n=22 studies). **Panel F)** Combined data of surgery grade II and III (n=67 studies).

Figure 3 – Impact of age, sex and mean duration of surgery on total serum cortisol up to 48h after surgery. All values are expressed in nmol/L and are reported as means \pm 95% CI, obtained after meta-analysis of all included studies. The first value in each panel corresponds to baseline cortisol measurements before initiation of surgery. The cortisol measurement at time 0 corresponds to the initiation of surgery. **Panel A)** Impact of patient age after combining data of surgery II and III – comparison between cohorts with a mean age of \leq 60 years (n=32 studies) or $>$ 60 years (n=21 studies). **Panel B)** Impact of gender after combining data of surgery II and III – comparison between cohorts including either $>$ 50% females (n=26

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3 studies) or >50% males (n=25 studies). **Panel C**) Impact of the mean duration of surgery
4 grade II – either ≤ 180 min (n=21 studies) or >180 min (n=4 studies). **Panel D**) Impact of the
5 mean duration of surgery grade III – either ≤ 180 min (n=2 studies) or >180 min (n=10
6 studies).
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13 **Figure 4** – Total serum cortisol measurements according to differences in the surgical
14 approach, anaesthetic techniques and four cortisol assays. All values are expressed in nmol/L
15 and are reported as means \pm 95% CI, obtained after meta-analysis of all included studies. The
16 first value in each panel corresponds to baseline cortisol measurements before initiation of
17 surgery. The cortisol measurement at time 0 corresponds to the initiation of surgery. **Panel A**)
18 Studies comparing laparotomy (n=24 studies) and laparoscopic techniques (n=18 studies).
19 **Panel B**) Studies either not using etomidate as an anaesthetic agent (n=38) or administering it
20 to >50% of the patients (n=8). **Panel C**) Studies comparing general and regional anaesthesia
21 (n=3). **Panel D**) Comparison of four cortisol assays (RIA, radioimmunoassay – n=33 studies;
22 ECLIA, electrochemiluminescence immunoassay – n=17 studies; ELISA, enzyme-linked
23 immunosorbent assays – n=6 studies; LC-MS/MS, liquid chromatography–tandem mass
24 spectrometry – n=2 studies).
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Table 1 – Included studies.

Author (year)	Country	Study type	Surgical procedure	Grade of surgery ^a	Population Sample size	Total cortisol assay
Høgevoid (1990) ¹⁹	Norway	Prospective, observational	Total hip replacement for osteoarthritis	II	7	RIA
Bartalena (1990) ²⁰	Italy	Prospective, observational	Surgery for breast cancer, non-functioning adrenal cancer, adenocarcinoma of the colon, lung cancer, urethral obstruction	II	10	RIA
Hosokawa (1990) ²¹	Japan	Prospective, observational	Minor surgeries (e.g. tympanoplasty) and major surgeries (cholecystectomy)	I, II	22	Double isotope dilution
Bickel (1991) ²²	Germany	Prospective, randomized	Elective cholecystectomy	II	26	RIA
Naito (1991) ²³	Japan	Prospective, observational	Elective upper abdominal surgery	II	15	RIA
Juma (1991) ²⁴	Saudi Arabia	Prospective, observational	Elective major orthopaedic surgery	II	16	RIA
Harris (1991) ²⁵	USA	Prospective, observational	Surgery for traumatic thoracic and/or abdominal injuries	III	10	RIA
Donald (1993) ²⁶	New Zealand	Prospective, interventional	Elective cholecystectomy	II	12	ELISA
McMahon (1993) ²⁷	UK	Prospective, randomized	Elective cholecystectomy	II	20	Fluorescent immunoassay
Deuss (1994) ²⁸	Germany	Prospective, observational	Elective cholecystectomy	II	65	ELISA
Crozier (1994) ²⁹	Germany	Prospective, randomized	Elective hysterectomy for non-malignant diseases	II	20	RIA
Jakeways (1994) ³⁰	UK	Prospective, non-randomized	Elective cholecystectomy	II	24	RIA
Dionigi (1994) ³¹	Italy	Prospective, randomized	Elective cholecystectomy	II	57	RIA
Frank (1995) ³²	USA	Prospective, randomized	Vascular, abdominal and thoracic surgery	II, III	74	RIA
Ellstrom (1996) ³³	Sweden	Prospective, randomized	Hysterectomy for benign disorders	II	24	Not reported
Jameson (1997) ³⁴	UK	Prospective, randomized	Hysterectomy	II	16	RIA
Karayiannakis (1997) ³⁵	Greece	Prospective, randomized	Elective cholecystectomy	II	83	RIA
Roth-Isigkeit (1997) ³⁶	Germany	Prospective, observational	Coronary artery bypass grafting surgery	III	50	RIA
Stratton (1997) ³⁷	UK	Prospective, observational	Total hip replacement for osteoarthritis	II	6	RIA
Plunkett (1997) ³⁸	USA	Prospective, randomized	Coronary artery bypass grafting surgery	III	121	Fluorescent immunoassay

Eriksson-Mjöberg (1997) ³⁹	Sweden	Prospective, randomized	Surgery for rectocele and cystocele	II	30	RIA
Bellón (1998) ⁴⁰	Spain	Prospective, observational	Elective cholecystectomy	II	28	RIA
Engin (1998) ⁴¹	Turkey	Prospective, randomized	Elective cholecystectomy	II	32	RIA
Yamauchi (1998) ⁴²	Japan	Prospective, observational	Laparoscopic cholecystectomy, modified radical-mastectomy, pulmonary lobectomy, thoracic oesophagectomy	II, III	24	IRMA
Delogu (1999) ⁴³	Italy	Prospective, observational	Elective cholecystectomy	II	46	RIA
Friedrich (1998) ⁴⁴	Germany	Prospective, observational	Surgery for either uterine leiomyomas, chronic pelvic discomfort or desire for definitive contraception	II	20	RIA
Vogeser (1999) ⁴⁵	Germany	Prospective, observational	Cardiac surgery	III	14	ECLIA
Roth-Isigkeit (2000) ⁴⁶	Germany	Prospective, observational	Coronary artery bypass grafting surgery	III	28	RIA
Schricker (2000) ⁴⁷	Germany	Prospective, randomized	Hysterectomy	II	20	RIA
Cho (2000) ⁴⁸	South Korea	Prospective, observational	Elective radical gastrectomy for gastric adenocarcinoma	II	31	RIA
Ogata (2000) ⁴⁹	Japan	Prospective, observational	Elective partial gastrectomy	II	16	RIA
Mahla (2000) ⁵⁰	Austria	Prospective, observational	Non-cardiac elective surgeries	II	67	ELISA
Nguyen (2002) ⁵¹	USA	Prospective, randomized	Gastric bypass	II	48	RIA
Ozarda İlçöl (2002) ⁵²	Turkey	Prospective, observational	Major abdominal or gynaecological surgery	II	16	ECLIA
Holub (2002) ⁵³	Czech Republic	Prospective, observational	Hysterectomy for benign or premalignant pelvic disorders	II	77	Fluorescent immunoassay
Marana (2003) ⁵⁴	Italy	Prospective, randomized	Ovarian cyst removal	II	20	RIA
Vogeser (2003) ⁵⁵	Germany	Prospective, observational	Coronary artery bypass grafting surgery	III	12	LC-MS/MS
Vogeser (2003) ⁵⁶	Germany	Prospective, observational	Coronary artery bypass grafting surgery	III	16	LC-MS/MS
le Roux (2003) ⁵⁷	UK	Prospective, observational	Major elective surgery	III	31	ELISA
Lattermann (2003) ⁵⁸	Canada	Prospective, randomized	Elective colorectal surgery	II	16	RIA
Shahbazi (2004) ⁵⁹	Iran	Prospective, interventional	Coronary artery bypass grafting surgery	III	30	RIA
Maciejczyk-Pencula (2004) ⁶⁰	Poland	Prospective, randomized	Hysterectomy for leiomyomas	II	49	ELISA
Haque (2004) ⁶¹	Bangladesh	Prospective, interventional	Elective cholecystectomy	II	30	Not reported
Ledowski (2005) ⁶²	Germany	Prospective, randomized	Minor elective ear-nose-throat surgery	I	43	ECLIA
Crema (2005) ⁶³	Brazil	Prospective, interventional	Elective cholecystectomy	II	31	ECLIA

Yeager (2005) ⁶⁴	USA	Prospective, randomized	Coronary artery bypass grafting surgery and/or cardiac valve replacement	III	20	RIA
Kudoh (2005) ⁶⁵	Japan	Prospective, observational	Abdominal surgery	II	115	Spectrophotometry
Nicholson (2005) ⁶⁶	UK	Prospective, observational	Pelvic and/or acetabular reconstruction surgery for extensive fractures	III	20	ELISA
Rahr (2006) ⁶⁷	Denmark	Prospective, randomized	Inguinal hernia repair	I	61	ECLIA
Buyukkocak (2006) ⁶⁸	Turkey	Prospective, randomized	Anorectal surgery for benign conditions	II	58	ECLIA
Kashiwabara (2007) ⁶⁹	Japan	Prospective, observational	Surgery of the digestive tract	I, II, III	50	IRMA
Baričević (2007) ⁷⁰	Serbia	Prospective, observational	Surgery for malignant gastric or pancreatic tumours	II	21	RIA
Christ-Crain (2007) ⁷¹	UK	Prospective, observational	Coronary artery bypass grafting surgery	III	24	ECLIA
Rapp-Kesek (2007) ⁷²	Sweden	Prospective, randomized	Coronary artery bypass grafting surgery	III	18	Fluorescent immunoassay
Spratt (2008) ⁷³	USA	Prospective, observational	Abdominal aortic aneurysm resection and coronary artery bypass grafting surgery	III	29	RIA
Mujagić (2008) ⁷⁴	Bosnia and Herzegovina, Croatia	Prospective, randomized	Low abdominal surgery (colon cancer, hysterectomy)	II	50	Fluorescent immunoassay
Bender (2009) ⁷⁵	Turkey	Prospective, randomized	Inguinal hernia repair	I	40	ECLIA
Kim (2010) ⁷⁶	South Korea	Prospective, randomized	Hysterectomy for non-malignant disease	II	24	RIA
Mu (2010) ⁷⁷	China	Prospective, observational	Coronary artery bypass grafting surgery	III	243	ECLIA
Engin (2010) ⁷⁸	Turkey	Prospective, observational	Elective abdominal surgery (for cholelithiasis, for gastroesophageal reflux or for gastric carcinoma)	II	106	ECLIA
Celic-Spuzic (2011) ⁷⁹	Bosnia and Herzegovina	Retrospective-prospective	Prostatectomy for benign conditions	III	100	RIA
Mello (2011) ⁸⁰	Brasil	Prospective, observational	Surgery requiring intensive care unit stay	III	20	ECLIA
Debono (2011) ⁸¹	UK	Prospective, observational	Coronary artery bypass grafting surgery	III	30	ECLIA
Adas (2013) ⁸²	Turkey	Prospective, observational	Endoscopic retrograde cholangiopancreatography for bile duct stones	I	50	Spectrophotometry
Mu (2013) ⁸³	China	Prospective, observational	Coronary artery bypass grafting surgery	III	166	ECLIA
Ferreira (2014) ⁸⁴	Brasil	Prospective, interventional	Cardiac surgery with cardiopulmonary bypass	III	27	Not reported

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Kahveci (2014) ⁸⁵	Turkey	Prospective, randomized	Lower extremity surgery	II	60	ECLIA
Maas (2014) ⁸⁶	The Netherlands	Prospective, randomized	Oesophagectomy for oesophageal carcinoma	III	27	ECLIA
Gu (2015) ⁸⁷	China	Prospective, randomized	Oesophagectomy for oesophageal carcinoma	III	57	RIA
Lebherz (2016) ⁸⁸	Germany	Prospective, observational	Cardiac surgery with cardiopulmonary bypass	III	22	ECLIA
Możański (2016) ⁸⁹	Poland	Prospective, randomized	Elective abdominal laparoscopic surgery	II	62	ECLIA
<p>^a Refer to Supplementary Table 2 for the classification of the surgical procedures. When a subgroup analysis could not be performed within the study cohort(s), the grade of surgery was assigned according to the most frequent surgical procedure(s).</p> <p>Abbreviations: ECLIA: electrochemiluminescence; ELISA: enzyme-linked immunosorbent assay; IRMA: immunoradiometric assay; LC-MS/MS: liquid chromatography-tandem mass spectrometry; RIA: radioimmunoassay.</p>						

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Table 2 – Areas under the curve (AUCs) for total cortisol values, divided by 24-h periods and by the grade of surgery.

		AUC 0-24h	AUC Day 1 post-op.	AUC Day 2 post-op.	AUC Day 3 post-op.	AUC Day 4 post-op.	AUC Day 5 post-op.	AUC Day 6 post-op.	AUC Day 7 post-op.
Surgery grade I	Absolute value (nmol*h/L)	9,541	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	%difference to surgical baseline ^a	+11%	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	%difference to a standard 24-h AUC ^b	+116%	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Surgery grade II	Absolute value (nmol*h/L)	18,066	13,152	13,032	13,272	13,320	12,972	10,980	10,392
	%difference to surgical baseline ^a	+102%	+47%	+46%	+48%	+49%	+45%	+23%	+16%
	%difference to a standard 24-h AUC ^b	+309%	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Surgery grade III	Absolute value (nmol*h/L)	16,010	14,904	12,636	11,820	n/a	n/a	13,056	n/a
	%difference to surgical baseline ^a	+77%	+65%	+40%	+31%	n/a	n/a	+44%	n/a
	%difference to a standard 24-h AUC ^b	+262%	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Surgery grade II+III (combined)	Absolute value (nmol*h/L)	17,567	13,812	12,864	12,528	12,972	12,360	12,348	12,372
	%difference to surgical baseline ^a	+95%	+53%	+43%	+39%	+44%	+37%	+37%	+37%
	%difference to a standard 24-h AUC ^b	+297%	n/a	n/a	n/a	n/a	n/a	n/a	n/a

During the first 24-h after surgery, multiple total cortisol measurements are available; therefore, the AUCs have been compared to a standard 24-h AUC for cortisol derived from the literature.^{17,18} From the first post-operative day onwards only measurements every 24-h are available, therefore the AUCs have been compared to AUCs calculated according to the baseline cortisol values.

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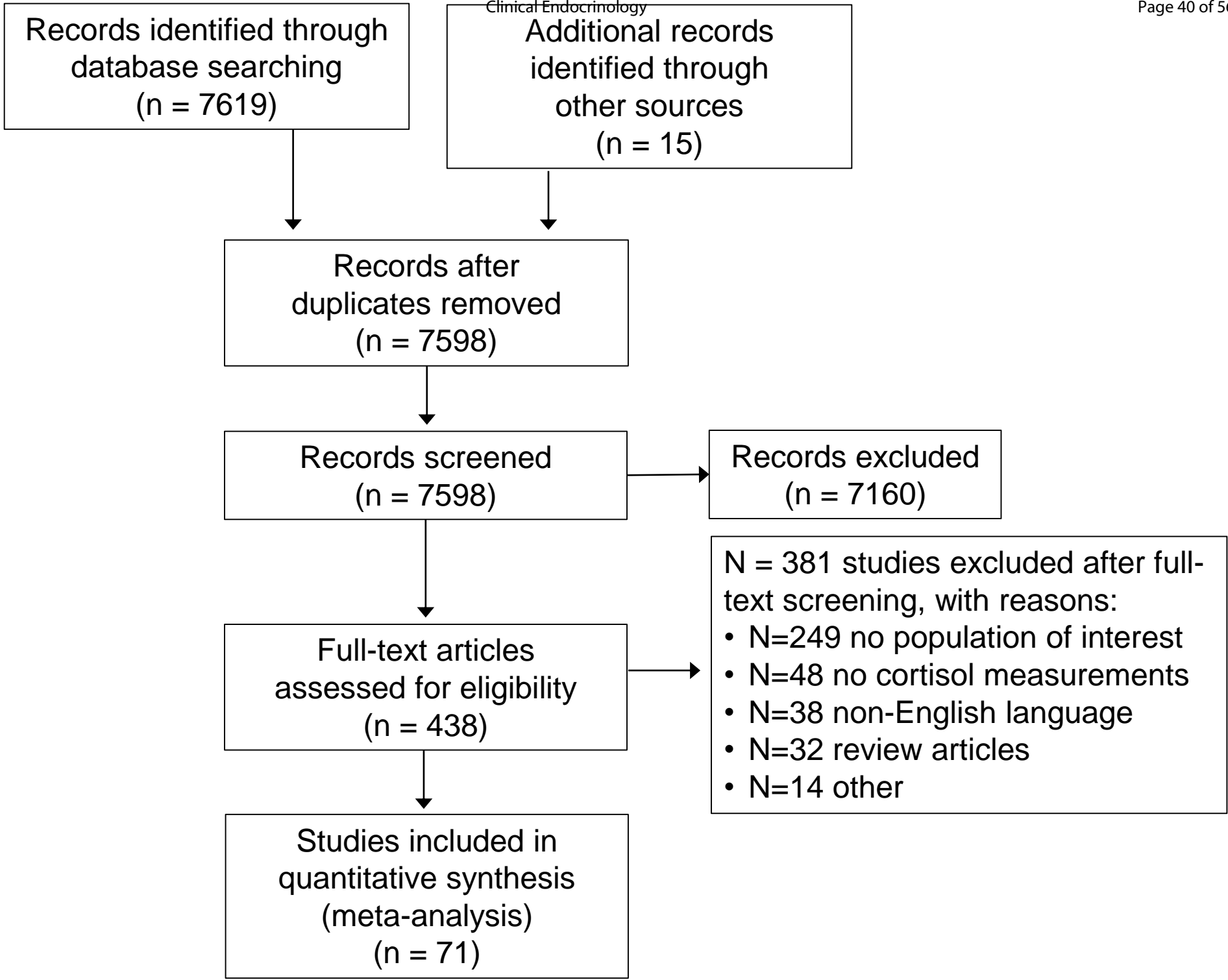
^a Percentage difference between the AUC and the pre-surgical AUC. The pre-operative AUC has been calculated by considering a 24-h period between two identical total cortisol values, derived from the baseline cortisol measurements (prior to the initiation of surgery). The calculated pre-operative AUCs for surgery grade I, II, III and II+III are 8,616 nmol*h/L, 8,952 nmol*h/L, 9,048 nmol*h/L, 9,000 nmol*h/L, respectively.

^b Percentage difference between the AUC and a standard 24-h AUC for cortisol obtained by 24-h cortisol profiling of 33 healthy adults (4,420 nmol*h/L).^{17,18}

Abbreviations: AUC: area under the curve for serum cortisol values; n/a: not available or not applicable.

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Identification

Screening

Eligibility

Included

Records identified through database searching (n = 7619)

Additional records identified through other sources (n = 15)

Records after duplicates removed (n = 7598)

Records screened (n = 7598)

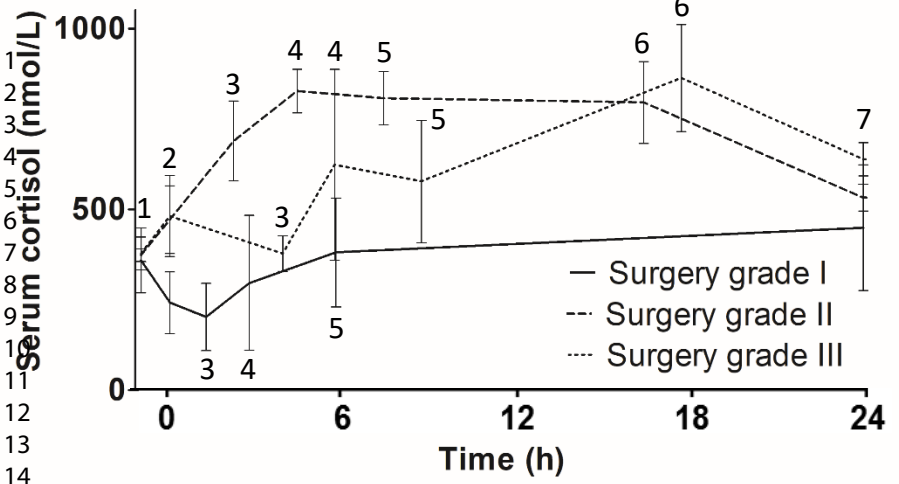
Records excluded (n = 7160)

Full-text articles assessed for eligibility (n = 438)

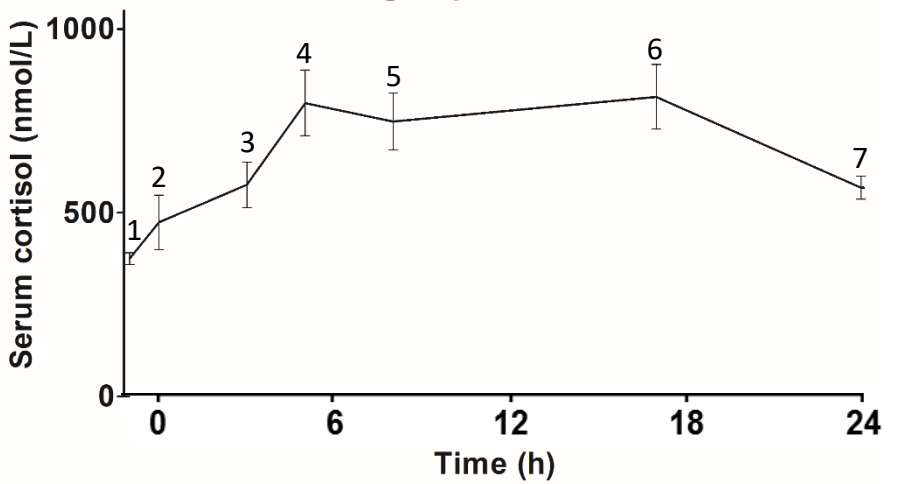
N = 381 studies excluded after full-text screening, with reasons:
• N=249 no population of interest
• N=48 no cortisol measurements
• N=38 non-English language
• N=32 review articles
• N=14 other

Studies included in quantitative synthesis (meta-analysis) (n = 71)

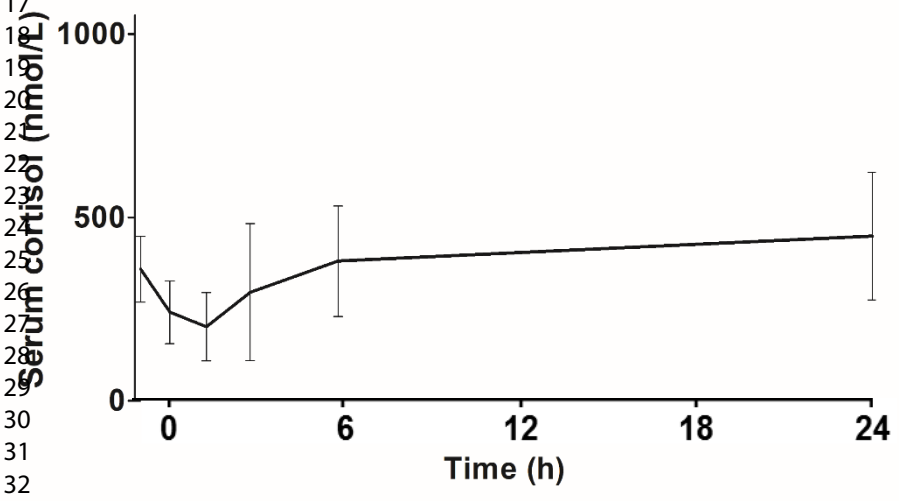
A - First 24h



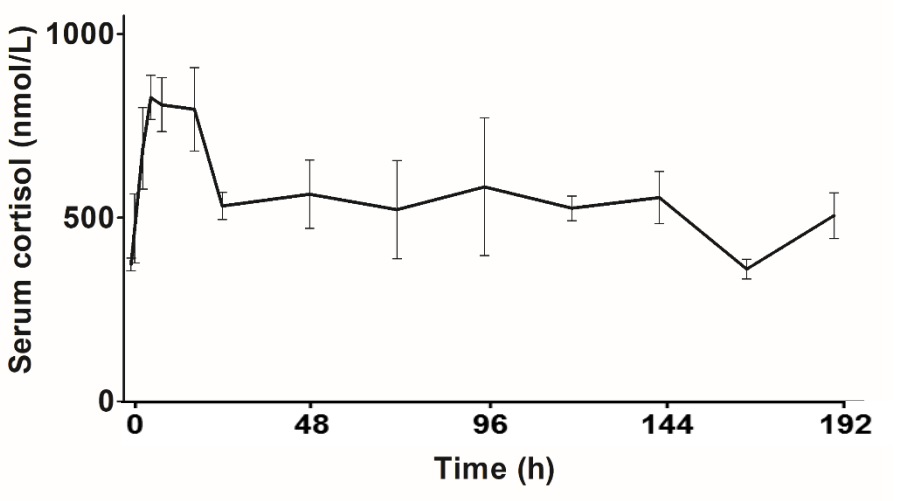
B - First 24 (surgery II + III)



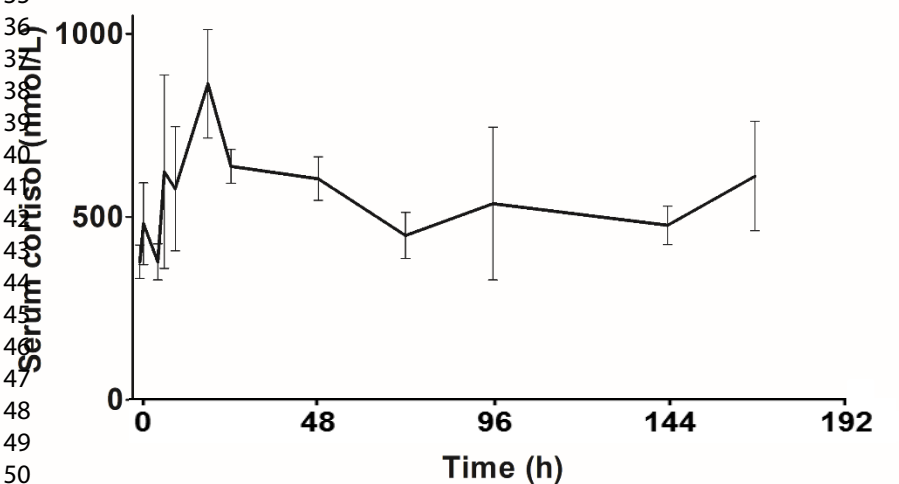
C - Surgery grade I



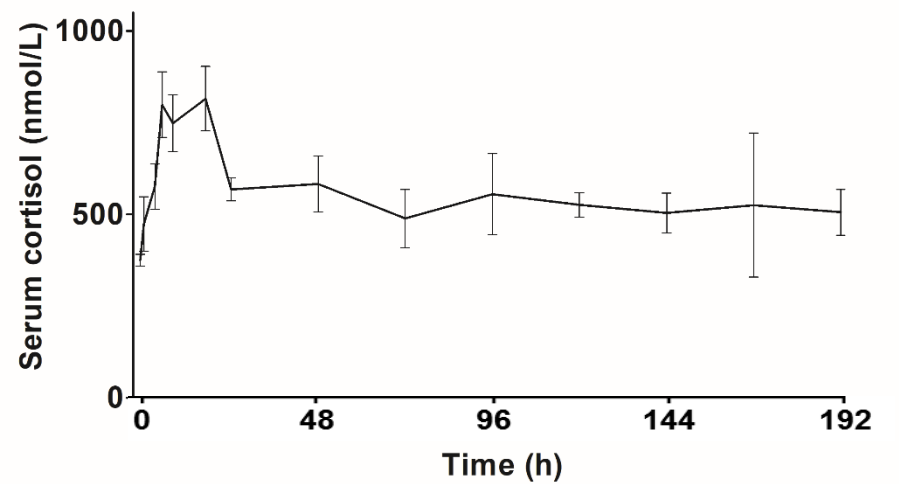
D - Surgery grade II

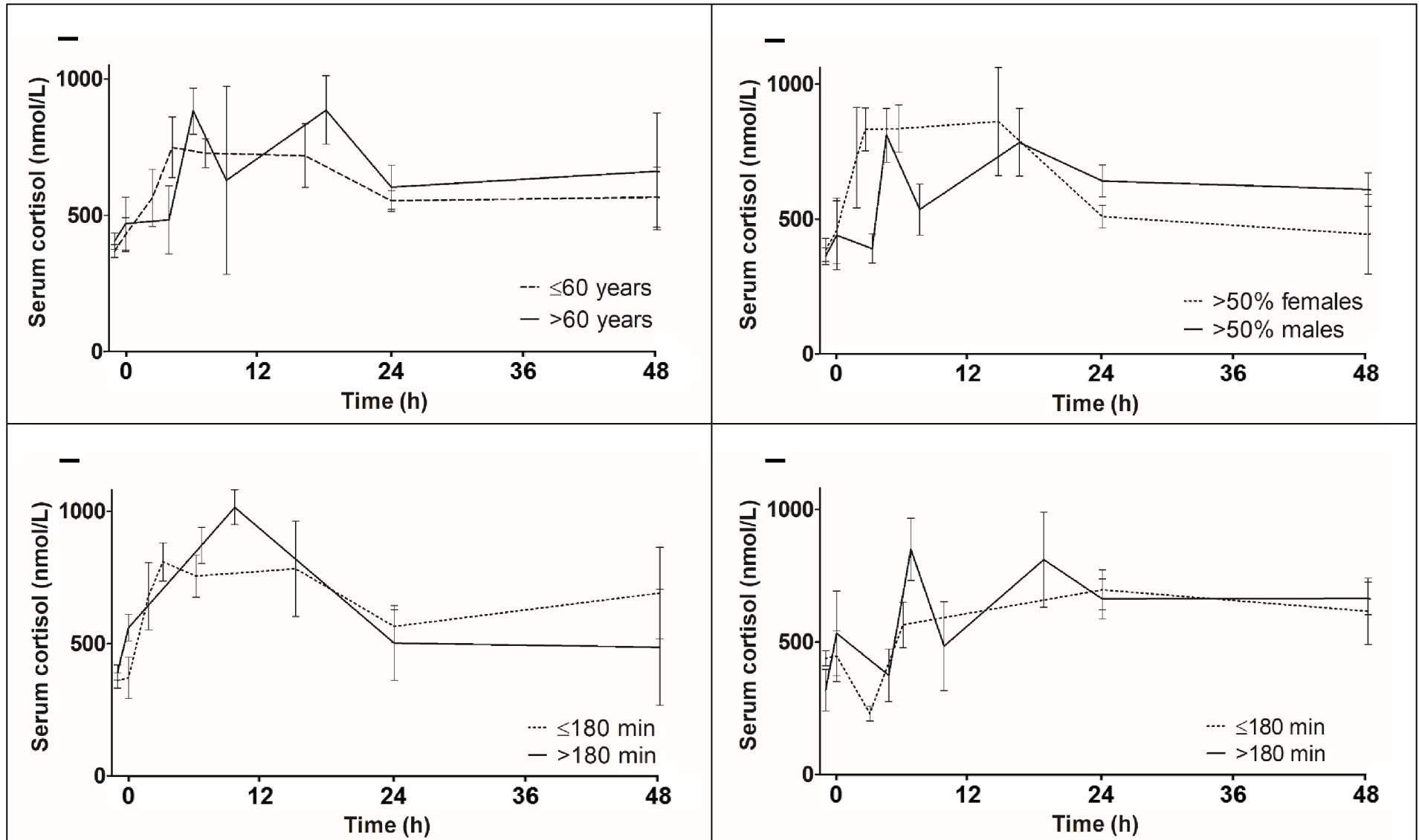


E - Surgery grade III



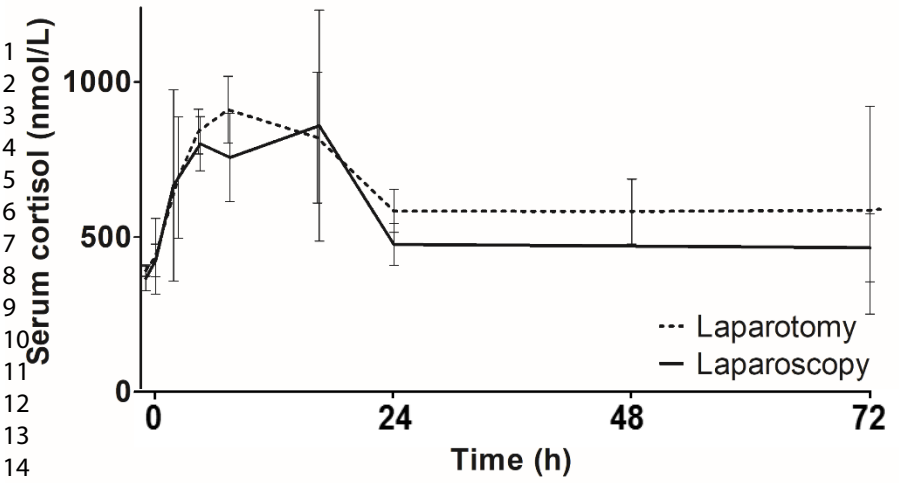
F - Surgery II + III (combined)



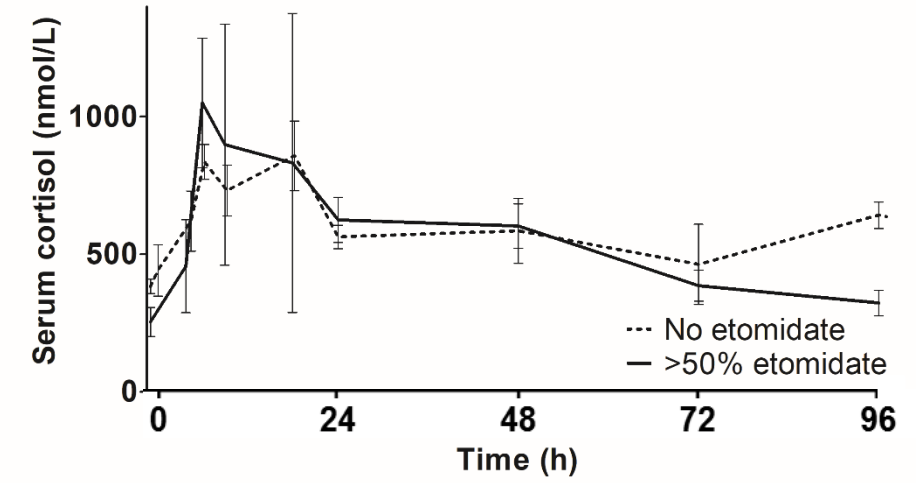


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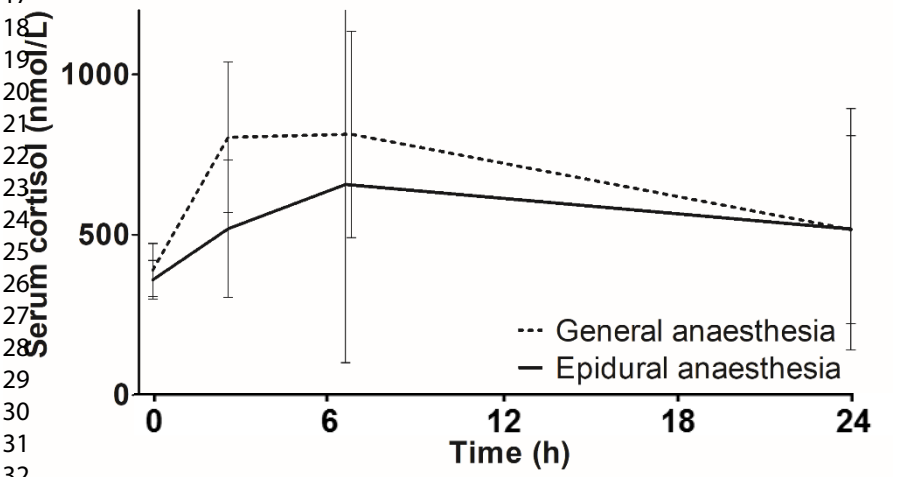
A - Laparotomy vs. laparoscopy



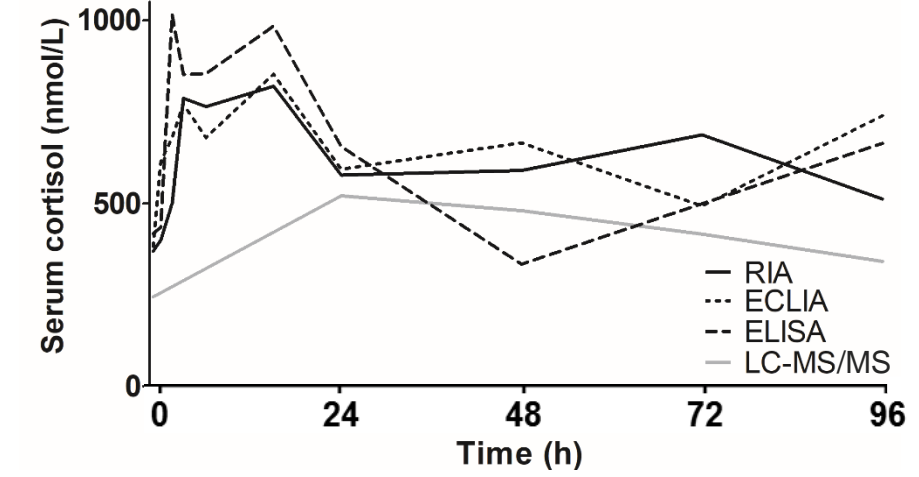
B - Use of etomidate



C - General vs. regional anaesthesia



D - Total serum cortisol assays



Supplementary Table 1 – Full search strategy.

Ovid			
Database(s): Embase 1988 to 2016 Week 21, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present, EBM Reviews - Cochrane Central Register of Controlled Trials April 2016, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to May 25, 2016			
Search Strategy:			
#	Searches	Results	Annotations
1	exp Hydrocortisone/	149584	
2	exp Cortisone/	29070	
3	cortisone acetate/	1061	
4	Glucocorticoids/	106016	
5	Dehydroepiandrosterone Sulfate/	11203	
6	(adreson or corticosteroid* or cortifair or cortisol or cortisone or cortril or dehydrocortisone or "Dehydroepiandrosterone Sulfate" or DHEAS or epicortisol or Glucocorticoid* or hydrocortisone).mp.	658684	
7	1 or 2 or 3 or 4 or 5 or 6	661993	
8	blood.fs.	1554351	
9	metabolism.fs.	4636381	
10	("adrenal function*" or "adrenal reserve" or "adrenal response" or analys* or analyz* or assay* or assess* or blood or concentration* or measur* or pharmacokinetic* or saliva or serum or urine).mp.	23423278	
11	8 or 9 or 10	25720523	
12	exp *Hydrocortisone/ or exp *Cortisone/ or *cortisone acetate/ or *Glucocorticoids/ or *Dehydroepiandrosterone Sulfate/ or (adreson or corticosteroid* or cortifair or cortisol or cortisone or cortril or dehydrocortisone or "Dehydroepiandrosterone Sulfate" or DHEAS or epicortisol or Glucocorticoid* or hydrocortisone).ti.	184113	
13	12 and ("adrenal function*" or "adrenal reserve" or "adrenal response" or analys* or analyz* or assay* or assess* or blood or concentration* or measur* or pharmacokinetic* or saliva or serum or urine).ti.	18392	
14	((critical* adj3 ill*) or burn or burns or "multi-organ dysfunction*" or "multi-organ failure" or "multiple organ dysfunction*" or "multiple organ failure" or polytrauma* or trauma*).mp.	919041	
15	7 and 11 and 14	12792	
16	13 or 15	30747	
17	16 not "traumatic brain injur*".ti.	30284	
18	17 not "conference abstract".pt.	28307	
19	limit 18 to yr="1980 -Current"	25076	

20	(exp animals/ or exp nonhuman/) not exp humans/	8423008
	((alpaca or alpacas or amphibian or amphibians or animal or animals or antelope or armadillo or armadillos or avian or baboon or baboons or beagle or beagles or bee or bees or bird or birds or bison or bovine or buffalo or buffaloes or buffalos or "c elegans" or "Caenorhabditis elegans" or camel or camels or canine or canines or carp or cats or cattle or chick or chicken or chickens or chicks or chimp or chimpanze or chimpanzees or chimps or cow or cows or "D melanogaster" or "dairy calf" or "dairy calves" or deer or dog or dogs or donkey or donkeys or drosophila or "Drosophila melanogaster" or duck or duckling or ducklings or ducks or equid or equids or equine or equines or feline or felines or ferret or ferrets or finch or finches or fish or flatworm or flatworms or fox or foxes or frog or frogs or "fruit flies" or "fruit fly" or "G mellonella" or "Galleria mellonella" or geese or gerbil or gerbils or goat or goats or goose or gorilla or gorillas or hamster or hamsters or hare or hares or heifer or heifers or horse or horses or insect or insects or jellyfish or kangaroo or kangaroos or kitten or kittens or lagomorph or lagomorphs or lamb or lambs or llama or llamas or macaque or macaques or macaw or macaws or marmoset or marmosets or mice or minipig or minipigs or mink or minks or monkey or monkeys or mouse or mule or mules or nematode or nematodes or octopus or octopuses or orangutan or "orang-utan" or orangutans or "orang-utans" or oxen or parrot or parrots or pig or pigeon or pigeons or piglet or piglets or pigs or porcine or primate or primates or quail or rabbit or rabbits or rat or rats or reptile or reptiles or rodent or rodents or ruminant or ruminants or salmon or sheep or shrimp or slug or slugs or swine or tamarin or tamarins or toad or toads or trout or urchin or urchins or vole or voles or waxworm or waxworms or worm or worms or xenopus or "zebra fish" or zebrafish) not (human or humans)).mp.	7384547
22	19 not (20 or 21)	20693
	limit 22 to ("all adult (19 plus years)" or "young adult (19 to 24 years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)") [Limit not valid in Embase,CCTR,CDSR; records were retained]	16937
24	limit 23 to (adult <18 to 64 years> or aged <65+ years>) [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) In-Process,CCTR,CDSR; records were retained]	11411
25	limit 22 to ("all infant (birth to 23 months)" or "all child (0 to 18 years)" or "newborn infant (birth to 1 month)" or "infant (1 to 23 months)" or "preschool child (2 to 5 years)" or "child (6 to 12 years)" or "adolescent (13 to 18 years)") [Limit not valid in Embase,CCTR,CDSR; records were retained]	14125
26	limit 25 to (embryo or infant or child or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>) [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) In-Process,CCTR,CDSR; records were retained]	3963
27	26 not 24	1469
28	22 not 27	19224
29	limit 28 to (editorial or erratum or letter or note or addresses or autobiography or bibliography or biography or blogs or comment or dictionary or directory or interactive tutorial or interview or lectures or legal cases or legislation or news or newspaper article or overall or patient education handout or periodical index or portraits or published erratum or video-audio media or webcasts) [Limit not valid in Embase,Ovid MEDLINE(R),Ovid MEDLINE(R) In-Process,CCTR,CDSR; records were retained]	1178
30	from 29 keep 1-1066	1066
31	28 not 30	18158
32	limit 31 to yr="2012 -Current"	4498

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5	33 remove duplicates from 32	3067
6	34 limit 31 to yr="2007 -2011"	4237
7	35 remove duplicates from 34	2957
8	36 limit 31 to yr="2001 -2006"	3749
9	37 remove duplicates from 36	2499
10	38 limit 31 to yr="1993 -2000"	3075
11	39 remove duplicates from 38	1945
12	40 31 not (32 or 34 or 36 or 38)	2599
13	41 remove duplicates from 40	1945
14	42 33 or 35 or 37 or 39 or 41	12413
15	43 (case adj3 report*).mp,pt.	3575111
16	44 (systematic adj3 review).mp,pt.	235991
17	45 review.mp,pt.	5358492
18	46 45 not 44	5122501
19	47 42 not 46	9903
20	48 47 not 43	9131
21	49 limit 48 to yr="1990 -Current"	7919
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Supplementary Table 2 – Classification of surgical procedures (adapted from the modified Johns Hopkins surgical criteria).¹²

Grade	General description	Includes	Excludes
I	Minimal to mild risk independent to anaesthesia. Minimal to moderately invasive procedure. Potential blood loss less than 500 ml.	Breast biopsy; removal of minor skin or subcutaneous lesions; myringotomy tubes; hysteroscopy; cystoscopy; vasectomy; circumcision; fibre-optic bronchoscopy; diagnostic laparoscopy; dilatation and curettage; fallopian tube ligation; arthroscopy; inguinal hernia repair; laparoscopic lysis of adhesion; tonsillectomy; rhinoplasty.	Open exposure of internal body organs; repair of vascular or neurological structures; placement of prosthetic devices; post-operative monitored care setting; open exposure of abdomen, thorax, neck, cranium; resection of major body organs.
II	Moderately to significantly invasive procedures. Potential blood loss 500–1500 ml. Moderate risk to patient independent of anaesthesia.	Thyroidectomy; hysterectomy; myomectomy; cystectomy; cholecystectomy; laminectomy; hip/knee replacement; nephrectomy; major laparoscopic procedures; resection/reconstructive surgery of the digestive tract.	Open thoracic or intracranial procedure; major vascular repair (e.g. aorto-femoral bypass); planned post-operative monitored care setting (intensive care unit, post anaesthesia care unit).
III	Highly invasive procedures. Potential blood loss greater than 1500 ml. Major to critical risk to patient independent of anaesthesia. Usual post-operative intensive care unit stay with invasive monitoring.	Major orthopaedic-spinal reconstruction; major reconstruction of the gastrointestinal tract; major genitourinary surgery (e.g. radical retro-pubic prostatectomy); cardiothoracic procedures; intracranial procedures; major procedures on the oropharynx; major vascular, skeletal, neurological repair.	

Supplementary Table 3 – Subgroup analyses performed for meta-analysis.

Parameters		Day of surgery ^a	Day 1 post-op.	Day 2 post-op.	Day 3 post-op.	Day 4 post-op.	Day 5 post-op.	Day 6 post-op.	Day 7 post-op.	References
Grade of surgery^b	Grade I	SS: 659	SS: 90	n/a	n/a	n/a	n/a	n/a	n/a	21, 62, 67, 69, 75, 82
	Grade II	SS: 3,829	SS: 981	SS: 366	SS: 121	SS: 75	SS: 16	SS: 10	SS: 71	19-24, 26-35, 37, 39-44, 47-54, 58, 60, 61, 63, 65, 66, 68-70, 74, 76, 78, 85, 89
	Grade III	SS: 1,749	SS: 871	SS: 209	SS: 67	SS: 55	n/a	SS: 18	SS: 27	25, 32, 36, 38, 42, 45, 46, 55-57, 64, 69, 71-73, 77, 79-81, 83, 84, 86-88
Age^c	Grade II, ≤60 years	SS: 2,987	SS: 601	SS: 150	SS: 69	n/a	n/a	n/a	n/a	22, 28, 30, 31, 34, 35, 40, 42-44, 47, 48, 51, 53, 54, 58, 61, 63, 65, 66, 68, 76, 78, 85, 89
	Grade II, >60 years	SS: 533	SS: 158	SS: 98	SS: 6	SS: 6	n/a	n/a	n/a	28, 37, 39, 50, 58, 65, 69, 78, 85
	Grade III, ≤60 years	SS: 597	SS: 320	SS: 135	n/a	n/a	n/a	n/a	n/a	36, 46, 57, 73, 83, 84, 87
	Grade III, >60 years	SS: 809	SS: 472	SS: 22	SS: 12	n/a	n/a	SS: 18	n/a	38, 42, 59, 64, 69, 71-73, 77, 80, 81, 88
Gender^d	Grade II+III, >50% females	SS: 2,205	SS: 588	SS: 119	SS: 77	SS: 49	n/a	n/a	SS: 49	19, 23, 25, 27-32, 36, 37, 40, 41, 44, 48, 50, 51, 54, 57, 58, 60, 67, 71, 73, 77
	Grade II+III, >50% males	SS: 2,143	SS: 1,088	SS: 345	SS: 39	SS: 55	n/a	n/a	SS: 43	42, 45, 47, 52, 53, 56, 62, 65, 66, 68, 74, 76, 80, 82, 83, 85
Duration of surgery^e	Grade II, ≤180 min	SS: 2,278	SS: 558	SS: 115	SS: 89	n/a	n/a	n/a	n/a	19, 23, 24, 27, 28, 31, 32, 38-41, 44, 50, 51, 55, 62, 65, 73, 82, 86
	Grade II, >180 min	SS: 221	SS: 31	SS: 31	n/a	n/a	n/a	n/a	n/a	45, 48, 66
	Grade III, ≤180 min	SS: 279	SS: 57	SS: 57	n/a	n/a	n/a	n/a	n/a	84, 87
	Grade III, >180 min	SS: 865	SS: 668	SS: 100	SS: 12	n/a	n/a	n/a	n/a	36, 38, 42, 46, 69, 71, 77, 81, 83, 88
Surgical technique^f	Laparoscopy	SS: 1,086	SS: 270	n/a	SS: 64	n/a	n/a	n/a	n/a	26-28, 30, 31, 33, 35, 40-44, 51, 53, 61, 63, 76, 89
	Laparotomy	SS: 1,676	SS: 411	SS: 221	SS: 34	SS: 49	n/a	n/a	n/a	23-25, 27, 28, 30, 32, 37, 38, 40, 41, 45, 46, 48-50, 57, 58, 60, 62, 66, 73, 75

Anaesthesia ^g	Grade II+III, etomidate used in >50% of patients	SS: 320	SS: 523	SS: 104	SS: 12	SS: 12	n/a	n/a	n/a	34, 36, 45, 46, 55, 77, 83, 89
	Grade II+III, no etomidate used	SS: 3,761	SS: 884	SS: 268	SS: 40	SS: 10	SS: 16	SS: 10	SS: 6	16, 17, 19, 20, 23, 25, 27-32, 34-40, 44, 51, 54-56, 61-63, 65, 66, 68, 71, 76-78, 82, 84, 86
	General anaesthesia	SS: 142	SS: 59	n/a	n/a	n/a	n/a	n/a	n/a	58, 68, 85
	Regional anaesthesia	SS: 142	SS: 59	n/a	n/a	n/a	n/a	n/a	n/a	
Assay ^h	RIA	SS: 2,715	SS: 548	SS: 223	SS: 16	SS: 26	SS: 16	SS: 10	SS: 22	19, 20, 22-25, 29-32, 34-37, 39-41, 43, 44, 46-49, 51, 54, 58, 59, 64, 70, 73, 76, 79, 87
	ECLIA	SS: 1,117	SS: 683	SS: 67	SS: 43	SS: 27	n/a	n/a	SS: 27	45, 52, 63, 68, 71, 77, 78, 80, 81, 83, 85, 86, 88, 89
	ELISA	SS: 547	SS: 229	SS: 114	n/a	SS: 49	n/a	n/a	SS: 49	26, 28, 50, 57, 60, 66
	LC-MS/MS	SS: 28	SS: 28	SS: 28	SS: 28	SS: 28	n/a	n/a	n/a	55, 56
ALL STUDIES n=2,953 patients		SS: 6,460	SS: 2,149	SS: 590	SS: 257	SS: 130	SS: 16	SS: 28	SS: 141	Listed in Table 1

The studies included in each subgroup analysis are reported in the last column. For each parameter assessed the cumulative sample size (SS – number of single cortisol measurements) is reported. These are divided by time points, which cover from the baseline assessment (prior to surgery) up to the 7th post-operative day. The cortisol responses for each subgroup analysis are reported in Figures 2 to 4.

^a Serum cortisol measurements during the day of surgery have been captured according to six time points: time 1, baseline (before surgery); time 2, initiation of surgery; time 3, during surgery; time 4, end of surgery; time 5, first 6h after surgery; time 6, between 6 and 18h after surgery. The SSs reported in this column correspond to the sum of all the six time points.
^b The grade of surgery has been defined according the classification reported in Supplementary Table 2.
^c The cohorts have been divided according to the grade of surgery and to the mean age of patients being ≤ or >60 years.
^d The cohorts have been divided according to the percentage of males and females. Only cohorts with either >50% females or >50% males have been included.
^e The cohorts have been divided according to the grade and the mean duration of surgery (either ≤180 or >180 minutes).
^f Only the cohorts of patients who underwent either laparotomies or abdominal/pelvic laparoscopies have been included for analysis.
^g We included only cohorts for which the anaesthetic technique was described in detail. As for the use of etomidate, we compared cohorts in which etomidate was not used as an anaesthetic agent to cohorts where this was used in >50% of patients. As far as the anaesthetic technique is concerned, we used data derived from prospective interventional studied comparing general and regional anaesthesia (either spinal or epidural thoracolumbar anaesthesia).
^h We have divided studies according to the cortisol assays used.

Abbreviations: ECLIA: electrochemiluminescence; ELISA: enzyme-linked immunosorbent assay; IRMA: immunoradiometric assay; LC-MS/MS: liquid chromatography-tandem mass spectrometry; n=number of studies; SS: sample size; RIA: radioimmunoassay; n/a: not available.

Supplementary Table 4 – Methodological quality assessment of the included studies.

First author (year of publication)	Patients (inclusion criteria) ^a	Patients (exclusion criteria) ^b	Cortisol measurement (methodology) ^c	Cortisol measurement (timing) ^d	Cortisol measurement (reporting) ^e	Cortisol measurement (time points) ^f
Høgevoid (1990) ¹⁹	Yes	Unclear	Yes	Yes	Yes	Yes
Bartalena (1990) ²⁰	Yes	Unclear	Yes	Yes	Yes	Yes
Hosokawa (1990) ²¹	Yes	Unclear	Yes	Yes	Yes	Yes
Bickel (1991) ²²	Somewhat	Yes	Yes	Yes	Yes	Yes
Naito (1991) ²³	Somewhat	Somewhat	Yes	Somewhat	Somewhat	Yes
Juma (1991) ²⁴	Yes	Unclear	Yes	Yes	Yes	Yes
Harris (1991) ²⁵	Somewhat	Unclear	Yes	Yes	Yes	Yes
Donald (1993) ²⁶	No	Unclear	Yes	Yes	Yes	Yes
McMahon (1993) ²⁷	Somewhat	Unclear	Yes	Yes	Yes	Somewhat
Deuss (1994) ²⁸	Somewhat	Unclear	Yes	Yes	Yes	Yes
Crozier (1994) ²⁹	Yes	Unclear	Yes	Yes	Yes	Yes
Jakeways (1994) ³⁰	Yes	Unclear	Somewhat	Yes	Yes	Yes
Dionigi (1994) ³¹	Yes	Unclear	Somewhat	Yes	Yes	Somewhat
Frank (1995) ³²	Unclear	Unclear	Yes	Somewhat	Yes	Yes
Ellstrom (1996) ³³	Yes	Unclear	No	Yes	Yes	Yes
Jameson (1997) ³⁴	Somewhat	Unclear	Yes	Yes	Yes	Yes
Karayiannakis (1997) ³⁵	Yes	Yes	Yes	Yes	Yes	Yes
Roth-Isigkeit (1997) ³⁶	Yes	Yes	Yes	Yes	Yes	Yes
Stratton (1997) ³⁷	Yes	Unclear	Yes	Yes	Yes	Yes
Plunkett (1997) ³⁸	Yes	Unclear	Yes	Yes	Yes	Yes
Eriksson-Mjöberg (1997) ³⁹	Yes	Yes	Yes	Yes	Yes	Somewhat
Bellón (1998) ⁴⁰	Somewhat	Unclear	Yes	Yes	Yes	Yes
Engin (1998) ⁴¹	Yes	Yes	Yes	Somewhat	Yes	Yes
Yamauchi (1998) ⁴²	Yes	Yes	Yes	Yes	Yes	Yes
Delogu (1999) ⁴³	Yes	Yes	Yes	Somewhat	Yes	Yes
Friedrich (1998) ⁴⁴	Yes	Yes	Somewhat	Yes	Yes	Yes
Vogeser (1999) ⁴⁵	Yes	Yes	Yes	Yes	Yes	Yes
Roth-Isigkeit (2000) ⁴⁶	Yes	Somewhat	Yes	Yes	Yes	Yes
Schricker (2000) ⁴⁷	Yes	Yes	Yes	Yes	Yes	Yes

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5	Cho (2000) ⁴⁸	Yes	Yes	Yes	Somewhat	Yes	Yes
6	Ogata (2000) ⁴⁹	Yes	Unclear	Yes	Yes	Yes	Yes
7	Mahla (2000) ⁵⁰	Yes	Unclear	Yes	Yes	Yes	Yes
8	Nguyen (2002) ⁵¹	Yes	Unclear	Yes	Yes	Yes	Yes
9	Ozarda Ilçöl (2002) ⁵²	Yes	Unclear	Yes	Yes	Yes	Yes
10	Holub (2002) ⁵³	Yes	Unclear	Yes	Yes	Yes	Yes
11	Marana (2003) ⁵⁴	Yes	Yes	Yes	Yes	Yes	Yes
12	Vogeser (2003) ⁵⁵	Yes	Unclear	Yes	Yes	Yes	Yes
13	Vogeser (2003) ⁵⁶	Yes	Unclear	Yes	Somewhat	Yes	Yes
14	le Roux (2003) ⁵⁷	Yes	Yes	Yes	Yes	Yes	Yes
15	Lattermann (2003) ⁵⁸	Yes	Yes	Yes	Somewhat	Yes	Yes
16	Shahbazi (2004) ⁵⁹	No	Unclear	Yes	Yes	Yes	Yes
17	Maciejczyk-Pencula (2004) ⁶⁰	Yes	Unclear	Yes	Yes	Yes	Yes
18	Haque (2004) ⁶¹	Yes	Unclear	No	Yes	Yes	Yes
19	Ledowski (2005) ⁶²	Yes	Yes	Yes	Yes	Yes	Yes
20	Crema (2005) ⁶³	Yes	Unclear	Yes	Yes	Yes	Yes
21	Yeager (2005) ⁶⁴	Yes	Yes	Yes	Yes	Yes	Yes
22	Kudoh (2005) ⁶⁵	Yes	Unclear	Somewhat	Yes	Yes	Yes
23	Nicholson (2005) ⁶⁶	Yes	Yes	Yes	Yes	Yes	Yes
24	Rahr (2006) ⁶⁷	Somewhat	Unclear	Yes	Yes	Yes	Yes
25	Buyukkocak (2006) ⁶⁸	Yes	Yes	Yes	Yes	Yes	Yes
26	Kashiwabara (2007) ⁶⁹	Yes	Yes	Yes	Yes	Yes	Yes
27	Baričević (2007) ⁷⁰	Yes	Unclear	Yes	Yes	Yes	Yes
28	Christ-Crain (2007) ⁷¹	Yes	Yes	Yes	Yes	Yes	Yes
29	Rapp-Kesek (2007) ⁷²	Yes	Unclear	Yes	Yes	Yes	Yes
30	Spratt (2008) ⁷³	Yes	Yes	Yes	Yes	Yes	Yes
31	Mujagić (2008) ⁷⁴	Yes	Yes	Yes	Yes	Yes	Yes
32	Bender (2009) ⁷⁵	Yes	Unclear	Yes	Yes	Yes	Yes
33	Kim (2010) ⁷⁶	Yes	Yes	Yes	Yes	Yes	Yes
34	Mu (2010) ⁷⁷	Yes	Yes	Yes	Yes	Yes	No
35	Engin (2010) ⁷⁸	Yes	Yes	Yes	Somewhat	Yes	Somewhat
36	Celic-Spuzic (2011) ⁷⁹	Yes	Unclear	Yes	Yes	Yes	Somewhat
37	Mello (2011) ⁸⁰	Yes	Yes	Yes	Yes	Yes	Yes
38	Debono (2011) ⁸¹	Yes	Yes	Yes	Yes	Yes	Yes
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Adas (2013) ⁸²	Yes	Unclear	Somewhat	Yes	Yes	Yes
Mu (2013) ⁸³	Yes	Yes	Yes	Yes	Yes	Yes
Ferreira (2014) ⁸⁴	Yes	Unclear	No	Yes	Yes	Yes
Kahveci (2014) ⁸⁵	Yes	Unclear	Yes	Yes	Yes	Yes
Maas (2014) ⁸⁶	Somewhat	Unclear	Yes	Yes	Yes	Yes
Gu (2015) ⁸⁷	Yes	Unclear	Yes	Yes	Yes	Yes
Lebherz (2016) ⁸⁸	Yes	Yes	Yes	Yes	Yes	Yes
Możański (2016) ⁸⁹	Yes	Yes	Yes	Yes	Yes	Yes
<p>^a Question answered to assess the quality of the study – Are inclusion criteria for cohort selection described in sufficient detail?</p> <p>^b Question answered to assess the quality of the study – Are patients on steroids or any other disease influencing endogenous steroid production excluded?</p> <p>^c Question answered to assess the quality of the study – Is the cortisol assay used clearly reported?</p> <p>^d Question answered to assess the quality of the study – Is the timing of cortisol measurement clearly reported?</p> <p>^e Question answered to assess the quality of the study – Is the cortisol measurement reported for the whole cohort?</p> <p>^f Question answered to assess the quality of the study – Is it possible to correlate the cortisol measurement to a specific time point for the cohort reported?</p>						

Peer Review

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Supplementary Table 5 – Areas under the curve (AUCs) for total cortisol values, divided by 24-h periods and by different parameters (age, gender, duration of surgery, surgical technique, anaesthesia, serum cortisol assays).

Parameters		Number of studies	AUC 0-24-h (nmol*h/L)	AUC Day 1 post-op. (nmol*h/L)	AUC Day 2 post-op. (nmol*h/L)	AUC Day 3 post-op. (nmol*h/L)	AUC Day 4 post-op. (nmol*h/L)	AUC Day 5 post-op. (nmol*h/L)	AUC Day 6 post-op. (nmol*h/L)	AUC Day 7 post-op. (nmol*h/L)
Age	Grade II, ≤60 years	25	17,130	12,276	11,724	n/a	n/a	n/a	n/a	n/a
	Grade II, >60 years	9	17,448	14,268	14,796	n/a	n/a	n/a	n/a	n/a
	Grade III, ≤60 years	7	13,658	15,456	n/a	n/a	n/a	n/a	n/a	n/a
	Grade III, >60 years	12	16,574	18,372	15,816	n/a	n/a	n/a	n/a	n/a
	Grade II+III (combined), ≤60 years	32	16,443	13,428	12,480	n/a	n/a	n/a	n/a	n/a
	Grade II+III (combined), >60 years	21	17,258	15,168	13,620	n/a	n/a	n/a	n/a	n/a
Gender	Grade II+III (combined), >50% females	26	18,696	11,436	12,972	15,600	n/a	n/a	n/a	n/a
	Grade II+III (combined), >50% males	25	15,817	15,012	13,092	12,168	n/a	n/a	n/a	n/a
Duration of surgery	Grade II, ≤180 min	21	17,542	15,072	13,800	n/a	n/a	n/a	n/a	n/a
	Grade II, >180 min	4	18,954	11,856	n/a	n/a	n/a	n/a	n/a	n/a
	Grade III, ≤180 min	2	14,005	15,752	n/a	n/a	n/a	n/a	n/a	n/a
	Grade III, >180 min	10	15,516	15,917	12,791	n/a	n/a	n/a	n/a	n/a
	Grade II+III (combined), ≤180 min	23	17,203	14,793	13,458	n/a	n/a	n/a	n/a	n/a
	Grade II+III (combined), >180 min	14	16,451	14,995	12,172	n/a	n/a	n/a	n/a	n/a

Surgical technique	Laparoscopy	18	17,968	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Laparotomy	24	19,063	13,987	14,016	14,994	n/a	n/a	n/a	n/a
Anaesthesia	Grade II+III (combined), etomidate used in >50% of patients	8	18,480	14,729	11,862	8,508	n/a	n/a	n/a	n/a
	Grade II+III (combined), no etomidate used	38	17,677	13,772	12,576	13,260	14,008	12,963	n/a	n/a
	General anaesthesia	3	16,270	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Regional anaesthesia	3	13,517	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Assays	RIA	33	17,765	14,007	15,326	14,389	12,448	12,963	10,976	9,936
	ECLIA	17	18,127	15,098	13,895	14,782	n/a	n/a	n/a	n/a
	ELISA	6	21,114	11,865	n/a	n/a	n/a	n/a	n/a	n/a
	LC-MS/MS	2	9,569	12,005	10,750	9,091	n/a	n/a	n/a	n/a
Abbreviations: AUC: area under the curve for serum cortisol values; n/a: not available or not applicable.										

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Supplementary Table 6 – Factors potentially affecting the perioperative cortisol response and the measurement of total serum cortisol.

Factors	Assessed in this article	Other factors
Patient characteristics	<ul style="list-style-type: none"> • Patient age; • Patient gender. 	<ul style="list-style-type: none"> • Comorbidities: these are not always clearly reported in the inclusion/exclusion criteria of the articles included. Some disorders can alter the cortisol metabolism (e.g. liver disease, nephrotic syndrome, thyrotoxicosis, hypothyroidism and diabetes mellitus). The exclusion of patients with adrenal or pituitary disorders is not always specified in the articles included in this systematic review; • ASA physical status: not all the studies included in this article specify the ASA physical status. When it is specified, it can vary considerably among the included cohorts. The ASA physical status correlates with the duration of hospital stay and post-operative complications, that can affect the cortisol response; • Nutrition status: malnutrition can enhance the cortisol output; • Studies including patients undergoing surgery for traumatic lesions do not always specify if some of the patients experienced head trauma. Head trauma can lead to temporary or long-term central adrenal insufficiency; • Several medications can potentially affect the cortisol metabolism and measurement, and their use is not always specified in the included articles (medications specifically used for the treatment of endogenous hypercortisolism and adrenocortical cancer are not reported): <ul style="list-style-type: none"> ○ Increase of CBG – e.g. Oestrogens; Tamoxifen. ○ Medications enhancing the CYP3A4 activity – e.g. Barbiturates; Carbamazepine; Oxcarbazepine; Phenytoin; Reverse transcriptase inhibitors; Rifampicin; ○ Medications inhibiting the CYP3A4 activity – e.g. Amiodarone; Azole antifungals; Chloramphenicol; Clarithromycin; Nefazodone; Nicardipine; Protease inhibitors; ○ Medications binding to the glucocorticoid receptor: Medroxyprogesterone acetate; Megestrol acetate; ○ Medications having an action on pituitary ACTH production: Glitazones; ○ Cross-reactivity with cortisol assays: Biotin; Quinine; Quinidine; Spironolactone.
Features of surgery	<ul style="list-style-type: none"> • Grade of surgery (as per the modified Johns Hopkins surgical criteria); • Laparotomy vs. laparoscopy; 	<ul style="list-style-type: none"> • Surgery for malignant conditions: radical resection for cancer is often associated with greater surgical trauma and longer operative time; • Surgery for post-traumatic lesions: surgery after trauma can be associated with longer operative time, greater blood loss and higher risk of complications; • Non-elective surgery: it is associated with higher rates of complications; • Perioperative haemodilution and/or hypoproteinaemia (due to blood loss or intravenous fluid administration): it can causes to falsely lower cortisol values; • Post-operative drop of CBG.
Anaesthetic techniques	<ul style="list-style-type: none"> • General vs. regional anaesthesia; • Use of etomidate. 	<ul style="list-style-type: none"> • Epidural anaesthesia techniques (especially when performed below the umbilicus) can lead to blunted cortisol responses after surgery, in comparison to general anaesthesia. When epidural anaesthesia is used for thoracic and upper abdominal surgeries, the modulatory effect on cortisol secretion is less evident.¹¹⁴ However, a recent study suggests that the combination of general anaesthesia and thoracic epidural blockade is more efficient in determining a reduction of the cortisol response in comparison to general anaesthesia alone.⁸⁷

		<ul style="list-style-type: none"> • Opiates are known to suppress cortisol secretion. General anaesthesia with opiates (especially when high doses are used) can blunt the cortisol response,^{47,115-117} but not all authors confirmed these observations.^{43,92,118} In cardiac surgery, the cortisol response induced by the cardiopulmonary bypass appears to overcome the inhibitory effects of high-dose opiates;¹¹⁴ • Sevoflurane anaesthesia in patients undergoing laparoscopic pelvic surgery was associated with significantly lower concentrations of ACTH and cortisol (during and immediately after surgery), when compared to Isoflurane;⁵⁴ • Patients receiving a balanced anaesthesia (Sevoflurane/Remifentanyl) showed higher cortisol levels after extubation, when compared to a total intravenous anaesthesia (Propofol/Remifentanyl).⁶² • Midazolam: it is a benzodiazepine containing an imidazole ring (like Etomidate). It can attenuate the cortisol response after surgery;^{2,119} • Perioperative use of steroids: not always specified as an exclusion criterion in the articles included in this systematic review and meta-analysis.
Post-operative complications		Post-operative complications (e.g. fever, haemorrhage, infections and sepsis, acute confusion) are a cause of stress and can affect the cortisol output. Not all studies included in this article specify post-operative complications. One study reported data from patients with post-operative sepsis. ⁷⁰
Post-operative care		<p>Several factors can potentially affect the stress cortisol response after surgery, for example:</p> <ul style="list-style-type: none"> • Admission to the intensive care unit; • Intraoperative normothermia: the fall of core body temperature can stimulate the stress response to surgery (cortisol and catecholamines), while post-operative forced air warming can blunt the cortisol surge;³² • Post-operative sedation: it helps reducing the surgical stress index post-operatively.¹²⁰ The use of sedatives and hypnotics can interfere with the sleeping patterns and the circadian rhythm; • Post-operative management of pain, nausea and vomiting; • Management of drains, tubes and catheters; • Timing of post-operative nutrition and mobilization.
Methodological factors	Total cortisol assays	<p>Several factors may have an impact on the total cortisol values that have been extracted for this systematic review and meta-analysis:</p> <ul style="list-style-type: none"> • The timing of cortisol measurements is not always clearly reported; • Most of pre- and post-operative cortisol measurements have been performed during the morning. However, this is not always specified; • Some of the included articles did not report the exact cortisol values, which have been therefore extracted from graphs.
Abbreviations: ACTH: adrenocorticotrophic hormone; ASA: American Society of Anesthesiologists; CBG: cortisol-binding globulin; CYP3A4: Cytochrome P450 3A4.		