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Review article

Mesenteric traction syndrome — Incidence, impact, and treatment: A systematic scoping review of the literature

August A. Olsen [a,*], Laser A. Bazancir [a], Stig Dahl [a], Daisuke Fukumori [a], Hironari Shiwaku [b], Lars Bo Svendsen [a], Michael P. Achiam [a]

[a] Department of Surgery and Transplantation, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark
[b] Department of Gastroenterological Surgery, Fukuoka University Faculty of Medicine, Fukuoka, Japan

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ABSTRACT

Background: Mesenteric traction syndrome (MTS) is commonly seen during major abdominal surgery and is characterised by facial flushing, hypotension, and tachycardia 15 min into surgery. MTS also impacts the postoperative course, as severe MTS has been associated with increased postoperative morbidity. However, despite MTS being common and severe MTS causing increased postoperative morbidity, the gaps in the literature are not clearly defined. We aimed to examine the diagnostic criteria, incidence, intraoperative and postoperative impact, and potential preventative measures of MTS while highlighting potential gaps in the literature.

Methods: We followed the Prisma guidelines and performed a systematic literature search. We included only human studies examining MTS. All hits were screened for title and abstract, followed by a full-text review by at least two authors for determining eligibility for inclusion. Data were extracted and risk of bias was assessed by two independent reviewers.

Results: A total of 37 studies, comprising 1102 patients were included in the review. The combined incidence of MTS during open abdominal surgery was found to be 76%, with 35% developing severe MTS. It was found that the development of MTS was associated with marked haemodynamic changes. It was also found that several different subjective diagnostic criteria exist and that severe MTS was associated with increased postoperative morbidity. Furthermore, several preventative measures for protecting against MTS have been examined, but only on the incidence of MTS and not on the postoperative course.

Conclusion: MTS occurs in 76% of patients undergoing major abdominal surgery and is associated with deleterious haemodynamic effects, which are more pronounced in patients developing severe MTS. Severe MTS is also associated with a worse postoperative outcome. However, gaps are still present in the current literature on MTS.

Contents

* Corresponding author at: Department of Surgery and Transplantation, Rigshospitalet, University of Copenhagen, Inge Lehmanns Vej 7, DK-2100 Copenhagen, Denmark.
E-mail addresses: August.Adelsten.Olsen.01@regionh.dk, wph457@alumni.ku.dk (A.A. Olsen).

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Introduction

Mesenteric traction syndrome (MTS) is defined as a triad of symptoms consisting of hypotension, tachycardia, and facial flushing 10−15 min into surgery [1,2]. MTS is caused by the mesenteric traction/abdominal exploration during the opening parts of intra-abdominal surgery [3–5], and is not related to the classic post-induction hypotension commonly seen during the early parts of anaesthesia. This relationship between mesenteric traction/abdominal exploration and facial flushing has been known in the literature since 1985 [6]. The three symptoms of hypotension, tachycardia, and facial flushing, was first described in 1986 as the ''Eventrations Syndrome'' [7], and later named as MTS in the English literature [8].

MTS is caused by a COX-1 mediated release of the potent vasodilator prostacyclin (PGI_2) arising from the mesentery [9–11]. This is thought to be a response to a decreased splanchnic blood flow following mesenteric traction during the early parts of surgery [5,12,13]. The PGI_2 release prevents splanchnic ischaemia through vasodilation [4], but also causes varying degrees of hypotension [13]. Normally, the haemodynamics are quickly normalised due to counter-acting sympathoadrenal activation with the release of various endogenic vasopressors [14]. However, in some cases, patients develop a massive PGI_2 release. This leads to significantly pronounced flushing of the face, as well as of the upper torso [15–17], which is known as severe MTS. In most cases, severe MTS is combined with marked haemodynamic instability requiring significant anaesthetic interventions [4,5,14,18,19]. However, it is not known why some patients develop this severe response, while others simply develop a short-lasting self-limiting response. Two possible mechanisms could be increased levels of comorbidity, possibly limiting the patient's counter-acting response to the PGI_2-induced vasodilation, and hypovolaemia, which could further reduce the patient's response [20].

MTS does not only affect the patients intraoperatively. Two recent studies have shown that the development of severe MTS was associated with increased incidence of severe postoperative complications, increased postoperative morbidity, and length of hospital stay following upper gastrointestinal cancer surgery [3,17]. This underlines the potential clinical significance of the syndrome. Especially when since increased postoperative morbidity is associated with a worse long-term outcome following major abdominal oncological surgery [21,22]. Currently, the diagnosis and grading of MTS are based on a subjective assessment of the degree of facial flushing. Due to the limitations of this approach, an objective method for MTS grading would be preferred. One recent study has assessed the objective grading of MTS with the use of laser speckle contrast imaging, showing good discrimination between the different degrees of MTS [23].

No systematic scoping review combining all the available research on MTS exists. Thus, the gaps in the literature on MTS are not clearly defined.

This systematic scoping review aims to examine the diagnostic criteria, incidence, intraoperative and postoperative impact, and potential preventative measures of MTS.

Methods

The protocol, flow chart, and manuscript all adhered to the PRISMA statement from 2020 [24] along with the PRISMA extension for scoping reviews [25,26]. The review followed the AMSTAR-2 checklist [27] with a moderate score of overall confidence. The protocol was submitted to PROSPERO with the following ID CRD42020210624, first registered on the 24th of September 2020.

Criteria and outcomes

The eligibility criteria for this systematic scoping review follow the principles of PICO (Participants, Intervention, Comparison, and Outcome). Only clinical studies that examined the effects of mesenteric traction during surgery, or described MTS, were included. All outcomes due to MTS or mesenteric traction were included, *e.g.*, diagnostic criteria, incidence, manifestation, intraoperative impact, postoperative impact, and preventative or therapeutic measures. With regards to the study design, animal studies and reviews were excluded, as this review focuses on MTS in human patients. This led to the inclusion of case reports and case series, observational studies, and randomised controlled studies independent of the year of publication. Articles of all languages were included.

Search strategy

The search string was built in PubMed (Table 1) and then adapted for Embase, Scopus, Cochrane Library, Cochrane Library, and Web of Science. The search string includes MTS, mesenteric traction, and symptoms of MTS combined with different types of surgery within the abdominal cavity. All databases were searched on the 9th of October 2020, again on the 2nd of April 2021, and lastly on the 11th of July 2022. All studies were imported to Covidence [28] and screened for duplicates by two reviewers (Olsen AA and Bazancir LA). Titles and abstracts were screened independently in Covidence by three authors (Olsen AA, Bazancir LA, and Dahl SS), and any conflicts were settled within the entire group of authors. A full-text review was performed independently in Covidence by two of five authors (Olsen AA, Bazancir LA, Dahl SS, Shiwaku H, and Fukomori D). During a full-text review, a scan of the literature lists was also performed to identify any additional studies. Any discrepancies regarding inclusion or exclusion during full-text review led to the article being re-examined within the entire group of authors until consensus was reached. Five authors (Olsen AA, Bazancir LA, Dahl SS, Shiwaku H, and Fukomori D) performed data extraction. Data was extracted without being modified. Data then underwent relevant statistical analysis (χ^2-test and frequencies) when missing in the original study. The authors extracted data regarding study characteristics, patient characteristics, diagnostic criteria of MTS, incidence, manifestation, intraoperative impact, postoperative impact, and preventative or therapeutic measures. Lastly, combined values were calculated as simple sums of all included studies, and relevant comparisons were made using χ^2-test and frequencies.

Quality assessment

The Newcastle-Ottawa scale [29] was used for risk of bias analysis in observational studies and is reported as a combined score, with the best achievable score (lowest risk of bias) being nine stars. In addition, the Cochrane Collaboration's tool for assessing the risk of bias was used for randomised controlled trials [30]. The risk of bias is reported as high, medium, or low, depending on the score of the study on the seven examined parameters. Low risk of bias required at least 6 of 7 parameters scored as high quality, while medium risk of bias required at least 4 of 7 parameters being high quality, with anything lower than this being high risk of bias. Risk of bias analysis was performed by two independent authors during data extraction, and any conflicts were settled within the author group. Lastly, all the evidence behind each preventative measure examined in this review underwent an assessment using Grading of Recommendations Assessment, Development and Evaluation (GRADE) [31].

Table 1
Search string.

Search string in PubMed, Embase, Scopus, and Web of Science
(((((((("Traction"[Mesh]) OR "Syndrome"[Mesh]) AND ("Mesentery"[Mesh])) OR (mesenteric traction syndrome)) OR ((("Tachycardia"[Mesh]) AND "Hypotension"[Mesh]) AND "Flushing"[Mesh])) OR (("Prostaglandins I"[Mesh] AND "Hypotension"[Mesh])) OR (((((((("Abdomen/surgery"[Mesh]) OR "Digestive System/surgery"[Mesh]) OR "Digestive System Diseases/surgery"[Mesh]) OR "Gastrointestinal Diseases/surgery"[Mesh]) OR "Aortic Aneurysm/surgery"[Mesh]) OR "Mesenteric Ischemia/surgery"[Mesh]) AND ("Hypotension"[Mesh]))) OR (("Traction"[Mesh]) AND (("Intestines"[Mesh]) OR "Mesentery"[Mesh])))

Results

The authors screened 1790 articles in Covidence and added four studies identified from other sources. After the removal of duplicates, 1463 articles remained; of these, 1390 articles were excluded following the screening of titles and abstracts. A total of 73 articles underwent full-text screening, of which 35 studies were excluded due to either having a topic other than MTS, being a study protocol, being a duplicate, or having a wrong study design. Finally, 38 studies, for a total of 1102 patients were included, comprising of 16 randomised controlled trials, 12 observational studies, and 10 case series and case reports. The included studies can be seen in Table 2. The completed screening process is shown in the PRISMA flow diagram (Fig. 1).

Quality assessment

Results of the risk of bias analysis are reported in Table 2. The results of the Grade assessment are reported in the results as well as in Table 4. For detailed description of risk of bias see **Supplementary Table 1** and **Supplementary Table 2**.

MTS diagnosis

MTS is diagnosed in various ways in the literature; however, all studies use at least parts of the symptom triad defining MTS. Some studies simply use the occurrence of facial flushing as their diagnostic criteria for the development of MTS [5,6,13,32–36]. This approach has, in some of the literature, been expanded, with MTS being divided into three levels, defined by three grades of facial flushing [3,8,15–17,37–43]. The three levels of MTS are no MTS (no flushing), moderate MTS (grade 1 flushing or partial facial flushing), and severe MTS (grade 2 flushing or full-face flushing), with the degree of facial flushing assessed subjectively. However, other approaches for diagnosing MTS also exist, with some studies using the occurrence of facial flushing combined with hypotension [13,41,44–47]. Only one of these studies defines hypotension and uses a definition of a decrease of the systolic blood pressure to 70 % or below of the baseline blood pressure or an absolute systolic blood pressure below 90 mmHg [44]. One study used the occurrence of decreased MAP combined with flushing or a decreased transcutaneous saturation [4]. Finally, some studies use the full symptom triad of MTS as their diagnostic criteria [11,13,48,49]. However, looking at the reported incidences of MTS with the different diagnostic criteria, all but one finds similar incidences of MTS of 70–77 %. Only the study using the whole triad as their diagnostic criteria reports an incidence of MTS of 95 %, which still is comparable to the other diagnostic criteria [49] (Randomised controlled trials and observational studies).

Incidence

The incidence of MTS (Table 3) varies greatly in the literature, with some studies reporting levels as low as 46% [38], while others report incidences higher than 90% [5,15,49]. One thing is certain, though, MTS is very common during open abdominal surgery, with a combined incidence of 76%. Seven of the studies have subdivided MTS into three different grades. In these studies, the combined incidence of severe MTS, or grade 2 flushing, was 35%. MTS also occurs during minimally invasive surgery, although with a much lower incidence of 17%, and 0% developing severe MTS. Lastly, the literature shows that MTS can occur during all types of open surgery in the abdominal cavity. (Randomised controlled trials and observational studies).

Table 2
Characteristics of included studies.

Randomised Controlled Trial						
Author	Examined intervention	Number of subjects	Types of surgery	Patient demographics	Usage of NSAIDs and Corticosteroids before surgery	Cochrane risk of bias
Brinkmann et al. [37] Germany, 1994	Thoracic epidural anaesthesia and Ibuprofen	40 patients 10 – General anaesthesia and placebo (a) 10 – General anaesthesia and 400 mg ibuprofen (b) 10 – General anaesthesia, epidural anaesthesia, and placebo (a) 10 - General anaesthesia, epidural anaesthesia, and 400 mg ibuprofen (b)	Major abdominal surgery (Infrarenal aortic, gastrointestinal, and pancreatic)	Age a) 53 ± 3 b) 58 ± 2.9 Gender a) 12/20 male b) 10/10 male ASA I/II/III/IV a) 0/13/6/1 b) 1/8/10/1	No reports of NSAID or corticosteroid usage	Medium risk of bias
Brinkmann et al. [19] Germany, 1996	Preoperative Ibuprofen	50 patients 25 – Placebo (a) 25 – 400 mg Ibuprofen (b)	Abdominal aortic surgery or pancreatic surgery	Age a) 59 ± 11 b) 61 ± 12 Gender a) 21/25 male b) 22/25 male ASA I/II/III/IV a) 0/10/14/1 b) 0/13/12/0	NSAIDs was discontinued seven days before surgery, and no reports of corticosteroid usage	Medium risk of bias
Brinkmann et al. [18] Germany, 1997	Preoperative Ibuprofen	52 patients 13 – Placebo and aortic surgery (a) 26–400 mg Ibuprofen and aortic surgery (b) 13 – Placebo and pancreatic surgery (c) 26–400 mg Ibuprofen and pancreatic surgery (d)	Abdominal aortic surgery or pancreatic surgery	Age, $p < 0.05$ a) 64 ± 3 b) 67 ± 2 c) 55 ± 2 d) 56 ± 4 Gender a) 11/13 male b) 11/13 male c) 11/13 male d) 12/13 male ASA I/II/III a) 0/3/10 b) 0/4/9 c) 0/9/4 d) 0/9/4	No reports of NSAID or corticosteroid usage	High risk of bias
Brinkmann et al. [14] Germany, 1998	Preoperative Ibuprofen	42 patients 21 – Placebo (a) 21 – 400 mg Ibuprofen (b)	Major abdominal surgery (Infrarenal aortic, gastrointestinal, and pancreatic)	Age a) 60 ± 10 b) 62 ± 10 Gender a) 18/21 male b) 19/21 male ASA I/II/III a) 0/11/10 b) 0/8/13	Patients excluded if pre-treated with NSAIDs, no reports of corticosteroid usage	Medium risk of bias

Table 2 (*Continued*)

Randomised Controlled Trial						
Author	Examined intervention	Number of subjects	Types of surgery	Patient demographics	Usage of NSAIDs and Corticosteroids before surgery	Cochrane risk of bias
Bucher et al. [11] Germany, 2006	Preoperative Parecoxib	40 patients 20 – placebo (a) 20 – Parecoxib 0.6 mg/kg i.v. (b)	Major open abdominal surgery	Age a) 60 ± 3 b) 58 ± 3 Gender a) 12/20 male b) 12/20 male ASA I/II/III a) 4/11/5 b) 0/18/2	No prior usage of NSAIDs or corticosteroids in any patients	High risk of bias
Chen et al. [44] China, 2020	Dexmedetomidine	71 patients 23 – Placebo (a) 25 – 0.5 μg/kg Dexmedetomidine (b) 23 – 1 μg/kg Dexmedetomidine (c)	Total gastrectomy	Age a) 61 ± 4 b) 59 ± 6 c) 60 ± 5 Gender a) 20/24 male b) 17/25 male c) 16/23 male All patients ASA I/II	Patients excluded if pre-treated with NSAIDs, no reports of corticosteroid usage	Medium risk of bias
Duda et al. [48] Germany, 2002	Preoperative Dimetidene and Cimetidine	17 patients 9 – Placebo (a) 8 – 0.1 mg/kg Dimetidene and 5 mg/kg Cimetidine (b)	Abdominal aortic surgery	No report of age or gender ASA I/II/III/IV a) 0/0/6/3 b) 0/0/6/2	No reports of NSAID or corticosteroid usage	High risk of bias
Fujimoto et al. [13] Japan, 2012	Preoperative Flurbiprofen Axetil	30 patients 15 – placebo (a) 15 – 50 mg Flurbiprofen Axetil (b)	Major abdominal surgery (Gastrectomy, colectomy, pancreatic surgery, hepatectomy and explorative laparotomy)	Age a) 63.3 ± 10.5 b) 68 ± 8.6 Gender a) 8/15 male b) 12/15 male All patients ASA I/II	Patients excluded if pre-treated with NSAIDs or corticosteroids	Medium risk of bias
Hudson et al. [40] United States, 1990	Preoperative Ibuprofen	27 patients 13 – Placebo (a) 14 – 800 mg Ibuprofen (b)	Abdominal aortic surgery	Age a) 66 ± 7 b) 56 ± 11 Gender a) 10/13 male b) 9/14 male ASA not reported	NSAID was discontinued seven days before surgery, and no reports of corticosteroid usage	High risk of bias
Koyama et al. [15] Japan, 1995	Indomethacin	36 patients 12 – Placebo (a) 12 – Preoperative Indomethacin 50 mg (b) 12 – Indomethacin 50 mg just after induction of anaesthesia (c)	Abdominal hysterectomy	Age a) 44.1 ± 5.5 b) 45.8 ± 6.6 c) 41.8 ± 5.2 No report of Gender, all patients ASA I/II	NSAID was discontinued seven days before surgery, and no reports of corticosteroid usage	High risk of bias

Table 2 (*Continued*)

Randomised Controlled Trial						
Author	Examined intervention	Number of subjects	Types of surgery	Patient demographics	Usage of NSAIDs and Corticosteroids before surgery	Cochrane risk of bias
Nomura et al. [16] Japan, 2010	Remifentanil	100 patients 50 – Placebo (a) - 36 open surgery - 14 Laparoscopic surgery 50 – Remifentanil (b) - 33 Open surgery - 17 Laparoscopic surgery	Major abdominal surgery (Gastrectomy, colectomy, hepatectomy and	pancreaticoduodenectomy) Age a) 64.7 ± 12.6 b) 65.8 ± 12 Gender a) 35/50 male b) 36/50 male All patients ASA I/II		Patients excluded if pre-treated with NSAIDs, no reports of corticosteroid usage
High risk of bias Strandby et al. [52] Denmark, 2021	Thoracic epidural anaesthesia	45 patients 25 – Early epidural activation (a) 20 – Late epidural activation (b)	Open esophagectomy	Age a) 64.1 ± 7.8 b) 65.1 ± 7.8 Gender a) 20/25 male b) 16/20 male ASA a) 2.2 ± 0.5 b) 2.2 ± 0.4	Patients excluded if pre-treated with NSAIDs or corticosteroids	Low risk of bias
Takada et al. [49] Japan, 2013	Flurbiprofen Axetil	76 patients 20 – Preoperative placebo (a) 19 – Preoperative Flurbiprofen Axetil 50 mg (b) 20 – Placebo following recognition of MTS (c) 20 – Flurbiprofen Axetil 50 mg following recognition of MTS (d)	Major abdominal surgery	Age a) 70 ± 12 b) 69 ± 11 c) 70 ± 9 d) 68 ± 11 Gender a) 14/20 male b) 14/19 male c) 13/19 male d) 12/18 male All patients ASA I-II	Patients excluded if pre-treated with NSAIDs or corticosteroids	High risk of bias
Takahashi et al. [46] Japan, 2013	Flurbiprofen Axetil	24 patients 13 – Placebo (a) 11 – Preoperative Flurbiprofen Axetil 50 mg (b)	Colorectal surgery	Age a) 70.6 ± 8.7 b) 67.1 ± 11.9 Gender a) 6/13 male b) 11/11 male No report of ASA	NSAIDs discontinued seven days before surgery, no reports of corticosteroid usage	Medium risk of bias
Takahashi et al. [47] Japan, 2016	Flurbiprofen Axetil	57 patients 34 – Placebo - 6 – No MTS - 28 – MTS (a) 23 – Preoperative Flurbiprofen Axetil 50 mg (b)	Colorectal surgery	Age a) 69.4 ± 9 b) 70 ± 11.3 Gender a) 19/28 male b) 18/23 male No report of ASA	No reports of NSAID or corticosteroid usage	High risk of bias

Table 2 (*Continued*)

Randomised Controlled Trial

Author	Examined intervention	Number of subjects	Types of surgery	Patient demographics	Usage of NSAIDs and Corticosteroids before surgery	Cochrane risk of bias
Takahashi et al. [35] Japan, 2017	Flurbiprofen Axetil	42 patients 14 – Placebo (a) 16 – Preoperative Flurbiprofen 50 mg/kg (b) 13 - Flurbiprofen Axetil 50 mg following recognition of MTS (c)	Colorectal surgery	Age a) 69.1 ± 10.2 b) 67.3 ± 11.3 c) 69 ± 8.2 Gender a) 9/14 male b) 13/16 male c) 8/13 male No report on ASA	Patients excluded if pre-treated with NSAIDs or corticosteroids	High risk of bias

Observational studies

Author	Number of subjects	Type of surgery and groups	Patient demographics	Usage of NSAIDs and Corticosteroids before surgery	Newcastle-Ottawa scale risk of bias
Ambrus et al. [3] Denmark, 2017	50 patients	25- Open esophagectomy (a) 25 - Robot-assisted esophagectomy (b)	Age a) 67.4 ± 8 b) 64.3 ± 10.4 Gender a) 19/25 male b) 22/25 male ASA score a) 2.4 ± 0.5 b) 2.3 ± 0.6	Patients excluded if pre-treated with NSAID or corticosteroids	5/9
Brinkmann et al. [4] Germany, 1999	46 patients	Pancreatic surgery 33 – Response to mesenteric traction (a). 13 – No response to mesenteric traction (b)	Age: a) 53 ± 11 b) 50 ± 17 Gender a) 24/33 male b) 7/13 male ASA I/II/III a) 0/27/6 b) 2/8/3	Patients excluded if pre-treated with NSAID, no reports of corticosteroid usage	5/9
Gottlieb et al. [8] United States, 1989	37 patients	Abdominal aortic surgery 31 – Control 6 – Daily Aspirin use	Age - 67 Gender - 27/37 male No report of ASA	NSAIDs was discontinued seven days before surgery in all but six patients and no reports of corticosteroid usage	4/9
Haraguchi et al. [38] Japan, 2018	37 patients	Open gastrectomy 18 – Low dose Sevoflurane (1.0%) (a) 19 – High dose Sevoflurane (1.4%) (b)	Age a) 72 ± 7 b) 70 ± 11 Gender a) 16/18 male b) 11/19 male ASA I/II/III a) 1/14/3 b) 16/3/0	Patients excluded if pre-treated with NSAIDs or corticosteroids	4/9

Table 2 (*Continued*)

Observational studies					
Author	Number of subjects	Type of surgery and groups	Patient demographics	Usage of NSAIDs and Corticosteroids before surgery	Newcastle-Ottawa scale risk of bias
Hudson et al. [39] United States, 1988	52 patients	Abdominal aortic surgery 33 – Transabdominal approach (a) 19 – Retroperitoneal approach (b)	Age – $p < 0.05$ a) 63.6 ± 9.2 b) 70.8 ± 8.3 Gender – $p < 0.05$ a) 23/33 male b) 17/19 male All patients ASA II/III	NSAIDs was discontinued seven days before surgery, and no reports of corticosteroid usage	4/9
Olesen et al. [54] Denmark, 2017	22 patients	Pancreatic surgery 10 – Patients with MTS (a) 12 – Patients without MTS (b)	Age a) 61 ± 9 b) 61 ± 8 Gender a) 6/10 male b) 6/12 male ASA I/II/III a) 1/6/3 b) 1/6/5	Patients excluded if pre-treated with NSAIDs, no prior usage of corticosteroids, however, all patients received 125 mg methylprednisolone as part of the standard anaesthetic management	5/9
Olsen et al. [17] Denmark, 2020	137 patients	Major abdominal surgery 94 – Moderate/no MTS (a) 43 – Severe MTS (b)	Age a) 65 ± 10 b) 64 ± 11 Gender – $p < 0.05$ a) 42/43 male b) 51/94 male ASA I/II/III + IV a) 10/61/23 b) 23/17/3	Patients were excluded if pre-treated with NSAIDs. No prior usage of corticosteroid, however 45 patients received 125 mg methylprednisolone as part of standard anaesthetic management	6/9
Olsen et al. [42] Denmark, 2021	67 patients	Esophagectomy and gastrectomy 41 – Moderate/no MTS (a) 26 Severe MTS (b)	Age a) 65.4 ± 10.3 b) 62.5 ± 11.7 Gender – $p < 0.05$ a) 23/41 male b) 25/26 male ASA I/II/III + IV a) 3/27/11 b) 1/16/9	Patients excluded if pre-treated with NSAID or corticosteroids	6/9
Olsen et al. [43] Denmark, 2022	45 patients	Whipple procedure (n = 22) and major liver resection (n = 23) 36 – Moderate/no MTS (a) 9 Severe MTS (b)	Age a) 65 (56.3–69.8) b) 70 (59–75) Gender – $p < 0.05$ a) 16/36 male b) 9/9 male ASA I/II/III + IV a) 5/25/6 b) 1/4/4	Patients were excluded if pre-treated with NSAIDs. No prior usage of corticosteroid, however, all patients received 125 mg methylprednisolone as part of standard anaesthetic management	6/9

Table 2 (*Continued*)

Observational studies

Author	Number of subjects	Type of surgery and groups	Patient demographics	Usage of NSAIDs and Corticosteroids before surgery	Newcastle-Ottawa scale risk of bias
Ring et al. [23] Denmark, 2019	66 patients	Major abdominal surgery 22 – Gastrectomy (a) 21 – Whipple (b) 23 – Liver surgery (c)	Age a) 66 (55-73) b) 69 (63−73) c) 61 (54−68) Gender a) 12/22 male b) 8/21 male c) 16/23 male ASA I + II/III + IV a) 13/9 b) 15/6 c) 19/4	Patients were excluded if pre-treated with NSAIDs. No prior usage of corticosteroid, however, 45 patients (Whipple and liver surgery) received 125 mg methylprednisolone as part of standard anaesthetic management	5/9
Seltzer et al. [6] United States, 1985	20 patients	Abdominal aortic surgery	Age - 62.8 ± 7.3 No report of gender, all patients ASA II-IV	No reports of NSAID or corticosteroids usage	4/9
Seltzer et al. [5] United States, 1988	12 patients	Abdominal aortic surgery 8 – Control 4 – Ibuprofen 12 mg/kg	Age - 63−79 No report of gender, all patients ASA II-IV	No reports of NSAID or corticosteroid usage	4/9

Case reports

Author	Patient description	Type of surgery
Aoki et al. [32] Japan, 2019	A 52-year-old male and a 62-year-old male with lung cancer. Both developed sudden blood pressure falls and facial flushing during surgery. Both were treated with Flurbiprofen Axetil, with quick haemodynamic normalisation.	Lung surgery
Comunale et al. [87] United States, 1992	An 85-year-old woman with lower gastrointestinal bleed. Developed massive drop in blood pressure, tachycardia, and facial flushing. Poor response to vasopressor treatment. Administered Octreotide Acetate with quick haemodynamic normalisation.	Colon surgery
Couto et al. [88] Brazil, 2017	A 66-year-old woman known with Morbus Chron undergoing intestinal resection developed a massive drop in blood pressure and facial flushing. She was treated with fluids and vasopressor therapy, with haemodynamic normalisation achieved after 60 min.	Intestinal resection
Greek et al. [33] United States, 1989	A 60-year-old man undergoing thoracoabdominal aneurysm repair developed facial flushing and severe hypotension, despite vasopressor treatment. Surgery paused, and haemodynamics normalised, but the patient again develops severe hypotension, why the surgery is aborted. New surgery 6 months later, premedicated with ibuprofen with an uneventful course.	Thoracoabdominal aneurysm repair
Hara et al. [34] Japan, 2020	A 68-year-old woman with rectal cancer and hypertrophic cardiomyopathy. Developed facial flushing and a massive drop in blood pressure. Flurbiprofen was administered with quick haemodynamic normalisation.	Rectum extirpation
Koyama et al. [41] Japan, 1997	A 64-year-old man undergoing coronary artery bypass graft using the right gastroepiploic artery. During the harvesting of the graft, the patient developed marked facial flushing and severe hypotension. Haemodynamics normalised following approximately 10 min of fluid and vasopressor therapy.	Coronary artery bypass graft using right gastroepiploic artery
Latson et al. [45] United States, 1992	An 84-year-old man with abdominal aortic aneurysm. Develops facial flushing and hypotension shortly after bowel manipulation. Hypotension was not normalised on fluid and vasopressor therapy. The patient is therefore administered i.v Ketorolac Tromethamine with quick haemodynamic normalisation.	Abdominal aortic repair
Woehlck et al. [36] United States, 2004	A 64-year-old woman with Colitis Ulcerosa undergoing a total colectomy. Develops facial flushing and severe hypotension following mesenteric manipulation. Stabilised with high dose vasopressor, and normalised at the end of mesenteric manipulation	Total colectomy
Woehlck et al. [89] United States, 2017	A 21-year-old woman known with Moyamoya Uninow undergoing omental to pial pedicle flap transfer. Develops severe hypotension during the traction of the omental flap. It was stabilised with vasopressor therapy, which is continued in the postoperative course, due to persistent hypotension.	Omental to pial pedicle flap transfer
Zaar et al. [53] Denmark, 2014	A 72-year-old man and a 67-year-old woman both undergoing pancreatic surgery. The man developed severe hypotension and facial flushing, while the woman had an uneventful surgery. Laser Speckle Contrast Imaging of facial perfusion showed increased levels in only the man.	Pancreatic surgery

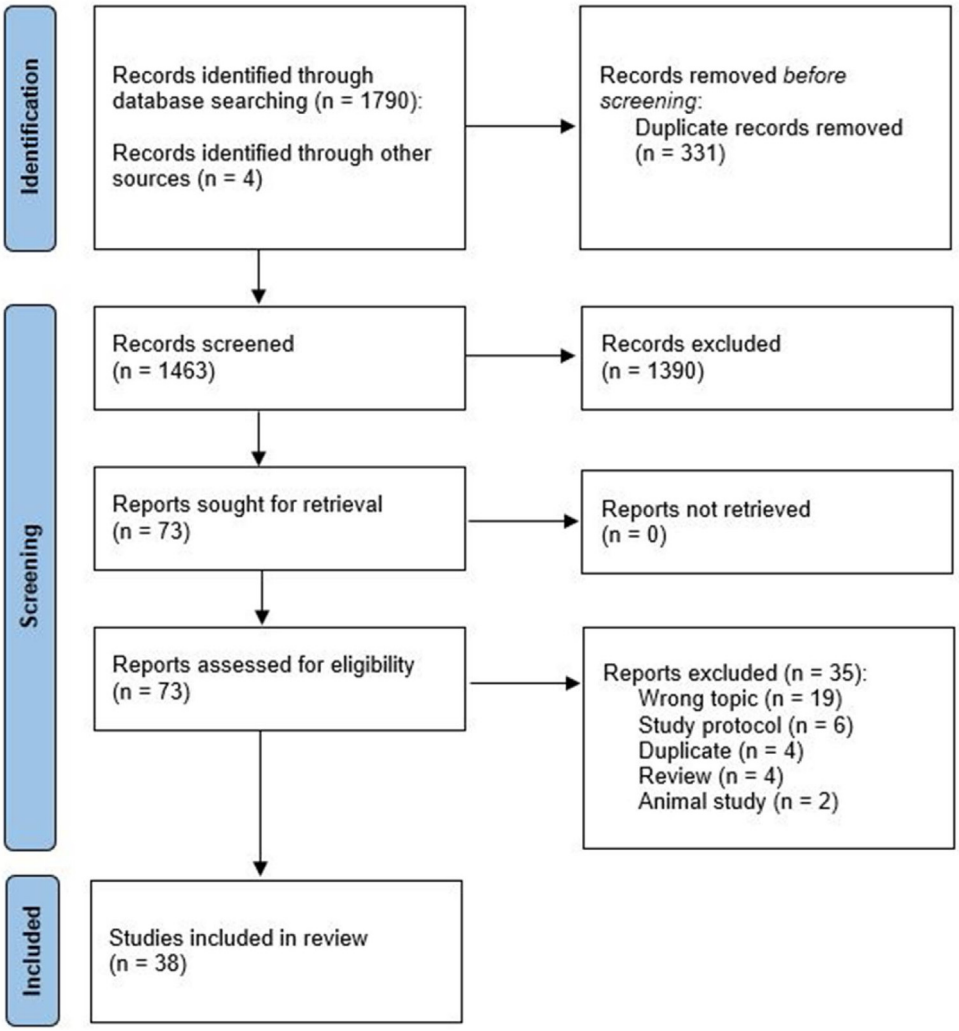

Fig. 1. PRISMA chart.

Intraoperative impact of MTS

MTS affects the intraoperative course significantly. Firstly, all patients develop an increased level of PGI_2 shortly following initial abdominal exploration. This increase, however, is significantly larger in patients developing MTS [3,37], with the highest levels of PGI_2 seen in patients developing severe MTS [8,23,42]. All studies examining the changes in PGI_2 use a surrogate marker, the stable metabolite 6-keto-$PGF1_{\alpha}$, due to the fast breakdown of PGI_2 in vivo. The measurement of 6-keto-$PGF1_{\alpha}$ is done in one of two ways in the assessed studies. The older studies, from prior to the year 2000, use radioimmunoassay [5,8,16,18,37,39,40,50,51], while the newer studies use a comparable enzyme-linked immunosorbent assay [3,11,13,17,23,35,42,44,52]. PGI_2, a potent vasodilator, leads to increased facial blood flow in patients developing severe MTS [23,53]. PGI_2 also leads to a decreased SVR in patients flushing [4–6,8], with the lowest levels seen in patients developing severe MTS [8,23]. This is combined with a decreased MAP in patients developing MTS [4,8,16,39]. However, some studies have not found any differences in MAP between patients developing severe MTS and those who do not, even though they had lower SVR [17,42]. This is probably due to the anaesthetic management of these patients, as it was also found that patients developing severe MTS received increased levels of vasopressor therapy [3,4,14,35]. Most studies also found patients developing MTS had an increase in HR [5,6,8,16,44,54]. However, a few studies did not find any difference [17,23,42], once again probably due to the anaesthetic management. Only four studies examined the impact of developing MTS on the duration of surgery, with two showing no difference [13,54], one study finding an increased duration of surgery in patients developing MTS [4], while the last study did not find an increased duration of surgery in patients developing severe MTS [42]. (Randomised controlled trials and observational studies).

Postoperative impact of MTS

The development of MTS may also affect the postoperative course (Table 4). One study assessed the association of developing MTS in general with the incidence of severe postoperative complications (Clavien-Dindo $\geq$ 3a), with no increased incidence in patients developing MTS [3].

However, two studies examined the effects of developing severe MTS. Both studies found a significant two to three times higher incidence of severe postoperative complications (Clavien-Dindo $\geq$ 3a/3b) [3,17]. One of the two studies also looked at the association with postoperative morbidity (Comprehensive Complication Index: a weighted sum of the occurrence and severity of all complications [55]), once again with two times higher relative risk of severe postoperative morbidity (Comprehensive Complication Index $\geq$ 26.2) in patients developing severe MTS, when compared to patients not developing severe MTS [17]. This study

Table 3
Incidence of MTS and severe MTS.

Study	Number of patients	Type of surgery	Patients with MTS	Patients with grade 0 flushing	Patients with grade 1 flushing	Patients with grade 2 flushing
Open surgery – no pre-treatment						
Diagnostic criteria: Facial flushing with different severities (Grade 0–2)						
Ambrus et al. [3] Denmark, 2017	25 patients	Oesophagectomy	17 (68)	8 (32)	9 (36)	8 (32)
Brinkmann et al. [37] Germany, 1994	20 patients	Major abdominal surgery	15 (75)	5 (25)	9 (45)	6 (30)
Gottlieb et al. [8] United States, 1989	31 patients	Abdominal aortic surgery	18 (58)	13 (42)	11 (35)	7 (23)
Hudson et al. [40] United States, 1990	13 patients	Abdominal aortic surgery	11 (85)	2 (15)	4 (31)	7 (54)
Koyama et al. [15] Japan, 1995	12 patients	Abdominal hysterectomy	11 (92)	1 (8)	9 (75)	2 (17)
Nomura et al. [16] Japan, 2010	33 patients	Major abdominal surgery	18 (55)	15 (45)	4 (13)	14 (42)
Olsen et al. [42] Denmark, 2021	67 patients	Oesophagectomy and gastrectomy	50 (75)	17 (25)	24 (36)	26 (39)
Combined	201 patients		140 (70)	61 (30)	70 (35)	70 (35)
Diagnostic criteria: A decrease in MAP combined with facial flushing or decreased transcutaneous saturation						
Brinkmann et al. [4] Germany, 1999	46 patients	Pancreatic surgery	33 (72)	Na	Na	Na
Combined	46 patients		33 (72)	Na	Na	Na
Diagnostic criteria: Hypotension combined with facial flushing						
Chen et al. [44] China, 2020	71 patients	Gastrectomy	56 (79)	Na	Na	Na
Haraguchi et al. [38] Japan, 2018	37 patients	Gastrectomy	17 (46)	Na	Na	Na
Seltzer et al. [6] United States, 1985	20 patients	Abdominal aortic surgery	15 (75)	Na	Na	Na
Seltzer et al. [5] United States, 1988	8 patients	Abdominal aortic surgery	8 (100)	Na	Na	Na
Takahashi et al. [46] Japan, 2013	13 patients	Colorectal surgery	11 (85)	Na	Na	Na
Takahashi et al. [47] Japan, 2016	34 patients	Colorectal surgery	28 (82)	Na	Na	Na
Takahashi et al. [35] Japan, 2017	27 patients	Colorectal surgery	24 (89)	Na	Na	Na
Diagnostic criteria: Facial flushing						
Fujimoto et al. [13] Japan, 2012	15 patients	Major abdominal surgery	12 (80)	Na	Na	Na
Hudson et al. [39] United States, 1988	33 patients	Abdominal aortic surgery	27 (82)	Na	Na	Na
Combined	258 patients		198 (77)	Na	Na	Na
Diagnostic Criteria: Hypotension, tachycardia, and facial flushing						
Takada et al. [31] Japan, 2013	60 patients	Major abdominal surgery	57 (95)	Na	Na	Na
Combined	60 patients		57 (95)	Na	Na	Na
Total combined	565 patients		428 (76)	61 (30)	70 (35)	70 (35)
Minimally invasive surgery – no pre-treatment						
Diagnostic criteria: Facial flushing with different severities (Grade 0–2)						
Ambrus et al. [3] Denmark, 2017	25 patients	Robot assisted esophagectomy	5 (20)	20 (80%)	5 (20)	0 (0)
Nomura et al. [16] Japan, 2010	17 patients	Major abdominal laparoscopic surgery	2 (12)	15 (88)	2 (12)	0 (0)
Total combined	42 patients		7 (17)	35 (83)	7 (17)	0 (0)

Values are count (%).
Combined values calculated as a simple sum.

also found an increased length of stay in patients developing severe MTS, and an increased risk of admission to the intensive care unit. (Observational studies)

Preventative measures against MTS

Various preventative and therapeutic measures have been examined for the prevention and/or treatment of MTS and the associated deleterious effects during and after surgery. The examined measures range from alternative surgical approaches to different anaesthetic management and pharmacological interventions (Table 5).

NSAID

Non-selective NSAID. The administration of non-selective NSAID was associated with a significantly decreased incidence of MTS (18% *vs.* 82%) and severe MTS (3% *vs.* 29%). (Randomised controlled trials and one observational study). This finding has a low quality of evidence, according to GRADE. Below results from each subtype of non-selective NSAID will be presented.

Ibuprofen. Six studies examined the impact of Ibuprofen on MTS. These studies found that patients treated with Ibuprofen had a much lower incidence of MTS (18% *vs* 83%) and severe MTS (7% *vs* 39%) compared with patients treated with placebo [5,37,40]. Ibuprofen works by almost eliminating the release of PGI_2, resulting in

Table 4
Incidence of severe postoperative complications and severe postoperative morbidity.

Study	Number of patients	Type of surgery	Incidence of severe postoperative complications	*p*-value	Incidence of severe postoperative morbidity[a]	*p*-value
MTS/no MTS						
Ambrus et al. [3] Danmark, 2017	MTS: 17 patients No MTS: 8 patients	Esophagectomy	Clavien Dindo ≥ 3a MTS: 8 (47) No MTS: 2 (25)	0.294	Na	Na
Grade 2 flushing *vs* Grade 1/Grade 0 flushing						
Ambrus et al. [3] Denmark, 2017	Grade 2: 8 patients Grade 0/1: 17 patients	Esophagectomy	Clavien Dindo ≥ 3a Grade 2: 6 (75) Grade 0/1: 4 (24)	**0.037**	Na	Na
Olsen et al. [17] Denmark, 2020	Grade 2: 43 patients Grade 0/1: 94 patients	Major abdominal surgery	Clavien Dindo ≥ 3a Grade 2: 18 (42) Grade 0/1: 22 (23)	0.078	Grade 2: 22 (51) Grade 0/1: 26 (28)	**0.03**
			Clavien dindo ≥ 3b Grade 2: 12 (28) Grade 0/1: 10 (11)	**0.023**		

Values are count (%). Severe postoperative complications are defined as complications scored as either Clavien Dindo ≥ 3a or Clavien Dindo ≥ 3b. Severe postoperative morbidity is defined as Comprehensive Complication Index ≥ 26.2.

Table 5
Preventative measures against the development of MTS.

Study	Number of patients	Type of surgery	Intervention	Patients with MTS	*p*-value	Patients with grade 2 flushing	*p*-value
NSAID (GRADE: low quality of evidence)							
***Ibuprofen* (GRADE: very low quality of evidence)**							
Brinkmann et al. [37] Germany, 1994	Control: 20 patients Ibuprofen: 20 patients	Major abdominal surgery	400 mg ibuprofen i.v. preoperative	Control: 15 (75) Ibuprofen: 3 (15)	< **0.001**	Control: 6 (30) Ibuprofen: 0 (0)	**0.02**
Hudson et al. [40] United States, 1990	Control: 13 patients Ibuprofen: 14 patients	Abdominal aortic surgery	800 mg Ibuprofen p.o. in 3 doses preoperative	Control: 11 (85) Ibuprofen: 4 (29)	**0.006**	Control: 7 (54) Ibuprofen: 1 (7)	**0.016**
Seltzer et al. [5] United States 1988	Control: 8 patients Ibuprofen: 4 patients	Abdominal aortic surgery	12 mg/kg Ibuprofen p.o. preoperative	Control: 8 (100) Ibuprofen 0 (0)	**0.002**	Na	Na
Combined	Control: 41 patients Ibuprofen: 38 patients			Control: 34 (83) Ibuprofen: 7 (18)	< **0.001**	Control: 13 (39) Ibuprofen 1 (3)	< **0.001**
***Flurbiprofen* (GRADE: low quality of evidence)**							
Fujimoto et al. [13] Japan, 2012	Control: 15 patients Flurbiprofen: 15 patients	Major abdominal surgery	50 mg Flurbiprofen Axetil i.v. preoperative	Control: 12 (80) Flurbiprofen: 1 (7)	< **0.001**	Na	Na
Takada et al. [49] Japan, 2013	Control: 20 patients Flurbiprofen: 19 patients	Major abdominal surgery	50 mg Flurbiprofen Axetil i.v. following induction	Control: 20 (100) Flurbiprofen: 4 (21)	< **0.001**	Na	Na
Takahashi et al. [46] Japan, 2013	Control: 13 patients Flurbiprofen: 11 patients	Colorectal surgery	50 mg Flurbiprofen Axetil i.v. preoperative	Control: 11 (85) Flurbiprofen: 0 (0)	< **0.001**	Na	Na
Takahashi et al. [47] Japan, 2016	Control: 34 patients Flurbiprofen: 23 patients	Colorectal cancer	50 mg Flurbiprofen Axetil i.v. preoperative	Control: 28 (82) Flurbiprofen: 0 (0)	< **0.001**	Na	Na
Takahashi et al. [35] Japan, 2017	Control: 29 patients Flurbiprofen: 16 patients	Colorectal cancer	50 mg Flurbiprofen Axetil i.v. preoperative	Control: 25 (89) Flurbiprofen: 0 (0)	< **0.001**	Na	Na
Combined	Control: 111 patients Flurbiprofen: 84 patients			Control: 96 (87) Flurbiprofen: 5 (6)	< **0.001**	Na	Na
***Aspirin* (GRADE: very low quality of evidence)**							

Table 5 (*Continued*)

Study	Number of patients	Type of surgery	Intervention	Patients with MTS	*p*-value	Patients with grade 2 flushing	*p*-value
Gottlieb et al. [8] United States, 1989	Control: 31 patients Aspirin: 6 patients	Abdominal aortic surgery	Daily aspirin usage	Control: 18 (58) Aspirin: 2 (33)	0.383	Control: 7 (23) Aspirin: 0 (0)	0.571
Combined				Control: 18 (58) Aspirin: 2 (33)	0.383	Control: 7 (23) Aspirin: 0 (0)	0.571
***Indomethacin* (GRADE: very low quality of evidence)**							
Koyama et al. [15] Japan, 1995	Control: 12 patients Indomethacin: 12 patients	Abdominal hysterectomy	50 mg Indomethacin sup. 90 min preoperative	Control: 11 (92) Indomethacin: 3 (25)	**0.003**	Control: 2 (17) Indomethacin: 0 (0)	0.478
Koyama et al. [15] Japan, 1995	Control: 12 patients Indomethacin: 12 patients	Abdominal hysterectomy	50 mg Indomethacin sup. following induction	Control: 11 (92) Indomethacin: 10 (83)	1	Control: 2 (17) Indomethacin: 1 (8)	1
Combined	Control: 12 patients Indomethacin: 24 patients			Control: 11 (92) Indomethacin: 13 (54)	**0.024**	Control: 2 (17) Indomethacin: 1 (4)	0.253
Total combined	Control: 195 patients NSAID: 152 patients			Control: 159 (82) NSAID: 27 (18)	< **0.001**	Control: 22/76 (29) NSAID: 2/64 (3)	< **0.001**
Corticosteroid (GRADE: very low quality of evidence)							
Ring et al. [23] Denmark, 2018	Control: 22 patients Corticosteroid: 44 patients	Gastrectomy, pancreatic surgery, and liver surgery	Liver and pancreatic surgery received 125 mg methylprednisolone preoperative	Control: 16 (73) Corticosteroid: 19 (43)	**0.04**	Control: 8 (36) Corticosteroid: 8 (18)	0.104
Anaesthesia without remifentanil (GRADE: very low quality of evidence)							
Nomura et al. [16] Japan, 2010	Control: 33 patients No Remifentanil: 34 patients	Major abdominal surgery	Anaesthesia without Remifentanil	Control: 18 (55) No Remifentanil: 4 (12)	< **0.001**	Control: 14/33 (42) No Remifentanil: 3/34 (9)	< **0.001**
Nomura et al. [16] Japan, 2010	Control: 17 patients No Remifentanil: 16 patients	Laparoscopic abdominal surgery	Anaesthesia without Remifentanil	Control: 2 (12) No Remifentanil: 1 (6)	1	Control: 0 (0) No Remifentanil: 0 (0)	1
Combined	Control: 50 patients No Remifentanil: 50 patients			Control: 20 (40) No Remifentanil: 5 (10)	< **0.001**	Control: 14 (28) No Remifentanil: 3 (6)	**0.006**
Perioperative Dexmedetomidine (GRADE: very low quality of evidence)							
Chen et al. [44] China, 2020	Control: 23 patients Dexmedetomidine 0.5 μg/kg: 25 patients Dexmedetomidine 1 μg/kg: 23 patients	Gastrectomy	Perioperative Dexmedetomidine 0.5 μg/kg 1 μg/kg	Control: 18 (78)		Dexmedetomidine0.5 μg/kg: 19 (76) Dexmedetomidine 1 μg/kg: 19 (83)	0.85
Na	Na						
Time of epidural activation (GRADE: very low quality of evidence)							
Strandby et al. [52] Denmark, 2021	Early epidural activation: 25 patients Late epidural activation: 20 patients	Open oesophagectomy	Early *vs* late epidural activation	Early activation: 21 (84 %) Late activation: 13 (65 %)	0.176	Early activation: 13 (52 %) Late activation: 5 (25 %)	0.08
Sevoflurane dosage (GRADE: very low quality of evidence)							
Haraguchi et al. [38] Japan, 2018	Sevoflurane 1.0 %: 18 patients Sevoflurane 1.4 %: 19 patients	Gastrectomy	Sevoflurane dosage 1.0 % 1.4 %	%: 12 (67) 1.4 %: 5 (26)	**0.03**	Na	Na
Operative approach							
***Minimally invasive surgery* (GRADE: very low quality of evidence)**							
Ambrus et al. [3] Denmark, 2017	Open oesophagectomy: 25 patients Robotic-assisted oesophagectomy: 25 patients	Esophagectomy	Open *vs* robotic-assisted approach	Open: 17 (68) Robotic assisted: 5 (20)	**0.001**	Open: 8 (32) Robotic assisted: 0 (0)	**0.004**
***Transabdominal and retroabdominal approach* (GRADE: very low quality of evidence)**							

Table 5 (*Continued*)

Study	Number of patients	Type of surgery	Intervention	Patients with MTS	*p*-value	Patients with grade 2 flushing	*p*-value
Hudson et al. [39] United States, 1988	Transabdominal approach: 33 patients Retroabdominal approach: 19 patients	Abdominal aortic surgery	Transabdominal *vs* retroabdominal approach	Transabdominal: 27 (82) Retroabdominal: 0 (0)	< **0.001**	Na	Na

Values are count (%).
Combined values are calculated as a simple sum of all studies examining the intervention.
GRADE assessment is reported for each preventative measure.

lower levels of PGI_2 in Ibuprofen pre-treated patients [5,14,37,40]. This leads to a reduced decrease of SVR [5,18,40] and higher MAP in patients pre-treated with Ibuprofen [14,18,37,40]. Further, patients receiving placebo had higher HR and higher cardiac output following mesenteric traction [18,40]. Patients receiving placebo had higher levels of endogenous vasopressors (renin, vasopressin, and epinephrine), and required higher levels of vasopressors therapy [14]. Patients receiving a placebo also showed an increased level of pulmonary venous shunting and a lower oxygenation ratio [18]. However, one study showed that patients who received Ibuprofen had higher levels of bacterial endotoxaemia and of bacterial translocation to mesenteric lymph nodes [19] (Randomised controlled trials). This finding has a very low quality of evidence, according to GRADE.

Flurbiprofen Axetil. Five studies examined the impact of Flurbiprofen Axetil on MTS. These studies found a significantly lower incidence of MTS (6 % *vs* 87 %) in patients receiving Flurbiprofen [13,35,46,47,49]. Only one of these studies examined the levels of PGI_2 in patients receiving Flurbiprofen and found increased levels only in placebo-treated patients [13]. Further, placebo-treated patients developed a significantly lower SVR [47], a significantly lower MAP [13,35,46,47], and higher HR [13]. It was also found that placebo-treated patients required increased levels of vasopressor support [35]. Two studies also examined the effects of administering Flurbiprofen after developing MTS and found that this led to a significantly quicker normalisation of the haemodynamics when compared with patients receiving placebo [35,49] (Randomised controlled trial). This finding has a low quality of evidence, according to GRADE.

Aspirin. One study examined the impact of a daily usage of aspirin before surgery and found no differences in the incidence of MTS, or severe MTS [8]. Further, this study did not find any differences in haemodynamic between aspirin users and placebo users. However, a significant decrease in MAP and increase in HR was only seen in the placebo group (Observational study). This finding has a very low quality of evidence, according to GRADE.

Indomethacin. One study examined the effect of Indomethacin on the incidence of MTS, this study found a significantly lower incidence of MTS (54% *vs* 92%), but not of severe MTS in patients treated with Indomethacin [15] (Randomised controlled trial). This finding has a very low quality of evidence according to GRADE.

COX-2 selective NSAID.

Parecoxib. One study examined the use of the COX-2 selective NSAID Parecoxib and found no difference in MAP, HR, or PGI_2 when compared with patients treated with placebo [11]. Patients treated with Parecoxib did, however, have a lower oxygenation rate following mesenteric traction (Randomised controlled trial). This finding has a very low quality of evidence, according to GRADE.

Corticosteroids

A single dose of 125 mg of Methylprednisolone just following induction of anaesthesia was found to be associated with a lower incidence of MTS (73% *vs* 43%) but not of severe MTS (36% *vs* 18%) during major abdominal surgery [23] (Observational study). Furthermore, in an exploratory study only looking at patients receiving corticosteroids, no differences in postoperative morbidity nor severe postoperative complications were identified when comparing patients developing severe MTS with patients not developing severe MTS [43]. These findings have a very low quality of evidence, according to GRADE.

Remifentanil

The usage of remifentanil during surgery was associated with an increased incidence of MTS (40% *vs* 10%) and a higher incidence of severe MTS (28% *vs* 6%). However, no differences were found in the haemodynamics between groups [16] (Randomised controlled study). This finding has a very low quality of evidence, according to GRADE.

Dexmedetomidine

The intraoperative usage of Dexmedetomidine did not impact the incidence of MTS, but it did lead to a significantly increased duration of hypotension in patients developing MTS [44] (Randomised controlled trial). This finding has a very low quality of evidence, according to GRADE.

Time of epidural activation

There were no differences in either the incidence of MTS or the incidence of severe MTS when comparing patients with early epidural activation (start of surgery) with patients receiving late epidural activation (end of surgery) [52]. However, it was shown that patients with epidural anaesthesia developed lower blood pressure during surgery than patients only receiving general anaesthesia [37]. Further, patients receiving early epidural activation required increased amounts of vasopressor therapy (52). However, no difference in morbidity was identified between patients receiving early epidural activation and patients receiving late epidural activation [42] (Randomised controlled trial). This finding has a very low quality of evidence, according to GRADE.

Sevoflurane dosage

One study found that patients receiving 1.0% sevoflurane during surgery had a higher incidence of MTS compared with patients receiving 1.4% sevoflurane (67% *vs* 26%) [38] (Observational study). This finding has a very low quality of evidence, according to GRADE.

Operative approach

Minimally invasive surgery. One study found that a robotic-assisted approach to oesophagectomies was associated with a significantly

lower incidence of both MTS (20% *vs* 68%) and severe MTS (0% *vs* 32%) when compared with an open approach. However, no differences were found regarding postoperative morbidity [3] (Observational study). This finding has a very low quality of evidence, according to GRADE.

Transabdominal and retroabdominal approach. One study found that a retroperitoneal approach to abdominal aortic aneurysm repairs leads to a lower incidence of MTS (0% *vs* 82%) compared to a transabdominal approach. It also eliminated the associated PGI_2 release, hypotension, and tachycardia [39], which was seen in patients undergoing abdominal aortic aneurysm repair with a transabdominal approach (Observational study). This finding has a very low quality of evidence, according to GRADE.

Discussion

Our review identified an incidence of MTS in the literature of 76%, with approximately 35% developing severe MTS, and an incidence of MTS of 17%, with 0% developing severe MTS when undergoing minimally invasive surgery. Further, it was identified that severe MTS was associated with an increased haemodynamic instability compared with patients developing no/moderate MTS. Lastly, patients developing severe MTS had an increased incidence of severe postoperative complications and of having increased postoperative morbidity.

In this review, MTS was found to be occurring in upwards of 76% of patients undergoing major open abdominal surgery, without any prophylactic treatment, with approximately a third of all patients developing severe MTS. These incidences underline the importance of MTS, especially severe MTS, in the clinical management of surgical patients. This importance is largely due to the findings of a possible increased postoperative morbidity in patients developing severe MTS, [17,42], and the possible worsening of the long-term outcome in patients undergoing major open cancer surgery [21,22]. These findings may indicate that future research should move from focusing on MTS in general to being more focused on the development of severe MTS. This review also identified one study describing the occurrence of a syndrome mimicking MTS during two cases of lung traction [32]. This may indicate that MTS may be a more general response by the human organism to traction or shear stress of the endothelium, as one study from 1992 showed that lung traction indeed causes a release of PGI_2 [56]. But the syndrome may be most well-recognised during abdominal surgery, due to the high incidence. This is probably caused by the high mobility of the abdominal viscera, leading to the highest levels of surgical shear stress/endothelial traction during these procedures.

A major problem with MTS research is the varying diagnostic criteria for MTS, although most studies to some degree use the occurrence of facial flushing as either the only or part of the diagnostic criteria of MTS. However, the different diagnostic criteria show comparable incidences of MTS, indicating a limited impact of different diagnostic criteria on the comparability of the published studies. Furthermore, only a few studies have subdivided MTS into different levels of severity, which should be the standard going forward as newer studies have shown that patients developing severe MTS have a more significant haemodynamic affection [8,17,42]. Moreover, the development of severe MTS may be associated with a significantly worse postoperative course, with an increased incidence of severe postoperative complications, increased postoperative morbidity, and increased length of stay [3,17]. So, in our opinion, the future standard should be the division of MTS into three levels of severity using the level of facial flushing, with the primary focus of future research being severe MTS. All included studies used a subjective assessment of the degree of facial flushing when grading the severity of MTS. However, this approach does have some major limitations. The subjective identification and grading of facial flushing can be very difficult, and in patients with a darker skin colour, patients who have anaemia, and patients with different dermatological conditions, causing discoloration of the facial skin, it can be almost impossible [57]. Further, a subjective assessment of the severity of MTS may vary among different investigators, possibly impacting the research on MTS. One newer study examined an objective approach for the grading of the MTS response. The study used Laser Speckle Contrast Imaging (LSCI) to quantitatively measure the skin blood flow in the forehead and cheek, thereby quantifying the degree of facial flushing [23]. The study found that LSCI identified higher levels of facial blood flow at 15 min into surgery in patients subjectively characterised as having severe MTS, while no difference was seen between patients with moderate MTS and no MTS. An objective measure of MTS would increase the quality and comparability between different studies and would enable multicentre studies. These results emphasise that a major goal of future research should be the development of an objective grading of MTS.

The development of severe MTS was found to be significantly associated with increased postoperative morbidity, increased incidence of severe postoperative complications, and increased length of stay in the only two studies examining the postoperative impact. These studies found a relative risk of two to three of developing severe postoperative complications and of developing increased postoperative morbidity when developing severe MTS, as compared with patients not developing severe MTS. This is a clinically significant increased risk, especially with the literature showing decreased long-term cancer survival when developing severe postoperative complications and increased postoperative morbidity [21,22]. However, since only two studies have examined this association, it must be validated in future research. Several pathophysiological reasons are thought to be part of the pathophysiology behind the increased postoperative morbidity in patients developing severe MTS. Firstly, MTS is associated with a haemodynamic response characterised by hypotension and tachycardia, with hypotension being a known risk factor for postoperative morbidity and mortality [58,59]. This haemodynamic response is significantly more pronounced in patients developing severe MTS, in which severe haemodynamic instability occurs. Furthermore, the increased hypotension seen in patients developing severe MTS leads to an increased sympathoadrenal activation, with increased levels of endogenous catecholamines [14]. Higher levels of catecholamines have been associated with increased morbidity and mortality in trauma patients and patients with out-of-hospital cardiac arrest [60–62] and could therefore also be correlated to postoperative morbidity. Besides the endogenous response to the haemodynamic impact of MTS, many patients, especially those developing severe MTS, require vasopressor therapy during surgery [3,4,14,52]. This is another well-known risk factor of postoperative complications [63]. One study found that patients who developed severe MTS, already prior to surgery had an increased level of epinephrine, which, furthermore, was associated with increased postoperative morbidity. Moreover, that study found that these patients had increased blood loss during surgery [42], a known risk factor of postoperative morbidity, both directly [64] and through the increased requirement of blood transfusions [65]. That study also found that patients who developed severe MTS had increased endothelial damage following their surgical procedure, as indicated by increased levels of sVEGFR-1 and Syndecan-1. Increased levels of these biomarkers have been shown in trauma patients to be associated with higher levels of morbidity and worse survival

[61,66,67]. Lastly, the levels of comorbidity could also differ between patients developing severe MTS, and those who do not develop severe MTS, possibly impacting the postoperative course. A high level of comorbidity is a well-known risk factor for increased postoperative morbidity [68], and could also indicate a lower baseline resistance against the PGI_2-release of the MTS response. No studies have yet examined the impact of levels of comorbidity on the incidence or the impact of MTS. However, no significant differences in age or ASA score were reported between those developing MTS or severe MTS and those who did not develop it. The impact of specific comorbidities on MTS would therefore be a very interesting topic for future studies. All combined, it clearly shows that the pathophysiology behind the possible increased postoperative morbidity seen in patients developing severe MTS is very complex. It may at least consist of haemodynamic changes, sympathoadrenal activation, intraoperative factors, and endothelial damage, and more research should focus on this topic.

The increased postoperative morbidity in patients developing severe MTS makes it clear that therapeutic or prophylactic measures against MTS are warranted. Multiple preventative measures have been tested. NSAID is the most thoroughly tested intervention against the development of MTS and has been shown almost to eliminate the occurrence of MTS and attenuate the haemodynamic effects of the response. NSAIDs are COX inhibitors and work by blocking the synthesis of PGI_2, the primary instigator of the MTS-response [5,13,14,18,19,35,37,40]. No studies have yet examined whether NSAID attenuates the increased postoperative morbidity seen in patients developing severe MTS. One study did, however, find that patients who received a single NSAID dose just before their surgery developed higher levels of endotoxaemia and bacterial translocation to mesenteric lymph nodes [19]. But this study did not assess the impact on postoperative morbidity. The administration of NSAIDs in surgical patients is controversial. One review has found that NSAID administration for at least four days increases the risk of upper gastrointestinal complications (bleeding, ulcer, and perforation) [69]. Another review showed that postoperative NSAID administration was associated with an increased risk of anastomotic leakage following abdominal surgery [70]. However, both these reviews examined multiple doses of NSAID, and it is, therefore, unknown whether the same complications arise from a single dose of NSAID given just before surgery. Future research, therefore, needs to assess the safety of a single perioperative NSAID dose. Furthermore, whether the attenuation of the acute MTS response also leads to an attenuation of the increased postoperative morbidity. Lastly, one study examined the effects of administering NSAID following the identification of the development of MTS. Quite interesting, this study found that the patients who received NSAID had a significantly lower release of PGI_2, a quicker haemodynamic normalisation, and a lower vasopressor requirement. This finding is interesting as it potentially enables personalised treatment of MTS, in which only patients developing MTS receive treatment. This would lower the general risk of side effects. However, more research is required to validate this finding, and examine the impact on the postoperative course.

Corticosteroids may also be a good candidate for attenuating the MTS response. Only one observational study has examined the association between corticosteroids and MTS and showed that 125 mg of Methylprednisolone, equivalent to 23.4 mg of Dexamethasone [71], was associated with a lower incidence of MTS [23]. This is probably through a down-regulation of COX-1 [72]. This study did not find a significantly lower incidence of severe MTS, in patients receiving Methylprednisolone, even though it halved the incidence. This could be due to missing power to detecting such a difference in the incidence, as this was not the primary aim of that study. All other studies either did not report the usage of corticosteroids before and during surgery or excluded patients treated with corticosteroids. However, corticosteroids are commonly used today as PONV prophylaxis and as part of an enhanced recovery after surgery approach in major abdominal surgery. This may lead to unreported corticosteroid usage, which could potentially impact the results of the included studies. Corticosteroids are also known to lower the proinflammatory surgical stress [73,74], and attenuate endothelial damage following surgery [75,76], thereby possibly lowering the postoperative morbidity in patients developing severe MTS. This was also identified in the only study examining the impact of corticosteroids on these parameters. The study found no difference in postoperative morbidity or the incidence of severe postoperative complications when comparing patients developing severe MTS with those not developing severe MTS [43]. Furthermore, no differences in biomarkers of the proinflammatory surgical stress response and endothelial damage were found. However, this was an exploratory study, only examining patients receiving corticosteroids, and the findings need to be validated in future randomised controlled trials. The literature on corticosteroids in surgical patients and the impact on postoperative morbidity varies. Studies either show a reduction in the incidence of postoperative complications [77–80], or show little to no effect [81–83]. Further, few studies highlight the possible adverse effects of corticosteroids in surgical patients. One study reported an increased risk of hyperglycaemia [82], and another reported an increased risk of anastomotic dehiscence [84]. Future studies should therefore examine whether corticosteroids do influence patients developing MTS, and especially if they have any effects on patients developing severe MTS, attenuating the increased postoperative morbidity.

It would also be interesting to examine the impact of preoperative fluid optimisation, attenuating the possible hypovolaemia on MTS. This could possibly impact both the development of severe MTS and deleterious haemodynamic and postoperative effects of developing severe MTS.

Lastly, a few potentially non-pharmacological preventative pharmacological measures have been examined. One is a retroabdominal approach to the repair of abdominal aortic aneurysms. An approach that eliminates the occurrence of MTS [39]. This is probably due to the elimination of abdominal exploration, manipulation of the abdominal viscera, and mesenteric traction. The other approach is minimally invasive surgery, which significantly lowers the incidence of MTS, and eliminates the occurrence of severe MTS [3,16]. It has also been shown to lower the postoperative proinflammatory surgical stress response [85,86]. Once again, this is probably due to the approach lowering the degree of abdominal viscera manipulation and mesenteric traction being performed. This limits the potential development of splanchnic hypoperfusion and thereby lowers the PGI_2-release. However, both these approaches to the surgical procedure are not useful for all surgical patients, and as such more research must be performed into potential surgical measures which can be used during open surgery to lower the incidence of MTS.

It is, however, clear that more research is required focusing on the preventative measures since all examined preventive measures only reach a GRADE assessment of low or very low. Furthermore, no studies have examined the impact of pharmacological preventative measures on the postoperative course. As such, it is not yet known whether total prevention of the PGI_2-response following mesenteric traction is beneficial.

This review does have some limitations. Firstly, it is based on a wide variety of surgical procedures, with different anaesthesiologic management, different levels of surgical stress, and different degrees of postoperative morbidity. However, we believe this approach to be the best, as the inclusion of several different

surgical procedures increases the application of findings from this review to future research and daily clinical practice. Another significant limitation is the different definitions used for the diagnosis of MTS. However, we tried to present the different diagnostic criteria of MTS used in the literature and found that the incidence of MTS is comparable with the different diagnostic criteria used in the literature. Further, we tried to present a new objective measure of MTS. None of the included studies examined the effects of comorbidity on the incidence, intraoperative impact, or postoperative impact on MTS, even though the patients' comorbidities could impact all of these. Length of stay was only reported in one study. However, it may not be a good indicator of the recovery following surgery due to it relying partly on logistical factors. Only five studies reported vasopressor usage, which could impact the haemodynamics and the postoperative course of MTS. Lastly, most of the included studies were found to have either a high or moderate risk of bias, and for the preventative measures, the GRADE assessments had either low or primarily very low quality of evidence. This was to be expected, as no large randomised controlled trials exist on the subject, and only two studies have included at least 100 patients. However, it is not believed to have shifted the results in any direction, as almost all included studies have comparable results. But it clearly emphasises the need for more research on MTS in the future. Our review has a major strength of being the first review performed about MTS in the last 15 years. This is the first review on MTS performed with a systematic methodology presenting all existing data about MTS, ensuring a good quality of evidence.

Conclusion

This review found an incidence of MTS of 76% in patients undergoing major open abdominal surgery, with 35% developing severe MTS. However, only subjective diagnostic criteria exist limiting the comparability of MTS studies. The development of MTS and especially of severe MTS is associated with significant haemodynamic alterations in the form of loss of SVR, hypotension, and tachycardia. The development of severe MTS was found to be associated with increased postoperative morbidity. Lastly, several potential preventative measures for lowering the incidence of severe MTS or protecting against the adverse effects of developing severe MTS were identified. However, more research about MTS and especially on severe MTS. However, more research is needed in the future due to high levels of risk and bias and low to very low quality of evidence. All combined, this scoping review clearly emphasises that MTS, and especially severe MTS may have major clinical implications, and that the syndrome should receive more attention in the future, both in the clinical and the research settings. Future research should focus on developing an objective diagnosis, increasing knowledge of the pathophysiology behind the MTS and behind the increased postoperative morbidity in patients developing severe MTS, identifying risk factors of developing severe MTS, and identifying and testing preventative measures and potential therapeutic measures against MTS or severe MTS.

Author contributions

- Study conception and design: AAO, LBS, MPA.
- Acquisition of data: AAO, LAB, SSD, DF, HS.
- Analysis and interpretation of data: AAO, LAB, LBS, MPA.
- Drafting of the manuscript: AAO.
- Critical revision and final approval of the manuscript: AAO, LAB, SSD, DF, HS, LBS, MPA.

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The authors have no conflicts of interest to declare.

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Appendix A. Supplementary data

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