ACUTE ABDOMINAL PAIN: FROM ASSESSMENT TO MANAGEMENT

A registry analysis and a meta-analysis

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Ph.D. dissertation

Doctoral School of Clinical Medicine
Centre for Translational Medicine
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I. **Földi M**, Gede N, Kiss S, Vincze Á, Bajor J, Szabó I, Szepes Z, Izbéki F, Gervain J, Hamvas J, Vitális Zs, Fehér E, Crai S, Sallinen V, Ramirez Maldonado E, Meczker Á, Varjú P, Poropat G, Stimac D, Faluhelyi N, Miseta A, Nagy T, Márton Zs, Vereczkei A, Hegyi PJ, Párniczky A, Hegyi P, Szentesi A. The characteristics and prognostic role of acute abdominal on-admission pain in acute pancreatitis: A prospective cohort analysis of 1432 cases, Eur J Pain. 2021 Nov 10, doi:10.1002/ejp-1885. **(Q1, IF: 3.651)**

II. **Földi M**, Soós A, Hegyi P, Kiss S, Szakács Z, Solymár M, Pétervári E, Balaskó M, Krzysztof K, Molnár Zs. Transversus Abdominis Plane Block Appears to Be Effective and Safe as a Part of Multimodal Analgesia in Bariatric Surgery: A Meta-analysis and Systematic Review of Randomized Controlled Trials. Obesity Surgery. 2021;31(2):531-43, doi:10.1007/s11695-020-04973-8. **(Q1, IF: 3.479)**

PUBLICATIONS NOT RELATED TO THE SUBJECT OF THE DISSERTATION

III. **Földi M**, Farkas N, Kiss S, Zádori N, Váncsa S, Szakó L, Dembrovszky F, Solymár M, Bartalis E, Szakács Z, Hartmann P, Pár G, Erőss B, Molnár Z, Hegyi P, Szentesi A. Obesity is a risk factor for developing critical condition in COVID-19 patients: A systematic review and meta-analysis. Obesity reviews: an official journal of the International Association for the Study of Obesity. 2020;21(10):e13095, doi: 10.1111/OBR.13095 **(D1, IF: 9.213)**

IV. **Földi M**, Farkas N, Kiss S, Dembrovszky F, Szakács Z, Balaskó M, Erőss B, Hegyi P, Szentesi A. Visceral Adiposity Elevates the Risk of Critical Condition in COVID-19: A Systematic Review and Meta-Analysis. Obesity (Silver Spring, Md). 2021;29(3):521-8, doi:10.1002/OBY.23096 **(D1, IF: 9.298)**

V. Erőss B, Molnár Z, Szakács Z, Zádori N, Szakó L, Váncsa S, …**Földi M**,… et al. Personalized health education against health damage of COVID-19 epidemic in the elderly Hungarian population (PROACTIVE-19): protocol of an adaptive randomized controlled clinical trial. Trials. 2020;21(1):809. **(Q1, IF: 2.279)**

VI. Gombos K, **Földi M**, Kiss S, Herczeg R, Gyenesei A, Geiger L, et al. Analysis of COVID-19-Related RT-qPCR Test Results in Hungary: Epidemiology, Diagnostics, and Clinical Outcome. Frontiers in medicine. 2020;7:625673. **(D1, IF: 5.058)**

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VIII. Kiss S, Gede N, Hegyi P, Németh D, **Földi M**, Dembrovszky F, et al. Early changes in laboratory parameters are predictors of mortality and ICU admission in patients with COVID-19: a systematic review and meta-analysis. Medical Microbiology and Immunology. 2021;210(1):33-47. **(Q2, IF: 4.148)**

IX. Kiss S, Németh D, Hegyi P, **Földi M**, Szakács Z, Erőss B, et al. Granulocyte and monocyte apheresis as an adjunctive therapy to induce and maintain clinical remission in ulcerative colitis: a systematic review and meta-analysis. BMJ Open. 2021;11(5):e042374. **(Q1, IF: 3.017)**

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XIII. Kiss S, Pintér J, Molontay R, Nagy M, Farkas N, Sipos Z, Fehérvári P, Pecze L, **Földi M**, Vincze Á, Takács T, Czakó L, Izbéki F, Halász A, Boros E, Hamvas J, Varga M, Mickevicius A, Faluhelyi N, Farkas O, Váncsa S, Nagy R, Bunduc S, Hegyi PJ, Márta K, Borka K, Doros A, Hosszúfalusi N, Zubek L, Erőss B, Molnár Z, Párniczky A, Hegyi P, Szentesi A; Hungarian Pancreatic Study Group. Early prediction of acute necrotizing pancreatitis by artificial intelligence: a prospective cohort-analysis of 2387 cases. Sci Rep. 2022 May 12;12(1):7827. **(D1, IF: 4.996)**

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TARTALOM

LIST OF ABBREVIATIONS

IASP International Association for the Study of Pain

WHO World Health Organization

NRS Numerical Rating Scales

VAS Visual Analog Scales

NSAID Non-steroidal anti-inflammatory drugs

APS-POQ-R Revised American Pain Society Patient Outcome Questionnaire

AP Acute pancreatitis

CGRP Calcitonin-gene-related peptide

APACHE-II Acute Physiology and Chronic Health Evaluation

EA Epidural analgesia

ESPB Elector spinae plane block

ERAS Enhanced Recovery After Surgery

TAP block Transversus abdominis plane block

USG Ultrasound guidance

RCTs Randomized controlled trials

HPSG Hungarian Pancreatic Study Group

LOS Length of hospital stay

SF MPQ-2 Short-Form McGill Pain Questionnaire

PQAS Pain Quality Assessment Scale

BMI body mass index

CCI Charlson Comorbidity Index

PRISMA Preferred Reporting in Systematic Reviews and Meta-analyses

SD Standard deviation

SE standard error

RoB-2 revised Cochrane Risk of bias tool

CI Confidence Interval

TSA Trial sequential analysis

IQR Interquartile range

OR Odds ratio

ERCP Endoscopic Retrograde Cholangiopancreatography

CP Chronic pancreatitis

HT Hypertension

HL Hyperlipidemia

DM Diabetes mellitus

BIPAP Biphasic intermittent positive airway pressure

WMD Weighted mean difference

SHAM serious harm and morbidity

1. INTRODUCTION

1.1. Significance of pain

1.1.1. Definition

The International Association for the Study of Pain (IASP) published the revised definition of pain in 2020: "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage". International committees such as the World Health Organization (WHO) have adopted an earlier version of this definition.[1]

Since the precise description of pain poses a major challenge to scientists and clinicians, constant discussion is required on this topic. In other words, a shared understanding of pain that reflects patients' personal experiences should be aimed at and perfected.[1]

Among others, the revision emphasized that personal pain experience depends on various social, physiological, and biological factors, and it cannot be explained solemnly by the activity of sensory neurons. Although pain may be seen as an adaptive function of the body, it may have adverse effects on the well-being of patients.[1]

1.1.2. Classification of pain

Pain can be classified according to its etiology (causative agent), its duration (chronic or acute), the affected anatomic region (e.g. abdominal, low back pain), or its pathophysiology (nociceptive or neuropathic). Nociceptive pain results from tissue injury, while neuropathic pain occurs with abnormal activation of the central or peripheral nervous system.[2]

1.1.3. Assessment of pain

Adequate pain management is of the utmost importance when acute pain occurs. Proper and validated pain assessment should precede any intervention to provide individualized therapy. Also, pain should be regularly reevaluated to monitor the therapeutical efficacy.[3]

Pain is a self-reported variable with all the apparent limitations. The most used methods to assess pain are the pain intensity scales that try to quantify the subjective experience, such as the Numerical Rating Scales (NRS) or Visual Analog Scales (VAS) (Figure 1).

Their popularity lies in the fact that they are quick to use, even in emergency care. However, there is no consensus on what each number means: what is the limit to applying non-steroid anti-inflammatory drugs (NSAIDs), and when to use opioids in

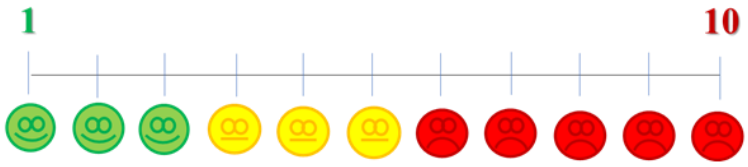

Figure 1. VAS score

low back pain or acute pancreatic pain.[4] Despite the doubts about the usefulness of these scales, these pain assessment tools can help communication between professionals and patients. Research can also profit from standardized pain assessment tools, especially when investigating pain management modalities.

Particularly encouraging that a shift toward more complex assessment tools can be observed. In chronic pain, validated multidimensional tools such as the Brief Pain Inventory[5] and the McGill Pain Questionnaire can be mentioned.[6] For acute pain, the Revised American Pain Society Patient Outcome Questionnaire (APS-POQ-R)[7] or International Pain Outcomes Questionnaire[8] can be considered here. The disadvantage of these methods is their lengthy nature. Thus, they are less useful for emergency care or frequent re-evaluation.

To substitute complex tools, mnemonic tools intend to help remind professionals about the most important questions (Table 1).[9]

OLDCARTS MNEMONIC
Onset
Location
Duration
Character
Alleviating & aggravating
Radiation
Time
Severity

Table 1. OLDCARTS mnemonic

According to these mnemonics, besides pain intensity, it is worth inquiring about pain duration, pain location, or pain type (quality descriptors). Of course, other factors such as radiation, association with other symptoms or aggravating/relieving factors, and effects on daily life can be interesting.

In conclusion, we can uniformly recommend no single pain assessment tool. The ideal tool in all contexts may depend on multiple factors.

1.1.4. Guidelines and gaps in the literature

Basic science is a fast-growing discipline in pain research. However, the transition of its valuable results towards clinical studies is prolonged.

As mentioned earlier, we currently lack an objective pain assessment tool; only self-reporting questionnaires exist. One of the most crucial goals is to find a pain assessment tool that reflects the underlying pathophysiological or targetable processes. Developing such a tool is very difficult, partially because of the complex nature of pain and the apparent limitations of the current pain research methods.

We also currently have a limited number of options for pain management. Most of them provide only partial pain relief or have potentially severe side effects or cause addiction.[10] Notably, most evidence is available in chronic pain. In acute pain, even less evidence is at hand. Research often neglects it because it is a self-limiting, short-term problem usually manageable with the available pain medications. However, acute pain management is frequently suboptimal and acute pain can turn into subacute or chronic pain.[11]

1.2. Acute abdominal pain

Acute abdominal pain is one of the most frequent findings during primary and emergency care caused by numerous acute and chronic diseases.[12] Therefore, acute abdominal pain is mainly studied from a differential diagnostic point of view. After the diagnosis, it gets less attention.

During my research, I focused on acute pancreatic pain and acute postoperative pain.

They are rarely mentioned on the same page, yet we can say that the same guidelines apply to both. However, the available analgesic methods for acute pancreatitis (AP) are more limited.[13]

We carried out a registry analysis to investigate the characteristics of acute pancreatic pain and a meta-analysis to study the efficacy and safety of a promising locoregional anesthetic technique in acute abdominal pain after bariatric surgery.

The WHO defines patient registries as "a file of documents containing uniform information about individual persons, collected in a systematic and comprehensive way, in order to serve a predetermined purpose". [14] While meta-analysis uses statistical methods to synthesize the available literature after a systematic search and selection of a predetermined clinical question.[15]

1.3. Abdominal pain in AP

1.3.1. AP and pain

AP is the most common acute gastroenterological disorder that requires hospitalization and commonly presents with acute abdominal pain. Its mortality can be as high as 20% in severe cases.[16] Pain is among the diagnostic criteria of AP,[17] and it is characterized by tissue injury around the nerve endings, leading to neurogenic inflammation. Tissue injury provokes the release of substance P, tachykinin, and calcitonin-gene-related peptide (CGRP) from nerve endings manifesting in inflammation.[18]

Since the pain can be excruciating, adequate pain management is of the utmost importance. However, we currently lack specific guidelines for pain management in AP; instead, general perioperative strategies are recommended.[13]

As we learned from previous studies, patients with AP experienced mostly VAS 7–10 pain intensity starting within 24 hours prior to hospitalization.[19-21] Furthermore, the most accepted diagnostic guideline, the revised Atlanta classification, defines acute pancreatic pain as "abdominal pain consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back)".[17]

The significance of pain type in different diseases has been researched extensively, primarily for chronic pain.[12-17] Recommendations and currently used complex pain assessment tools for acute and chronic pain also suggest pain type-based phenotyping of patients since pain is a complex phenomenon and pain type may influence the efficacy of certain drug classes.[3,22,23] In acute pancreatitis, there is no previous study on pain type or pain quality descriptors. Thus, there is a need for studies on the matter. Clarifying these issues could also help discover new targets for basic and clinical research.

1.3.2. Prognosis prediction in AP and Pain

Early identification of patients at a higher risk of severe AP and mortality is essential for proper monitoring and management. The Hungarian Pancreatic Study Group (HPSG) has extensively investigated risks and predictors for complications and mortality in AP that may improve future prognostic scores.[24] The most frequently used prognostic ones, such as the Ranson score and APACHE-II (Acute Physiology and Chronic Health Evaluation), are difficult to follow, can be evaluated only after 72 hours of hospitalization, and are not sufficiently accurate, according to the limited evidence in the literature. These traditional prognostic scores do not address questions concerning pain or other clinical symptoms.[25-27] The HPSG recently published an artificial intelligence model based on a large international database for severity prognosis. The model included the length of abdominal pain;[28] however, more detailed pain characteristics were unavailable.

Recently a new score, the Pancreatitis Activity Scoring System, has been proposed to provide an objective tool to evaluate disease activity.[29] This score was found to be associated with clinical outcomes of AP.[30] The interesting thing about the score is that pain intensity and the need for analgesia also play a role in addition to complications and feeding intolerance.

Indeed, the role of pain characteristics in AP prognosis has been suggested by a few studies but without strong supporting evidence.[21,31]

1.3.3. Risk groups for "worse" pain in AP

It is essential to identify risk groups requiring special attention regarding pain management and to choose or expand the available analgesics for them, thus providing personalized medicine.

Earlier studies have suggested that pain assessment in different diseases might depend on the patients' gender because women and men describe and process pain differently.[32,33] However, data are not consistent throughout the abdominal pain literature.[32] As with gender, there are contradictions in the literature about the effect of age on pain perception and analgesic consumption.[34]

In particular diseases, the effect of severity and forms of comorbidities on pain – including localization, intensity, type, and duration – has been emphasized.[35,36]

1.3.4. Pain management in AP

Since the pain can be excruciating in AP, adequate pain management is of the utmost importance.

According to previous systematic reviews,[37,38] only a few randomized clinical trials have investigated this topic. In addition, we need further descriptions of analgesic strategy in a real-world setting.[39]

Adequate analgesia may improve disease outcomes and patient satisfaction by enabling early feeding and mobilization. Non-opioid analgesics may be particularly recommended since morphine may worsen the severity of AP because of known and hypothesized side effects (hypotension, respiratory depression, nausea, etc.),[40] At the same time, NSAIDs can relieve inflammation, according to a systematic review of animal and clinical studies.[41]

A systematic review found that patients administered opioids might need fewer supplementary analgesics. Still, the pain intensity of these patients was similar to that of the controls (including NSAID treatment), pointing to the ongoing debate in this field. Moreover, a recent study comparing pentazocine - an opioid - and diclofenac has found a significantly longer pain-free period, less rescue analgesia, similar side effect profile and disease course in the pentazocine group. Nevertheless, patients in both groups had a rapid recovery. The

authors have explained it with the proper pain management, resulting in decreased sympathetic activity and neuroimmune inflammation.[41]

Non-pharmacological therapies have gained even less attention. Epidural analgesia (EA) is mainly used in the perioperative setting. However, after decades of being the "gold standard" in perioperative care, large meta-analyses and trials reported controversial effects of epidural analgesia on mortality and morbidity associated with frequent technical failures.[42,43]

In AP, its role is still debated, but promising data represented better survival, especially in critically ill patients, through improving pancreatic perfusion.[44,45] There is currently not enough data to properly evaluate the risk-benefit ratio of EA in AP.

Furthermore, a new approach, the ultrasound-guided elector spinae plane block (ESPB) may be an alternative to EA in managing pancreatic pain.[46]

Psychological interventions for pain can be critical in the case of underlying chronic pancreatitis or recurrent disease.[47]

1.3.5. Multimodal pain management in AP

Ideally, multiple analgesic modalities are applied. This concept is called multimodal analgesia. Since more than one underlying process is targeted, the "dose" or duration of each modality can be reduced, and it may be more effective and safer.

The ERAS (Enhanced Recovery After Surgery) guidelines used in perioperative care have long embraced this concept. ERAS guidelines, as the name implies, facilitate faster recovery after surgery. Besides multimodality, it also supports evidenced-based and patient-centered approaches.[48]

1.4. Acute abdominal pain after bariatric surgery

1.4.1. Postoperative pain

Pain in the postoperative period can cause severe patient suffering, prolong recovery, and increase healthcare costs. Moreover, postoperative pain management can be a significant challenge, as previous studies demonstrated.[13,49-51]

With an increasing number of surgeries, surgical techniques are evolving quickly, and proper postoperative pain management receives more and more attention. New methods are certainly welcomed in this field.

1.4.2. Postoperative pain management

Although growing evidence supports multimodal analgesic techniques in clinical practice, opioids remain among the first choice for postoperative pain management.[52] Postoperative opioid overuse could be particularly problematic. For example, in the United States, the opioid epidemic causes serious health crisis.[53]

Instead of opioids, NSAIDs and other pharmacological options (e.g. ketamine, gabapentin), or locoregional analgesic techniques are among the alternatives in a postoperative setting. Infiltrative techniques—including transversus abdominis plane block (TAP block)—have gained increasing attention in recent years as they can be safely and efficiently applied.[52] Its principles are like that of the previously mentioned ESPB. During TAP block, a local anesthetic solution is injected between planes of abdominal muscles to anesthetize the anterior abdominal wall.[54] As ultrasound guidance (USG) has become more widely available, TAP block's popularity has increased. USG facilitates the performance of TAP block in cases where anatomic landmarks are poorly defined, e.g., in patients with obesity.[55]

Many studies have been published about TAP block in different abdominal surgeries, including bariatric surgeries. The existing randomized controlled trials (RCTs) with small sample sizes have been inadequate to define the role of TAP block in bariatric surgery. Besides, technical challenges of this block in patients with obesity have been subjects of concern. Thus, until our publication, ERAS society has released no clear recommendation. However, TAP block may contribute to reducing opioid requirement, which is particularly important in this patient group that is highly susceptible to opioid-related side effects.

2. AIMS

2.1. Acute abdominal pain in AP

We aimed to identify clinical parameters that potentially influence pain intensity, type, localization, and duration prior to admission in AP. Also, we would like to elucidate the relationship between the characteristics of pain on admission and the main outcomes of AP (possible prognostic role of pain). Finally, we described pain management in the everyday practice of AP care.

2.2. Acute abdominal pain after bariatric surgery

We aimed to assess the effects of USG-TAP block as a part of multimodal analgesia for postoperative pain management in patients undergoing laparoscopic bariatric surgery

3. METHODS

3.1. Methods – "Acute pancreatic pain" registry analysis

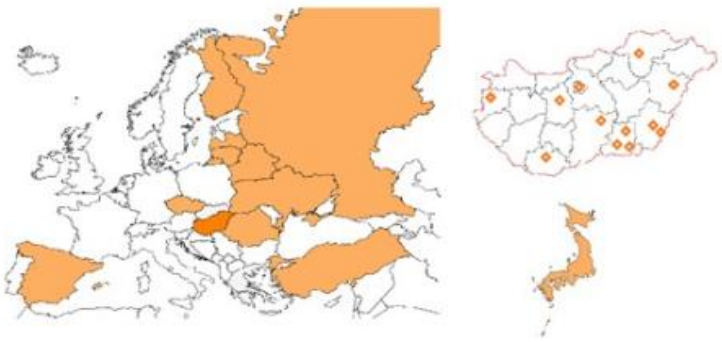

Figure 2. Centre Distribution

3.1.1. Study design, setting, and population

This study is a post-hoc cohort analysis of a prospective international registry conducted by the HPSG, which collected data on consecutive acute pancreatitis cases between 2012 and 2017. There was 1435 adult (>18 years) patients enrolled from 19 Hungarian and eleven foreign institutions (Figure 2 and Supplementary Table 1). Acute pancreatitis was diagnosed when two out of the three criteria were met (typical abdominal pain for acute pancreatitis, pancreas enzymes at least three times greater than the normal upper limit, and abnormal findings on abdominal imaging).[17,56] Data on demographics, alcohol consumption, smoking, family and personal medical history, and symptoms were collected by physicians and trained clinical administrators through predefined patient questionnaires on admission and each day during the hospital stay. Clinical data on diagnostic and therapeutic approaches and main outcomes (severity, mortality, complications, length of hospital stay (LOS), and necessity of analgesia) were also collected during physical examinations and from medical records into standardized forms. The process was approved through a four-level quality check system. As regards on-admission abdominal pain, we had information on 1432 cases. The quality of data is shown in Supplementary Table 2.

3.1.2. Pain assessment (groups)

Patients were classified into subgroups based on pain assessment. To our knowledge, there are no specific recommendations for pain assessment in acute pancreatitis; hence, we evaluated pain based on categories commonly used in clinical practice.

Our analysis involved four on-admission pain characteristics: pain intensity, pain type, pain localization, and pain duration. Pain-free cases were not analyzed.

Patients were interviewed on admission to the ward, but they had to recall their pain characteristics in the period immediately before hospital admission. Clinicians were responsible for interviewing patients within a relatively short time on admission. Failure to do so might result in missing data.

All these variables were patient-reported. Of the initial population with acute abdominal pain, 727 patients answered questions on pain intensity (this question was only included in 2015), 1148 on pain type, 1134 on pain localization, and 1202 on pain duration, resulting in four different sample sizes for the analyses (Figure 3).

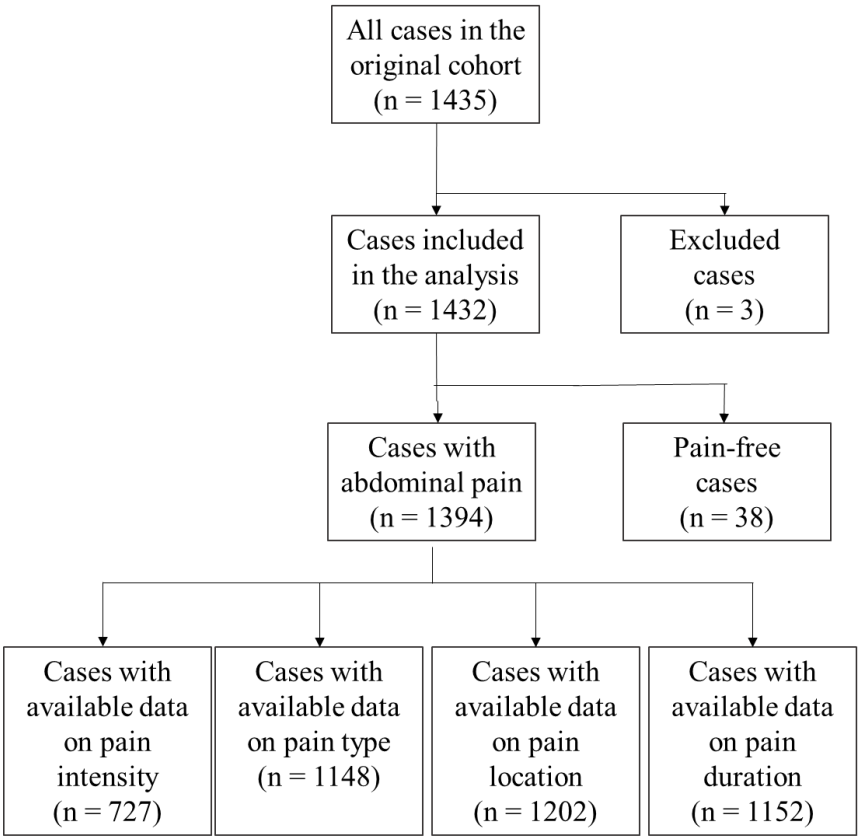

Figure 3. Flowchart of included cases

For each pain characteristic, we used the highest possible case numbers where the data investigated were available.

Pain intensity was measured by the VAS on a scale from 1 (one) to 10 (ten). One indicated "very mild pain" and ten "the worst pain imaginable".[21] We categorized pain intensity into the following subgroups: VAS 1–6 (mild or moderate) and VAS 7–10 (intense) (Figure 4).

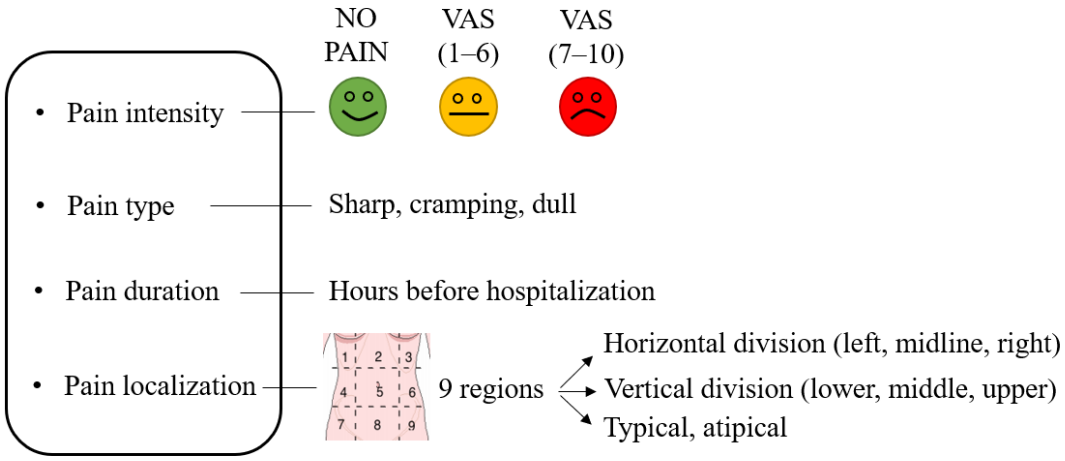

Figure 4. Pain characteristics groups (VAS; Visual Analog Scale)

Patients assessed *pain type* by three predefined categories (cramping, dull, or sharp pain) (Figure 4). We used these descriptors as collective concepts, sharp pain for "incisive pressure", cramping pain for "constructive pressure", and dull pain for dullness categories with multiple possible vocabularies. The original Hungarian version of the questionnaire was then translated into the relevant languages. Other questionnaires frequently used for different disorders, including the Short-Form McGill Pain Questionnaire (SF MPQ-2) and the Pain Quality Assessment Scale (PQAS) in chronic pancreatitis, contain similar categories.[57]

Pain localization was established by routine physical examination according to the nine abdominal regions (1: right hypochondrium; 2: epigastrium; 3: left hypochondrium; 4: right flank; 5: umbilical; 6: left flank; 7: right groin; 8: pubic; 9: left groin). The localization of pain was then grouped into typical and atypical pain. Typical pain meant pain in the epigastrium or in the upper abdomen in a belt-like fashion; atypical meant everything else (Figure 4).

Data on *pain duration prior to hospitalization* were primarily collected in the database in terms of hours. We used a division by days (0–24 h, 25–48 h, 49–72 h, >72 h) in the analyses (Figure 4).

3.1.3. Other confounding factors

The patients were also asked whether they had a history of acute or chronic pancreatitis. Study nurses or trained clinical administrators measured weight and height, then body mass

index (BMI) was calculated. BMI ≥30 kg/m^2 was defined as obesity according to the WHO classification.[58] We considered hypertension if blood pressure was above 140/90 mmHg or the patient was on anti-hypertensive medication. Diabetes mellitus (DM) was defined according to the American Diabetes Association Criteria.[59] The Charlson Comorbidity Index (CCI) was defined by reviewing electronic discharge files as described by Szakács et al.[60,61]

3.1.4. Outcomes

*Primary outcome*s

The severity of AP and complications were defined based on the revised Atlanta classification (Banks et al., 2013). The revised classification differentiates between mild (no local or systemic complications), moderate (local complication or organ failure persisting no more than 48 hours), and severe AP (organ failure lasting more than 48 hours). We studied other outcome measures, such as hospital mortality, LOS, and new-onset diabetes.

Secondary outcomes

In-hospital opioid use was defined when there was evidence of opioid administration at least once during hospitalization. We also calculated the number of days with analgesics (NSAIDs, paracetamol, or opioids) if the details of pain management were available for the whole hospital stay. Where possible, the number of days with opioids was also calculated.

3.1.5. Statistical analyses

The analysis was performed with descriptive statistics – median with 25 and 75% quartiles (Q1 and Q3, respectively), and relative frequency – a goodness-of-fit $\chi 2$ test (for categorical data in the representativeness analysis), binominal (for dichotomous data in the representativeness analysis), and one-sample median tests (for continuous data in the representativeness analysis), odds ratio with 95% CI (for dichotomous data in the main analysis), $\chi 2$ test with the Z test (for categorical data in the main analysis), the Mann–Whitney test, the Kruskal–Wallis test with the Mann–Whitney test as a post hoc test, and the Bonferroni correction to adjust Spearman's rank correlation (for continuous data in the main analysis). A two-sided p-value of <0.05 was considered statistically significant. The available-case analysis was used for missing data. Statistical analyses were performed with SPSS 25.0 software (IBM Corporation).

3.2. Methods – "Pain after bariatric surgery" meta-analysis

We reported this systematic review and meta-analysis following the Preferred Reporting in Systematic Reviews and Meta-analyses (PRISMA) Statement.[62] We registered the protocol on PROSPERO under registration number CRD42020154384.

3.2.1. Eligibility criteria

We included full-text RCTs that assessed the efficacy of perioperative USG-TAP block in postoperative analgesia compared with no treatment or sham intervention in patients who underwent laparoscopic bariatric surgery.

The following outcomes were analyzed: pain scores measured by the VAS or the NRS on a scale from 0 to 10 within the first 24 postoperative hours, morphine requirement (mg) within the first 24 postoperative hours, rate of nausea during phase I recovery, time to ambulate (hours), length of hospital stay (hours), operation time (hours).

3.2.2. Search strategy

A systematic search was carried out in the following databases for studies published up to September 2019: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (via PubMed), Web of Science, and Embase. We designed a search key with synonyms to bariatric surgery (population) and TAP (intervention) linked with Boolean operators. We did not use any filters (e.g., language, full-text, human). The reference lists of included studies and previous systematic reviews and meta-analyses have also been screened for additional articles. Gray literature was not included in our meta-analyses.

3.2.3. Selection Strategy and Data Extraction

Two investigators independently removed all duplicate records, checked titles and abstracts to remove irrelevant articles, and evaluated full-text articles and whether they were eligible for inclusion. All disagreements were resolved by consensus.

Two researchers independently extracted data into a standardized data collection sheet. We resolved any disagreement by consensus. From the individual studies, we extracted the raw data (mean and standard deviation (SD) or standard error (SE)) in case of cumulative morphine dose, time to ambulate, length of hospital stay, operation time, and pain level in rest and at movement if it was given. In the case of nausea, the number of patients and event rates in the two groups were extracted from the individual studies.

3.2.4. Risk of Bias Assessment

Two independent investigators used the revised Cochrane risk-of-bias 2 (RoB 2) tool to assess the risk of bias of studies in the following categories.[63] Disagreements were resolved by consensus.

3.2.5. Statistical Analysis

We calculated mean differences with 95% CI between the control and USG-TAP groups. In the case of dichotomous data, we calculated risk ratio with 95% CI. A p value < 0.05 was considered statistically significant. Pooled estimates were calculated with a random effects model by using the DerSimonian-Laird method.[64] If mean with standard deviation was not reported, we estimated them from median, interquartile, and range.[65] Results of the meta-analysis were displayed graphically using forest plots.

Heterogeneity was tested by using the Cochrane's Q and the I^2 statistics, where $I^2 = 100\% \times (Q - \mathrm{df}) / Q$, and represents the magnitude of the heterogeneity (moderate: 30–60%, substantial: 50–90%, considerable: 75–100%).[52] A p value < 0.10 was considered statistically significant heterogeneity. All meta-analytical calculations were performed by Stata 11 data analysis and statistical software (Stata Corp LLC, College Station, TX, USA).

We performed trial sequential analysis (TSA) for each outcome if it was possible. We used the TSA tool to estimate the required number of patients in future studies and to quantify the statistical reliability of data if the condition of the tests were met. With this test, we assessed whether the intervention arm is effective applying adjusted significance tests and determined the necessity of conducting more studies in the topic to show significant differences.[66]

We planned to conduct the following subgroup analyses: gender, age, type of bariatric surgery, type and dose of local anesthetics, TAP approach. Because of the limited number of studies, we were unable to conduct any of the planned subgroup analyses.

3.2.6. Quality of Evidence

We assessed the overall quality of evidence using the GRADE profiler (GRADEpro).[67] Since data come from only RCTs, we downgraded the certainty of evidence from "high quality" by one level for serious (or by two levels for very serious) risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates, or potential publication bias.

4. RESULTS

4.1. Results – "Acute pancreatic pain" registry analysis

4.1.1. Characteristics of the overall cohort

In total, 1432 cases with AP were included in the analysis. All the patients were monitored until discharge. The clinical characteristics of the whole sample are shown in Table 2.

	Overall (n=1432)
Age, years, median (Ql-Q3)	57 (43-69)
Gender	
Male, n (%)	817 (56.9)
Female, n (%)	618 (43.1)
Medication taken regularly*	
NSAIDs or paracetamol	31 (2.9)
Opioid, n (%)	5 (0.5)
Benzodiazepines, n (%)	96 (9.0)
Antidepressants, n (%)	30 (2.8)
Anticonvulsant, n (%)	20 (1.9)
Etiology (pure)	
Biliary, n (%)	564 (39.4)
Alcoholic, n (%)	305 (21.3)
Hypertriglyceridemic	83 (5.8)
Post-ERCP, n (%)	41 (2.9)
Idiopathic, n (%)	300 (20.9)
Other, n (%)	139 (9.7)
Length of hospital stay, median (Ql-Q3)	9 (6-13)
Mortality, n (%)	36 (2.5)
Severity of pancreatitis	
Mild, n (%)	987 (68.9)
Moderate, n (%)	368 (25.7)
Severe, n (%)	77 (5.38)
Local complications, n (%)	435 (30.5)
Fluid collection, n (%)	373 (26.2)
Pseudocyst, n (%)	126 (8.8)
Necrosis, n (%)	132 (9.3)
Systemic complication, n (%)	115 (8.1)
Respiratory failure, n (%)	68 (4.8)
Heart failure, n (%)	26 (1.8)
Renal failure, n (%)	43 (3.0)

*data on medication taken regularly was available in 1069 cases

Table 2. General characteristics of the study population

More males were affected than females in our cohort (n=817, 56.9% vs. n=618, 43.1%). A biliary etiology (n=564, 39.4%) was the most common, followed by an alcoholic etiology (n=305, 21.3%). Most of the patients had a mild, non-fatal disease; mild AP was observed in 68.9% of the cases (n=987), moderate AP in 25.7% (n=368), and severe AP in 5.4% (n=77), while in-hospital mortality occurred in 2.5% (n=36).

4.1.2. Individual effect analysis of pain characteristics

Relations between the four pain characteristics and demographic and clinical outcomes were analyzed.

Most of the patients described their pain as VAS 7–10 (n=511; 70.3%), characterized as cramping (n=705; 61.4%), localized in the upper abdomen (n=525; 46.4%), and starting within 24 hours prior to admission (n=682; 56.7%).

Pain intensity

We found no statistically significant difference in age, gender, BMI, history of pancreatic diseases, other examined comorbidities, and etiology (Table 3).

Pain intensity as an ordinal variable was associated with the disease severity ($p<0.021$). However, we found no statistically significant difference between the VAS 1–6 and VAS 7–10 groups as regards the main outcomes (severity, mortality, complications, and LOS), although we detected a tendency towards a higher proportion of severe AP among patients with VAS 7– 10. The AP severity distribution of individuals with VAS 1–6 and VAS 7–10 was as follows: mild AP=74.5%/74.2%, moderate AP=23.1%/21.3%, and severe AP=2.3%/4.5%. Unexpectedly, VAS 1–6 was associated with a longer hospital stay (median eight days IQR (6–13) in VAS 1–6 vs median 7.5 days IQR (5–10) in VAS 7–10, $p=0.001$) (Table 3).

Patients with VAS 7–10 pain on admission were more likely to require opioids during their hospital stay (OR=2.561, 95% CI: 1.573–4.169) than patients with VAS 1–6. Higher pain intensity on admission was also associated with the duration of the analgesic treatment (median two days IQR (1–5) in VAS 1–6 vs median three days IQR (2–5) in VAS 7–10, $p=0.009$), but not with the duration of opioid treatment (Table 3).

	VAS 1-6	VAS 7-10	p value / OR (95% CI)
n (%)	216 (29.7)	511 (70.3)	
EPIDEMIOLOGY			
Age, years, median (Q1-Q3) [n]	57.5 (42-68) [216]	56 (43-67.3) [511]	0.205
Gender			
Male, n (%)	129 (59.7)	284 (55.6)	0.844 (0.602-1.166)
Female, n (%)	87 (40.3)	227 (44.4)	
BMI (kg/m2), mean (SD), [n]	27.8 (6.1) [203]	27.8 (5.6) [500]	0.905
Obesity (BMI 30>kg/m2), n (%)	81 (37.3%)	155 (30.4)	0.747 (0.535-1.044)
ETIOLOGY			
Biliary, n (%)	79 (36.6)	197 (38.6)	NS
Alcoholic, n (%)	56 (25.9)	129 (25.2)	
Hypert1iglyceridemic, n (%)	10 (4.6)	31 (6.1)	
Post-ERCP, n (%)	5 (2.3)	8 (1.6)	
Idiopathic, n (%)	45 (20.8)	105 (20.6)	
Other, n (%)	21 (9.7)	41 (8.0)	
ANAMNESTIC DATA			
AP in the personal history, n (%)	61 (28.2)	141 (27.7)	0.899 (0.624-1.296)
CP in the personal history, n (%)	7 (3.2)	27 (5.3)	1.622 (0.692-3.086)
HT in the personal history, n (%)	ll4 (55.6)	255 (51.0)	0.832 (0.600-1.l 55)
HL in the personal history, n (%)	24 (11.l)	65 (12.8)	1.253 (0.757-2.074)
DM in the personal history, n (%)	37 (17.1)	80 (15.7)	0.898 (0.586-1.386)
CCI			
0, n (%)	67 (37.9)	131 (36.6)	NS
1, n (%)	37 (20.1)	97 (27.1)	
2, n (%)	23 (13.0)	54 (15.1)	
>3, n (%)	50 (28.3)	76 (21.2)	
MAIN OUTCOMES			
Length of hospital stay (Q1-Q3) [n]	8 (6-13) (216]	7.5 (5-10) (511]	**p<0.001**
Mortality, n (%)	4 (1.9)	11 (2.2)	1.562
Severity of pancreatitis			Mild+moderate vs severe AP
Mild, n (%)	161 (74.5)	379 (74.2)	1.989 (0.746-5.302)
Moderate, n (%)	50 (23.2)	109 (21.3)	
Severe, n (%)	5 (2.3)	23 (4.5)	
All local complication	56 (25.9)	128 (25.3)	0.956 (0.682-1 342)
Fluid collection, n (%)	45 (20.8)	122 (24.1)	1.343 (0.927-1.944)
Necrosis, n (%)	18 (8.3)	48 (9.5)	0.814 (0 450-1.472)
Pseudocyst, n (%)	16 (7.4)	32 (6.3)	1.07 (0.620-1 845)
All systemic complications	18 (8.3)	40 (9.5)	1.392 (0 648-2 994)
New onset diabetes, n (%)	7 (3.2)	23 (4.5)	0.909 (0.508-1 628)
Renal failure, n (%)	8 (3.7)	11 (2.2)	0.572 (0 227-1.442)
Respiratory failure, n (%)	10 (4.6)	31 (6.1)	1.33 (0.640-2.764)
Heart failure, n (%)	2 (0.9)	13 (6.1)	2.793 (0.625-12.484)
ANALGESIC REQUIREMENT			
Opioid use. n (%)	22 (10.5)	111(22.2)	2.561 (1.573-4.169)
Number of days with analgesic, median (Q1-Q3) [n]	2 (1-5) (169)	3 (2-5) (429)	p=0.009
Number of days with opioid, median (Q1-Q3) [n]	2 (1-3.75) (22]	2 (1-3.5) (115]	p=0.844

Table 3. Pain intensity. CI: confidence interval; BMI: body mass index, ERCP: endoscopic retrograde cholangiography; AP: acute pancreatitis; CP: chronic pancreatitis; HT: hypertension; HL: hyperlipidemia; DM: diabetes mellitus; CCI: Charlson Comorbidity Index

Pain type

Comparing patients with different types of pain, we found no difference in age, gender, BMI, history of pancreatic diseases, DM or other metabolic diseases, or findings on the physical examination. Patients with cramping pain tended to have a biliary etiology, and they were less likely to have an alcoholic etiology compared to dull or sharp pain ($p<0.05$) (Table 4).

Sharp pain was associated with a 2.6-fold increase in mortality odds (OR=2.632, 95% CI 1.063–6.514) compared to other types of pain (dull + cramping pain). Sharp pain might also be a risk factor for severe disease (OR=2.206, 95% CI: 1.199–4.059), especially for systemic complications (OR=2.481, 95% CI: 1.550–3.969), including new-onset diabetes (OR=2.561, 95% CI: 1.472–4.456) and respiratory (OR=3.220, 95% CI: 1.806–5.740) and heart failure (OR=3.222, 95% CI: 1.319–7.869). There were also increased odds for necrosis development with sharp pain (OR=1.653, 95% CI: 1.060–2.580). Cramping pain was associated with a longer LOS ($p<0.05$) (Figure 5 and Table 4).

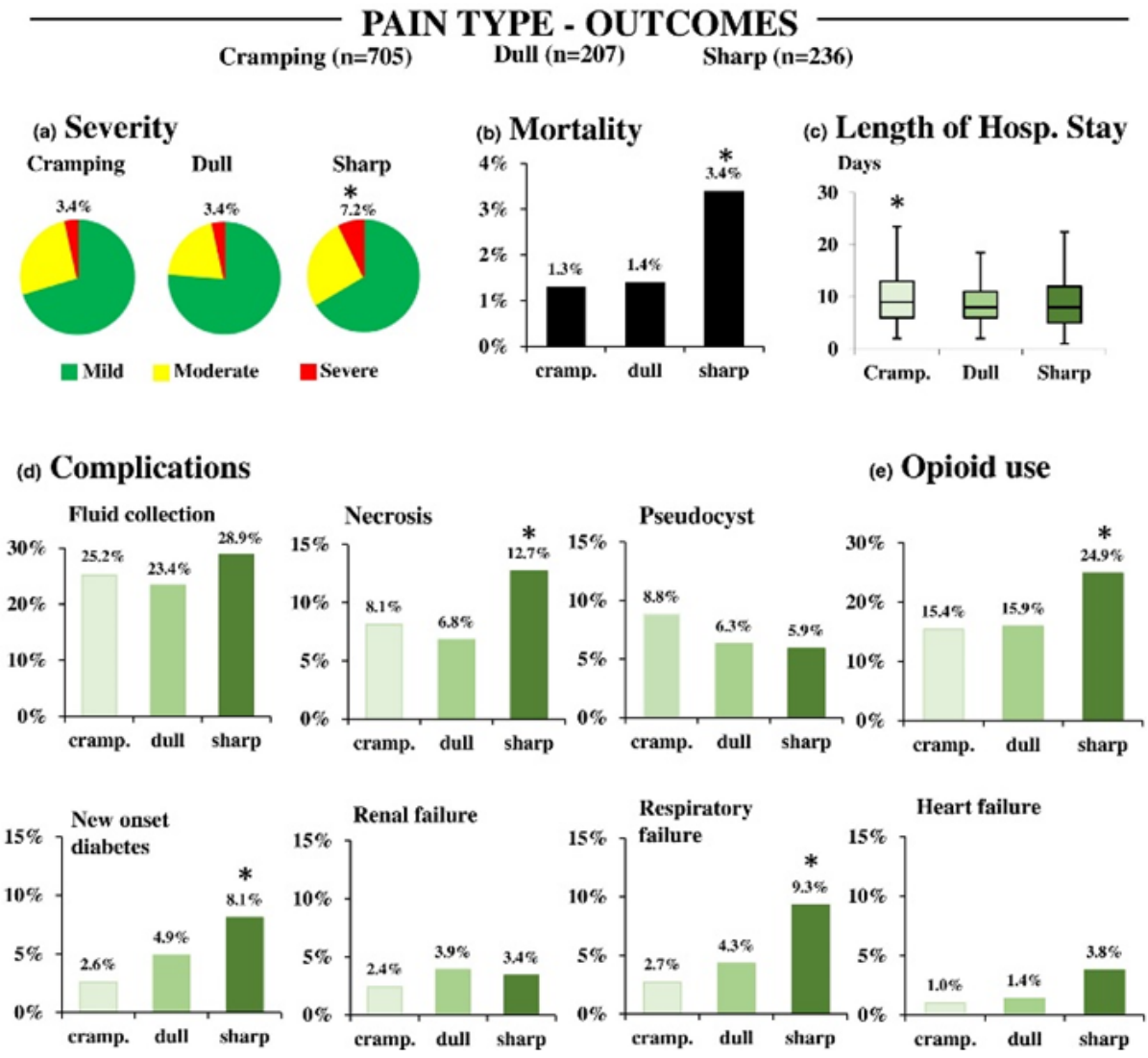

Figure 5. Main outcomes of AP in pain type groups (cramping and dull vs. sharp). (a) Severity (*OR = 2.206 95%: 1.199–4.059); (b) Mortality (*OR = 2.632 95% CI: 1.063–6.514) Length of hospital stay (*p < 0.05); (d) Complications: fluid collection; necrosis (*OR = 1.653 95% CI: 1.060–2.580); pseudocysts; new-onset diabetes (*OR = 2.561 95% CI: 1.472–4.456); respiratory failure (OR = 3.220 95% CI: 1.806–5.740); renal failure; heart failure (*OR = 3.222 95% CI: 1.329–7.869); (e) Opioid use (*OR = 3.250 95% CI: 1.585–3.194)

Sharp pain was associated with a higher proportion of opioid administration compared to cramping and dull pain (OR=2.250 95% CI: 1.585–3.194). Cramping and sharp pain were associated with longer analgesic requirements compared to dull pain (median four days IQR (2–6) and median four days IQR (2–7) vs median two days IQR (2–6), respectively, p=0.005). Pain type was not associated with the length of opioid administration (p=0.938) (Table 4).

	Pain type			
	cramping	dull	sharp	p value*/OR (95% CI)
n (%)	705 (61.4)	207 (18.0)	236 (20.6)	
EPIDEMIOLOGY				
Age, years, median (Q1-Q3)	58 (43.5-69)	55 (42-68.3)	54 (42-67)	0.144
Gender				
Male, n (%)	378 (53.6)	125(60.4)	138(58.5)	NS
Female, n (%)	327 (45.4)	82 (39.6)	98 (41.5)	
BMI (kg/m2), mean (SD), [n]	28.0±5.8(625)	27.7±5.9 [197]	27.9±5.3 [216]	0.807
Obesity (BMI 30>kg/m2), n (%)	281 (39.9)	68 (32.9)	75 (31.8)	NS
ETIOLOGY				
Biliary, n (%)	310 (44.0)	69 (33.3)	88(27.3)	**<0.05***
Alcoholic, n (%)	130 (18..4)	59 (28.5)	61 (25.9)	
Hypert1iglyceridemic, n (%)	39 (5.5)	10 (4.8)	16 (6.8)	
Post-ERCP, n (%)	15 (2.1)	5 (2.4)	5 (2.1)	
Idiopathic, n (%)	147 (20.9)	52 (25.1)	43 (18.2)	
Other, n (%)	64 (9.1)	12 (5.8)	23 (9.8)	
ANAMNESTIC DATA				
AP in the personal history, n (%)	158 (23.8)	66 (32.2)	56(24.1)	NS
CP in the personal history, n (%)	28 (4.2)	15 (7.3)	6 (2.6)	NS
HT in the personal history, n (%)	359 (57.4)	102 (51.8)	99 (54.8)	NS
HL in the personal history, n (%)	90 (17.1)	26 (13.4)	32 (14.6)	NS
DM in the personal history, n (%)	117 (16.9)	35 (16.9)	32 (13.4)	NS
CCI				
0, n (%)	252(38.2)	45 (32.4)	56 (35.2)	NS
1, n (%)	180(27.3)	25 (18.0)	46 (28.9)	
2, n (%)	100(15.4)	25 (18.0)	22 (13.8)	
>3, n (%)	128(19.4)	44 (31.7)	35 (22.0)	
MAIN OUTCOMES				
Length of hospital stay (Q1-Q3) [n]	9 (6-13) [705]	8 (6-11) [205]	8 (5-12) [236]	**p<0.05**
Mortality, n (%)	9 (1.3)	3 (1.4)	8 (3.4)	2.632 (1.063-6.514)
Severity of pancreatitis				
Mild, n (%)	496 (170.4)	158 176.3)	157 (66.5)	**2.206 (1.199-4.059)**
Moderate, n (%)	185 (26.2)	42 (20.3)	62 (26.3)	
Severe, n (%)	24 (3.4)	7 (3.4)	17 (7.2)	
All local complication	203 (28.9)	51 (24.9)	77 (32.8)	0.779 (0.571-1.062)
Fluid collection, n (%)	177 (25.2)	48 (23.4)	68 128.9)	1.197 (0.881-1.627)
Necrosis, n (%)	57 (8.1)	14 (6.8)	30 (12.7)	**1.653 (1.060-2.580)**
Pseudocyst, n (%)	57 (8.8)	14 (6.3)	30 (5.9)	0.571 (0.313-1.043)
All systemic complications	35 (5.0)	17 (8.2)	31 (13.1)	2.481 (1.550-3.969)
New onset diabetes, n (%)	18 (2.6)	10 (4.9)	19 (8.1)	**2.561 (1.472-4.456)**
Renal failure, n (%)	17 (2.4)	813.9)	8 (13.4)	1.235 (0.550-2.775)
Respiratory failure, n (%)	19 (2.7)	9 (4.3\	22 (9.3)	**3.22 (1.806-5.740)**
Heart failure, n (%)	10 (1.0)	2 (1.4)	9 (3.8)	**3.222 (1.319-7.869)**
ANALGESIC REQUIREMENT				
Opioid use. n (%)	65 (15.4)	29 (15.9)	48 (24.9)	2.25 (1.585-3.194)
Number of days with analgesic, median (Q1-Q3) [n]	4 (2-6) [598]	2 (2-6) [170]	4 (2-7)	p=0.05
Number of days with opioid, median (Q1-Q3) [n]	2 (1-4) [89]	2 (1-4) [31]	2 (1-5) [60]	p=0.938

Table 4. Pain type. CI: confidence interval; BMI: body mass index, ERCP: endoscopic retrograde cholangiography; AP: acute pancreatitis; CP: chronic pancreatitis; HT: hypertension; HL: hyperlipidemia; DM: diabetes mellitus; CCI: Charlson Comorbidity Index

Pain localization

An unexpectedly high percentage of patients (n=557, 50.8%) had atypical pain on admission, mainly with umbilical or right rib pain (Table 5).

In addition, we found a greater chance of atypical pain with obesity (OR=1.320 95% CI: 1.036–1.681), hypertension (OR=1.303 95% CI: 1.016–1.669), and hyperlipidemia (OR=1.889 95% CI: 1.302–2.741) (Table 5).

	Pain localization		
	typical	atypical	p value / OR (95% CI) (reference: typical)
n (%)	557(49.1)	577 (50.9)	
EPIDEMIOLOGY			
Age, years, median (Q1-Q3) [n]	56 (42-69) [557]	57 (44-70) [577]	0.192
Gender			
Male, n (%)	321 (57.6)	322 (55.8)	1.077 (0.852-1.363)
Female, n (%)	236 (42.4)	255 (44.2)	
BMI (kg/m2), mean (SD), [n]	27.5±5.5 [506]	28.1±6.0 [504]	0.137
Obesity (BMI 30>kg/m2), n (%)	**188 (44.8)**	**232 (55.2)**	**1.320 (1.036-1.681)**
ETIOLOGY			
Biliary, n (%)	224 (40.2)	236 (40.9)	NS
Alcoholic, n (%)	137 (24.6)	106 (18.4)	
Hypertiglyceridemic, n (%)	28 (5.0)	35 (6. 1)	
Post-ERCP, n (%)	11 (2.0)	15 (2.6)	
Idiopathic, n (%)	111 (9.9)	130 (22.5)	
Other, n (%)	46 (8.3)	55 (9.5)	
ANAMNESTIC DATA			
AP in the personal history, n (%)	137 (25.8)	126(23.1)	0.840 (0.628-1.124)
CP in the personal history, n (%)	23 (4.3)	28 (5. 1)	1.204 (0.677-2.141)
HT in the personal history, n (%)	**258(51.0)**	**290 (57.5)**	**1.303 (1.016-1.669)**
HL in the personal history, n (%)	**53 (12.0)**	**86 (20.4)**	**1.889 (1.302-2.741)**
DM in the personal history, n (%)	96 (17.4)	96 (16.8)	0.962 (0.705-1.313)
CCI			
0, n (%)	168 (30.8)	180 (34.8)	NS
1, n (%)	127 (27.8)	149 (28.8)	
2, n (%)	70 (15.3)	80 (15.5)	
>3, n (%)	92 (20.1)	108 (20.9)	
MAIN OUTCOMES			
Length of hospital stay (Q1-Q3) [n]	9 (6-13) [557]	8 (6-12) [577]	NS
Mortality, n (%)	9 (1.6)	14 (2.4)	1.706 (0.527-1.622)
Severity of pancreatitis			Mild+moderate vs severe AP
Mild, n (%)	388 (69.7)	418 (72.4)	0.924 (0.527-5.302)
Moderate, n (%)	143 (25.7)	134 (23.2)	
Severe, n (%)	26 (4.7)	25 (4.3)	
All local complication	171 (30.8)	149 (26.1)	0.8 (0.625-1.025)
Fluid collection, n (%)	151 (27.2)	130 (22.8)	0.83 (0.641-1.076)
Necrosis, n (%)	55 (9.9)	42 (7.3)	0.716 (0.475-1.079)
Pseudocyst, n (%)	39 (7.0)	45 (7.9)	1.019 (0.659-1.574)
All svstemic complications	40 (7.2)	46 (8.0)	1.096 (0.701-1.715)
New onset diabetes, n (%)	4 1 (7.2)	18 (3.2)	0.408 (0.231-0.720)
Renal failure, n (%)	13 (2.4)	19 (3.3)	1.425 (0.697-2.913)
Respiratorv failure, n (%)	26 (4.7)	27 (4.7)	0.963 (0.552-1.691)
Heart failure, n (%)	9 (1.6)	JO (1.8)	0.36 (0.360-2.449)
ANALGESIC REQUIREMENT			
Opioid use. n (%)	88 (15.8)	92 (15.9)	1.011 (0.735-1.390)
Number of days with analgesic, median (Q1-Q3) [n]	4 (2 7) [464]	4 (2-6) [488]	p=0.701
Number of days with opioid, median (Q1-Q3) [n]	2 (1-5) [88]	2 (1-5) [92]	p=0.705

Table 5. Pain localization. CI: confidence interval; BMI: body mass index, ERCP: endoscopic retrograde cholangiography; AP: acute pancreatitis; CP: chronic pancreatitis; HT: hypertension; HL: hyperlipidemia; DM: diabetes mellitus; CCI: Charlson Comorbidity Index

Pain duration

Median pain duration on admission was 24 hours (IQR 10–72 hours). Pain duration on admission was not associated with age, gender, smoking habit, history of pancreatic diseases or metabolic diseases, CCI, or findings on physical examination (Table 6).

Surprisingly, pain duration prior to hospitalization was not associated with severity, mortality, LOS, or different systemic or local complications.

While patients with pain duration of fewer than 24 hours prior to hospitalization required opioid administration more frequently compared to patients with longstanding pain (≥72 h) (22.9% vs 9.2%, $p<0.001$) (Table 6).

	Pain duration				
	<24 h	25-48 h	49-72 h	>72 h	p value*
n (%)	682 (57.7)	170 (14.4)	119 (10.1)	211 (17.8)	
EPIDEMIOLOGY					
Age, years, median (Q1-Q3)	57 (43-70)	53 (40.5-67)	57.5 (43-71)	57 (42-67)	0.099
Gender					
Male, n (%)	398 (58.4)	101 (59.4)	71 (59.7)	113 (53.4)	NS
Female, n (%)	284 (41.6)	69 (40.6)	48 (40.3)	98 (40.6)	
BMI (kg/m2), mean (SD), [n]	**27.9±5.3 [682]**	**27.5±6.1 [170]**	**27.6±5.1 [119]**	**27.1±6.4 [211]**	**0.0122***
Obesity (BMI 30>kg/m2), n (%)	245 (35.9)	72 (34.1)	60 (32.1)	44 (36.1)	NS
ETIOLOGY					
Biliary, n (%)	275 (40.3)	71 (38.0)	48 (39.3)	85 (40.3)	NS
Alcoholic, n (%)	141 (20.7)	48 (25.7)	29 (23.8)	45 (21.3)	
Hypert1iglyceridemic, n (%)	45 (6.6)	7 (3.7)	8 (6.6)	7 (3.3)	
Post-ERCP, n (%)	10 (1.5)	5 (2.7)	3 (2.5)	9 (4.3)	
Idiopathic, n (%)	144 (21.1)	40 (21.4)	21 (17.2)	46 (21.8)	
Other, n (%)	67 (9.8)	16 (8.6)	13 (10.7)	19 (9.0)	
ANAMNESTIC DATA					
AP in the personal history, n (%)	170 (25.9)	42 (23.9)	29 (25.9)	44 (21.6)	NS
CP in the personal history, n (%)	31 (5.9)	7 (4.0)	7 (6.3)	10 (4.9)	NS
HT in the personal history, n (%)	345 (54.8)	86 (49.4)	60 (54.1)	101 (54.3)	NS
HL in the personal history, n (%)	104 (18.2)	18 (12.4)	10 (10.8)	30 (18.5)	NS
DM in the personal history, n (%)	123 (18.1)	23 (12.4)	17 (14.1)	36 (17.1)	NS
CCI					NS
0, n (%)	188 (34.2)	57 (37.5)	39 (37.1)	77 (38.1)	
1, n (%)	155 (28.2)	50 (32.9)	28 (26.7)	44 (21.8)	
2, n (%)	83 (15.1)	21 (13.8)	14 (13.3)	35 (17.3)	
>3, n (%)	124 (22.6)	24 (15.8)	24 (22.9)	46 (22.8)	
MAIN OUTCOMES					
Length of hospital stay (Q1-Q3) [n]	9 (6-13) [682]	8 (6-13) [170]	8 (6-12.3) [119]	8 (6-13) [211]	0.162
Mortality, n (%)	17 (2.5)	5 (2.7)	3 (2.5)	4 (1.9)	NS
Severity of pancreatitis					NS
Mild, n (%)	463 (67.9)	132 (70.6)	86 (70.5)	164 (77.7)	
Moderate, n (%)	183 (26.8)	44 (23.5)	28 (23.0)	42 (19.9)	
Severe, n (%)	36 (5.3)	I I (5.9)	8 (6.6)	5 (2.4)	
All local complication	211 (31.1)	56 (29.9)	36 (29.5)	47 (22.3)	NS
Fluid collection, n (%)	187 (27.6)	50 (26.2)	28 (23.0)	37 (17.5)	NS
Necrosis, n (%)	52 (7.7)	24 (12.8)	18 (14.8)	12 (5.7)	NS
Pseudocyst, n (%)	52 (7.7)	24 (7.5)	18 (5.7)	12 (10.4)	NS
All systemic complications	56 (8.3)	16 (8.7)	10 (8.2)	12 (5.7)	NS
New onset diabetes, n (%)	31 (4.6)	12 (6.4)	7 (5.7)	1 (0.5)	NS
Renal failure, n (%)	19 (2.8)	8 (4.3)	6 (4.9)	3 (1.4)	NS
Respiratorv failure, n (%)	37 (5.5)	9 (4.9)	6 (5.0)	8 (3.8)	NS
Heart failure, n (%)	15 (2.2)	5 (2.7)	2 (1.6)	1 (0.5)	NS
ANALGESIC REQUIREMENT					
Opioid use. n (%)	**108 (22.9)**	**19 (15.5)**	**7 (8.9)**	**13 (9.2)**	**p<0.001***
Number of days with analgesic, median (Q1-Q3) [n]	4 (2-7) [603]	4 (2-6) [153]	3 (2-6) [103]	3 (2-6) [165]	p=0.13
Number of days with opioid, median (Q1-Q3) [n]	2 (1-4) [138]	4 (1.5-9) [25]	2 (1.75-3) [8]	2 (1-3) [17]	p=0.14

Table 6. Pain duration. CI: confidence interval; BMI: body mass index, ERCP: endoscopic retrograde cholangiography; AP: acute pancreatitis; CP: chronic pancreatitis; HT: hypertension; HL: hyperlipidemia; DM: diabetes mellitus; CCI: Charlson Comorbidity Index

4.1.2. Pain management

Analgesic data was complete for the total LOS in 882 (61.6%) cases.

745/882 (85.5%) patients were administered analgesics at least once during the hospital stay, out of whom 678/882 (76.6%) received them on the day of admission. Opioids were administered at least once during the hospital stay in 155 cases (17.6%).

The median duration of pain management was three days (IQR 2–6). In the patient group requiring analgesics, the median LOS was eight days (IQR 6–12) compared to patients without pain management, where LOS was seven days (IQR 5–11) ($p<0.001$).

The median length of opioid therapy was two days (IQR 1–4). In the patient group requiring opioids, the median LOS was nine days (IQR 5–14) compared to patients without opioid therapy, where LOS was eight days (IQR 6–13) ($p<0.001$).

4.2. Results – "Pain after bariatric surgery" meta-analysis

4.2.1. Results of Search and Selection

The PRISMA flow diagram describes the selection process in detail (Figure 6). A total of 351 records were identified through an electronic database search (CENTRAL: 89; MEDLINE: 36; Web of Science: 99; Embase 127), eight of which were included in this meta-analysis (n = 525; 262 in the "USG-TAP block" group and 263 in the "control" group).

Beyond the eight analyzed articles, two studies with active control groups were excluded,[68,69]

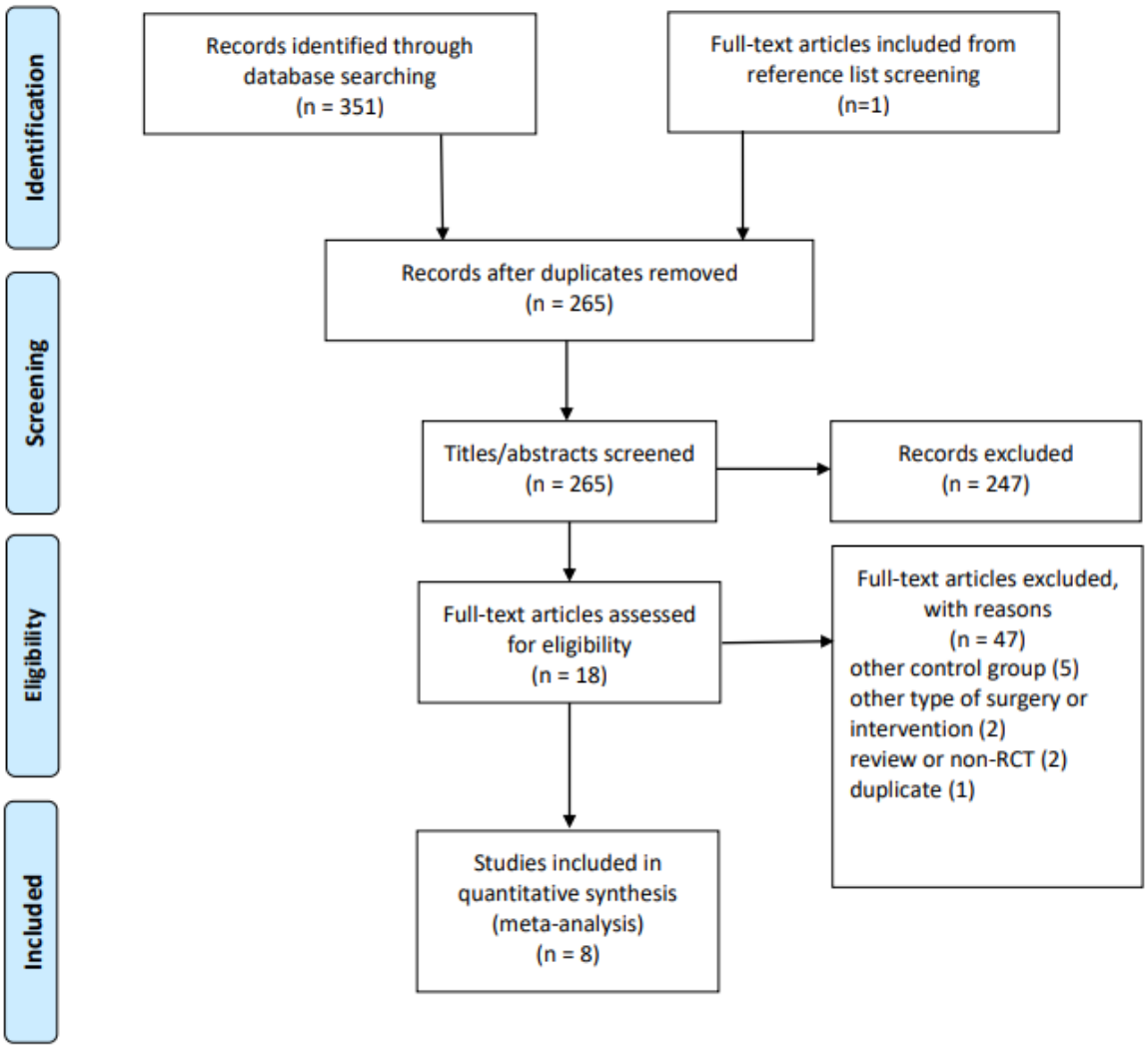

Figure 6. Flow chart of study selection and inclusion process

and in one excluded study, USG-TAP was not performed perioperatively.[70]

4.2.2. Characteristics of the Studies Included

All included studies were single-center RCTs (Table 7). Of the eight studies, five used sham-control (normal saline infiltration).[71-75] In three studies, the control group did not receive sham-control.[76-78] One study used port-site infiltration in both intervention and control groups.[78]

Studies reported data of patient group numbers ranging from 19 to 100. Studies enrolled women predominantly with a mean BMI over 40.[74] Four studies reported data of patients undergoing laparoscopic sleeve gastrectomy.[72-74] Two studies recruited patients who underwent laparoscopic gastric bypass surgery.[75,78] One trial studied patients with gastric band surgery [71] and one with several different types of laparoscopic bariatric surgery.[76]

The type and dose of local anesthetic agents and USG-TAP approaches differed among studies. In four of the studies, USG-TAP block was performed immediately after completion of surgery;[71-73,78] the remaining studies carried out surgeries with preoperative USG-TAP block after anesthesia induction.[74-77]

Postoperative analgesia regimens were also quite diverse among studies (see in detail in Table 1); most studies used regular or as-needed non-opioids supplemented with narcotics on demand. However, some studies—carried out in early 2010—applied opioids exclusively.[72,75]

Table 7. The' Characteristics of included studies' table

Study name	Country/Setting	Allocation	Parti-cipants	Characteristics of participants	Type of surgery	Type and dose of local anesthetic agent	TAP approach	Outcomes	Postoperative analgesia regimen (PACU)
Albrecht 2013	single center in Canada	USG-TAP	27	mean age 44.8 (95% CI, 40.8-48.8), 74% female, mean BMI 49.3 (95% CI 45.6-52.9)	lap. gastric bypass surgery	20 mL of 0.25% bupivacaine	preop. oblique subcostal	24-h cumulative opioid consumption, length of hospitalization, rate of nausea and vomiting	as needed with incremental doses of fentanyl 25–50 µg iv and morphine 1–2 mg iv or hydromorphone 0.2–0.4 mg iv to achieve a clinical target of 4/10 or lower on a numeric rating scale (NRS) for pain.
		no USG-TAP*	30	mean age 38.8 (95% CI, 34.9-42.8), 87% female, mean BMI 48.9 (95% CI, 49.5-51.8)					
De Oliveira 2014	single center in the United States	USG-TAP	9	median age 47.0 (39-53), 80% female, median BMI 44.2 (39.0-45.7)	lap. gastric band surgery	20 mL of 0.5% ropivacaine	preop. posterior	24-h cumulative opioid consumption, length of hospitalization, rate of nausea and vomiting, operation time	as needed with hydromorphone 0.4 mg iv to achieve 4/10 or lower on a numeric rating scale (NRS) for pain. When oral medications were tolerated, hydrocodone 10 mg plus acetaminophen 325 mg.
		sham	10	median age 50.0 (36-54), 78% female, median BMI 40.1 (39.0-45.7)					
Emile 2019	single center in Egypt	USG-TAP	46	mean age 35.8+8.9, 94% female, mean BMI 50.4±.9	lap. bariatric surgery	20 mL of 0.25% bupivacaine	postop. mid-axillary	pain scores at 1, 6, 12, 24 h at rest, time to ambulate, length of hospitalization	paracetamol (1 g every 8 h) iv. As needed with 0.2 mg/kg pethidine iv to achieve a clinical target of 4/10 or lower on a visual analog scale (VAS) for pain
		no USG-TAP*	46	mean age 33.6+9.8, 91% female, mean 48.6+5.3					

Ibrahim 2014	single center in Egypt	USG-TAP	21	mean age 38.3+10.2, 76% female, mean BMI 48.5+10.4	lap. gastrectomy	30 mL of 0.25% bupivacaine	preop. oblique subcostal	24-h cumulative opioid dose, operation time	as needed with fentanyl 25–50 µg iv or morphine 1-2 mg iv or pethidine 20–40 mg iv if patient had moderate or severe pain
		sham	21	mean age 37.4+11.3, 68% female, mean BMI 46.4+8.7					
Mittal 2018	single center in India	USG-TAP	30	mean BMI 46.2+6.7	lap. sleeve gastrectomy	40 mL of 0.375% ropivacaine	preop. mid-axillary	pain scores at 1, 3, 6, 12, 24 h at rest, time to ambulate	diclofenac (75 mg every 8 h) iv. As needed with 1 g diclofenac iv to achieve a clinical target of 4/10 or lower on a visual analog scale (VAS) for pain
		no USG-TAP*	30	mean BMI 44.9+7.2					
Saber 2018	single center in Canada	USG-TAP	30	mean age 37.0+10.7, 87% female, mean BMI 44.0+4.8	lap. sleeve gastrectomy	20 mL of 0.25% bupivacaine	preop. oblique subcostal	pain scores at 3 h at rest, operation time	acetaminophen 600 mg q6, gabapentin 100 mg. As needed with morphine and hydromorphone.
		sham	30	mean age 40.0+11.2, 94% female, mean BMI 44.0+7.1					
Sherif 2015	single center in Egypt	USG-TAP	48	mean age 40.9+8.75, 21% female, mean BMI 38.7+2.2	lap. gastric bypass	20 mL of 0.5% bupivacaine	postop. anterior axillary	pain scores at 1, 6, 12, 24 h at rest, 24-h cumulative opioid dose, time to ambulate, rate of nausea and vomiting	intravenous patient-controlled analgesia (PCA) system, which provided 1 mg of morphine on demand with a block-out interval of 20 min and a maximum 6 h dose of 10 mg in both groups
		sham	47	mean age 40.4+8.71, 26% female, mean BMI 38.9+2.2					
Sinha 2013	single center in India	USG-TAP	50	mean age 39.9+13.3, mean BMI 48.1+6.3	lap. gastric bypass	20 mL of 0.375% bupivacaine	postop. oblique subcostal	pain scores at 1, 3, 6, 12, 24 h at rest, time to ambulate	as needed with paracetamol, tramadol, diclofenac
		sham	50	mean age 39.1+10.6, mean BMI 45.6+6.6					

no USG-TAP*: no sham-control was applied.
Abbreviations: USG-TAP – ultrasound-guided transversus abdominis plane block, lap. – laparoscopic, preop. – preoperative, postop. - postoperative
Comments: Patients were always administered with standard medical therapy, including pain management (non-opioids and opioids), antiemetics, antibiotics, thromboprophylaxis, etc., if necessary

4.2.3. Effects of Intervention

Primary Endpoints

Pain Scores Within the First 48 h

Pooled analysis showed that USG-TAP block lowered postoperative pain scores (rated on a scale between 0 and 10) at rest by 2.25 ($p < 0.001$) at 1 h, by 1.08 ($p < 0.001$) at 3 h, by 2.25 ($p < 0.001$) at 6 h, by 1.23 ($p < 0.022$) at 12 h, and by 0.83 ($p = 0.006$) at 24 h (Fig. 6a). Heterogeneity was considerable in these analyses (Figure 7a). Two studies also examined pain scores at rest 48 h after surgery: they found significantly lower pain scores in the USG-TAP block group.[74,77]

In two included studies,[74,77] pain scores at movement were significantly lower at each evaluated time point (0.5, 3, 6, 12, 24, and 48 h postoperatively; $p < 0.001$ for all comparisons).

Postoperative Cumulative Morphine Dose

Four studies with 213 patients (106 in the intervention group and 107 in the control group) examined the postoperative cumulative morphine dose within the first 24 h.[71,72,74,78] Morphine requirements did not differ significantly between the intervention and control groups (-2 mg; 95% CI − 26.88, 2.89; $p = 0.114$). However, we observed high heterogeneity in this analysis (heterogeneity < 0.001 and $I^2 = 99.0\%$). We identified and removed the influential study with sensitivity analysis, which reduced heterogeneity to 0% and changed the direction of the main association to favoring TAP (Figure 7b).[74] Results of each study can be seen in Supplementary Material.

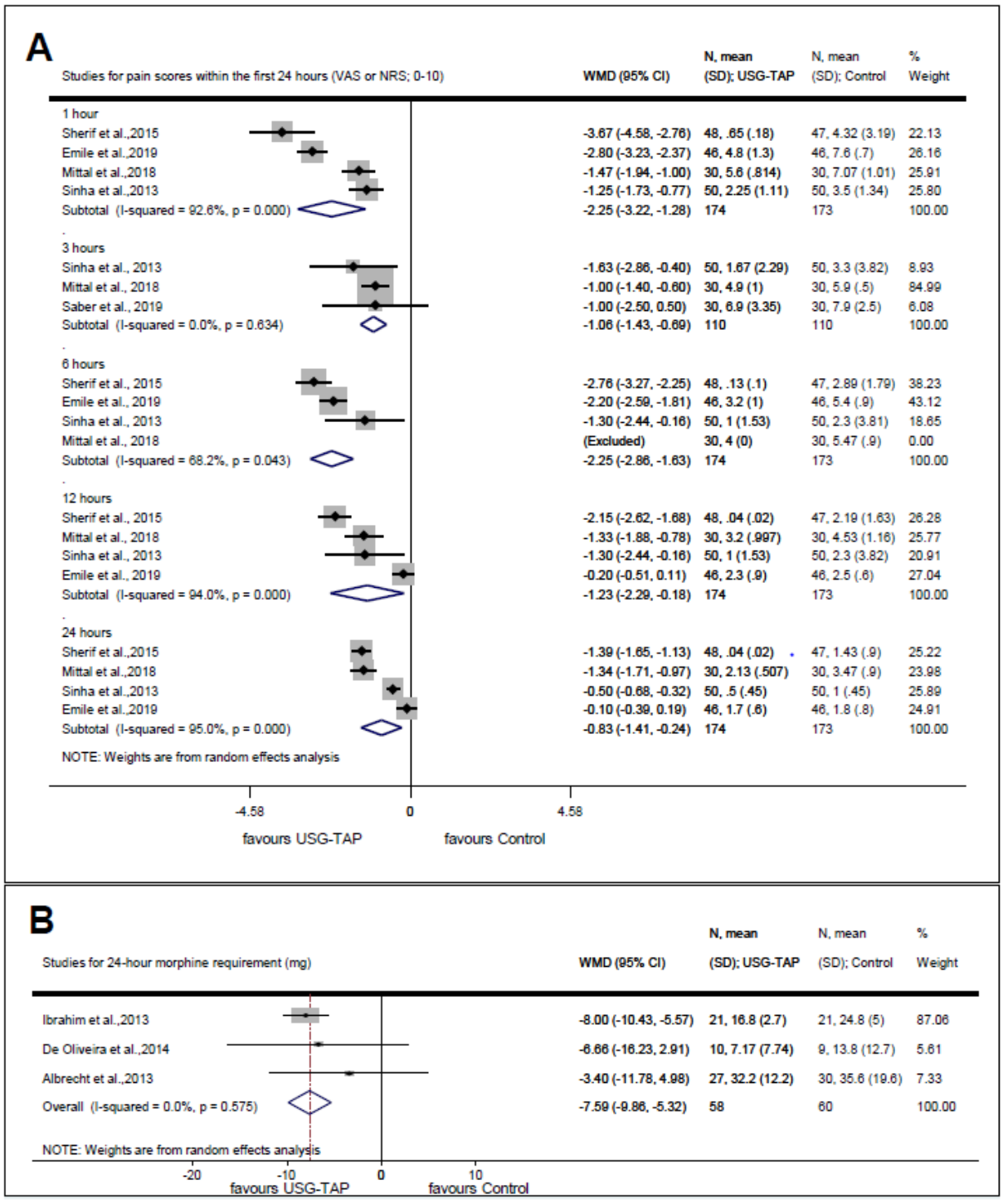

Figure 7. Forest plots that show efficacy endpoints for the comparison of ""USG-TAP"" and ""control"". A) Forest plot for pain score within the first 24 postoperative hours (VAS or NRS, 0–10). B) Forest plot showing 24-h postoperative morphine requirement (mg). VAS, Visual Analog Scale; NRS, Numbering Rating Scale

Secondary Endpoints

Nausea and Vomiting

Pooled analyses of three studies with 171 patients (85 in the intervention and 86 in the control groups) indicated a lower risk of nausea in the USG-TAP block groups compared with control patients (95% CI, RR = 0.24, p < 0.001) (Figure 8).[71,72,74,78] Emile and coworkers applied the Apfel score for postoperative nausea and vomiting: they also found a significant improvement with USG-TAP block for this outcome (2.1 ± 0.9 points in the USG-TAP group vs 3.0 ± 0.9 points, p < 0.001 in the control group).[76] Mittal and coworkers reported a pooled number of events of nausea and/or vomiting and found 8/30 and 24/30 cases in the USG-TAP and control groups, respectively.[77] However, both Emile et al. and Saber et al. found that the need for antiemetic use was similar between intervention and control groups.[73,76]

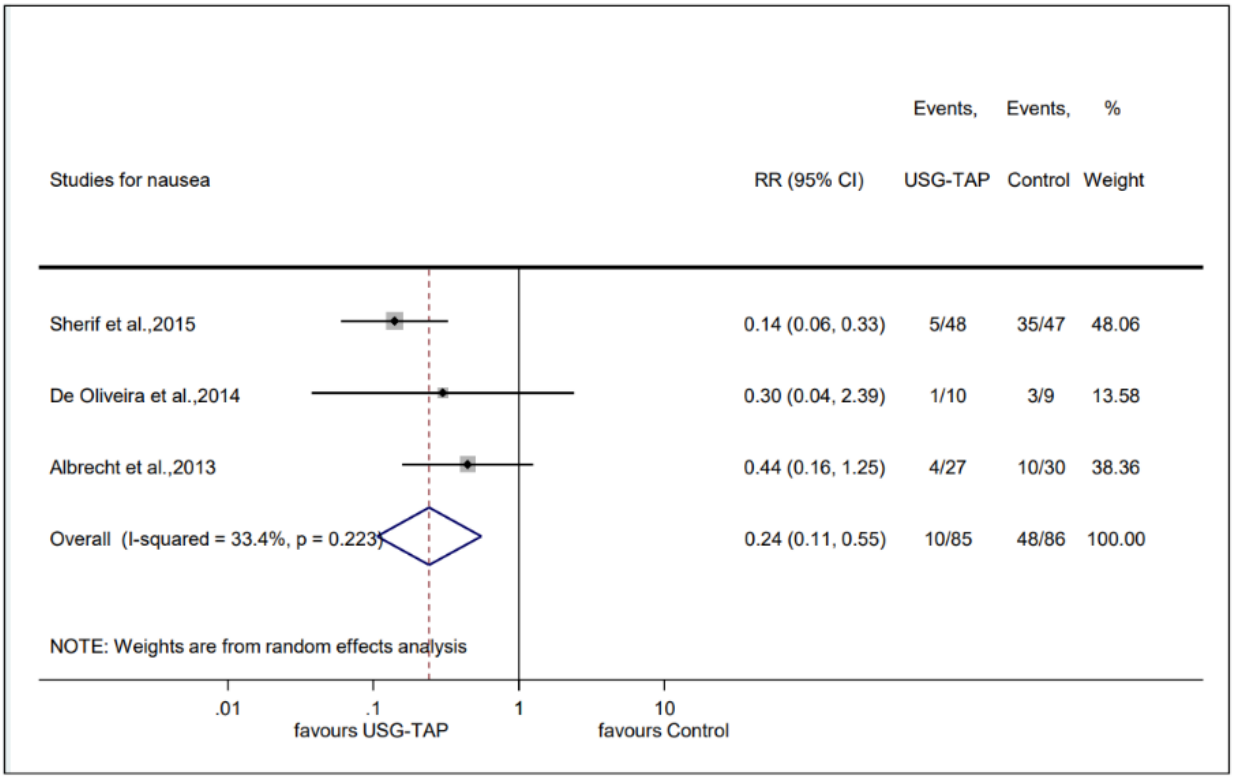

Figure 8. Forest plot showing risk for nausea and vomiting in USG-TAP and control group. USG-TAP, ultrasound-guided transversus abdominis plane block

Sedation

In the study of Sherif et al., four patients of 47 in the control group required postoperative biphasic intermittent positive airway pressure (BIPAP) ventilation support.[74]

According to the study of Sinha et al., four of 50 patients needed BIPAP in the control group.[75] None of these studies detected any need for BIPAP in the USG-TAP group. Sinha and coworkers also reported significantly lower Richmond Agitation and Sedation Score in the first 6 hours in the USG-TAP block group.[75]

Time to Ambulate

Pooled analysis of four trials with 347 patients (174 in the intervention group and 173 in the control group) demonstrated that the time to ambulate was shorter by 2.2 h in patients who underwent USG-TAP block (p = 0.009) (Figure 9).[74-77] We observed high heterogeneity in this meta-analysis (Figure 9). After sensitivity analysis, we identified an influential study.[75] Removal of this study changed the result to non-significant; however, heterogeneity remained high (weighted mean difference (WMD) = − 2.40; 95% CI −4.98, 0.18; p < 0.001 ($p_{heterogeneity}$ < 0.001 and I^2 = 96.6%)).

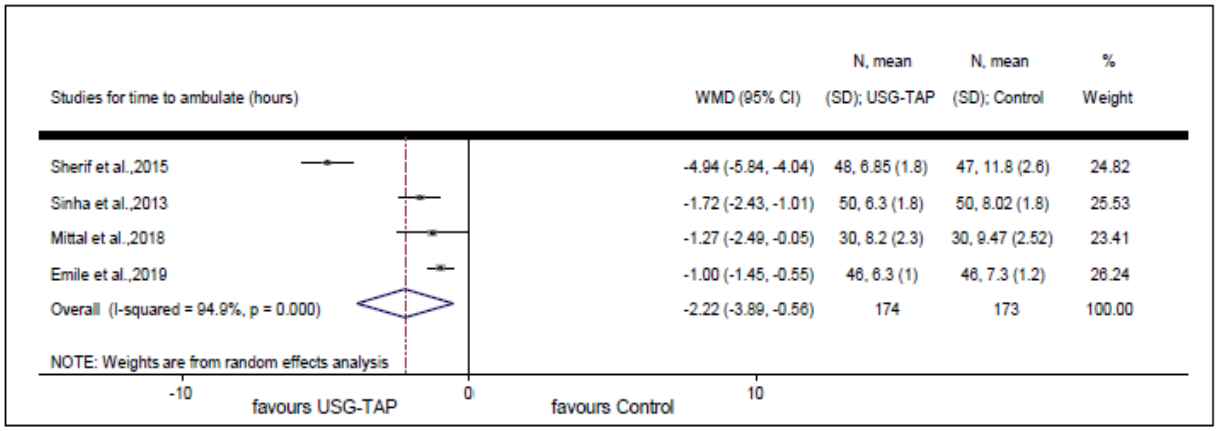

Figure 9. Forest plot showing time to ambulate (h). USG-TAP, ultrasound-guided transversus abdominis plane block

Length of Hospital Stay meta-analysis of three studies with 168 patients (83 in the intervention group and 85 in the control group) failed to identify a shorter length of hospital stay following USG-TAP block performance compared with that of controls (p = 0.102) (Figure 10).[71,76,78]

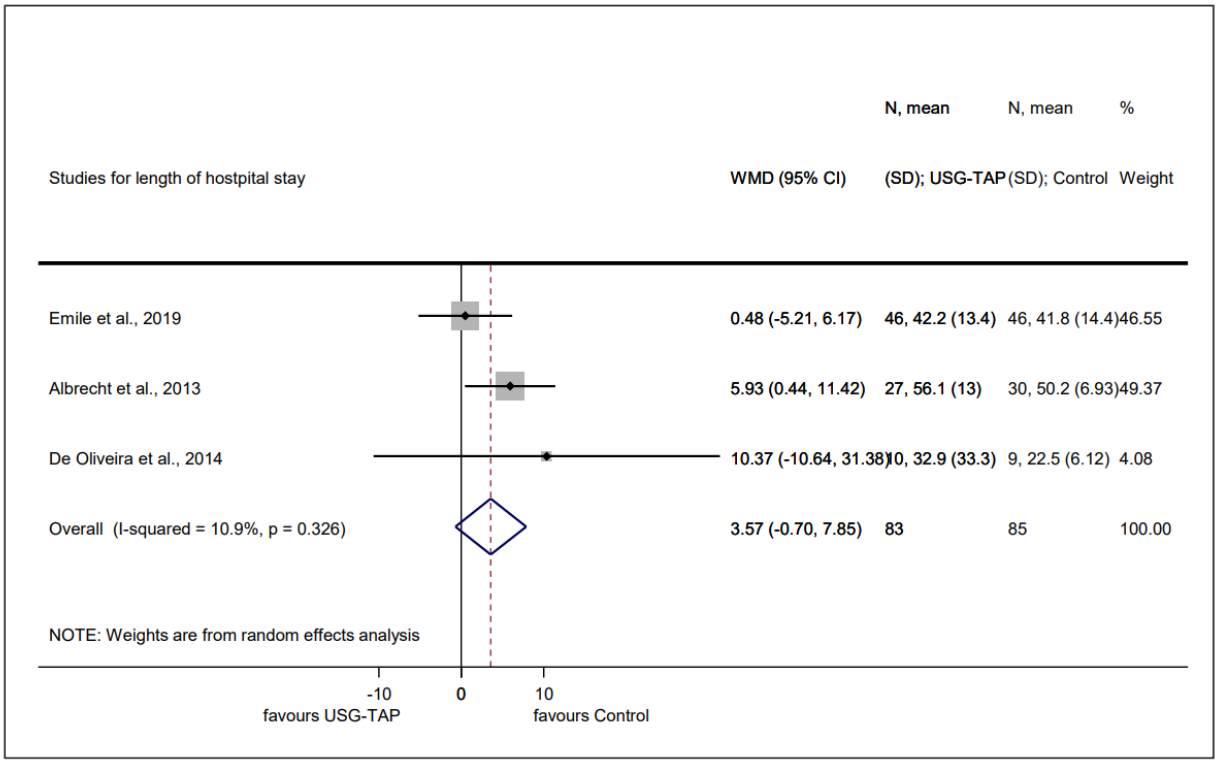

Figure 10. Forest plot showing length of hospital stay (h). USG-TAP, ultrasound-guided transversus abdominis plane block

Two studies investigated the patient satisfaction rate with different methods. In the study of Mittal and coworkers, it was assessed by the Capuzzo composite score (score range 0–10) in 60 patients: the authors reported significantly higher scores in the USG-TAP block group compared with the control group (8.2 ± 0.7 vs 7.1 ± 0.7; $p < 0.001$).[77] Sinha and coworkers also observed significantly higher satisfaction scores in the USG-TAP block group at the end of the first postoperative day.[75]

USG-TAP Block–Related Complications

Only three occurrences of local complications (two cases with hematoma formation, one case with severe pain at the site of injection) due to USG-TAP block were reported in only one study.[76]

4.2.4. Trial Sequential Analysis

The cumulative Z curve crossed the trial sequential significance boundary with regard to the outcomes: time to ambulate, nausea and vomiting, pain at 1 and 24 h. In addition, nausea and vomiting and pain at one h exceeded the required meta-analysis sample size, from which it can be inferred that inclusion of further clinical trials would not change these results (Figure 11)[79] TSA for morphine requirement and operation time could not be performed due to insufficient availability of data.

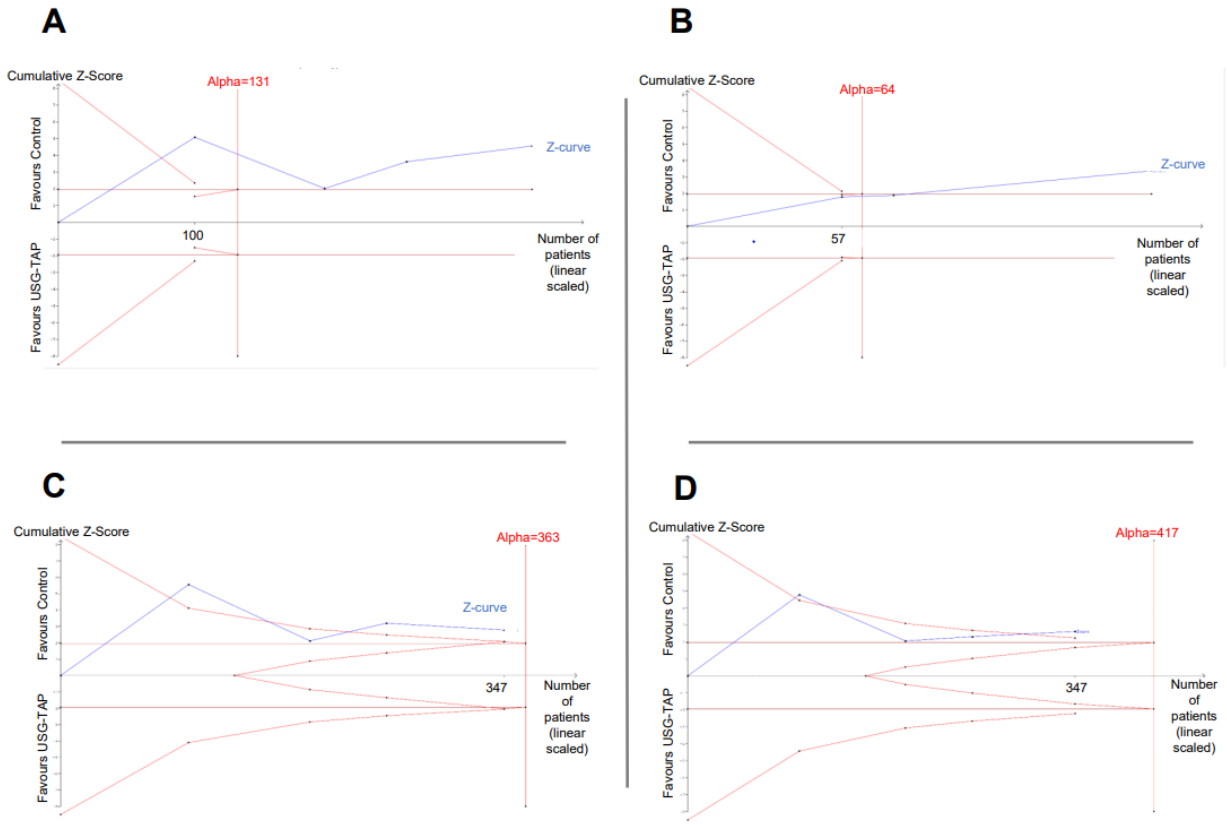

Figure 11. Trial sequential analyses (TSA) for efficacy endpoints

4.2.5. Risk of Bias in the Studies Included

We summarized the results of the risk of bias assessment for each included study in Figure 12.

The articles have been assessed according to five domains for risk of bias: 1. randomization process, 2. deviation from the intended intervention, 3. missing outcome data, 4. measurement of the outcome, 5. selection of the reported results. The overall column summarizes the five domains.

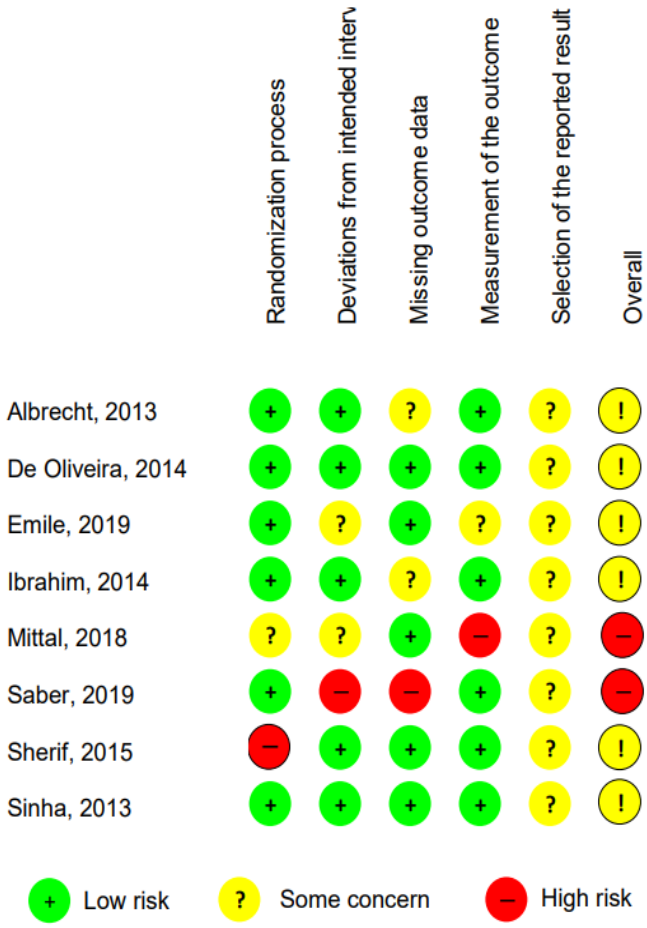

Figure 12. Trial sequential analyses (TSA) for efficacy endpoints

The Green sign means low risk of bias (*which was not given to any of the articles*), the yellow sign means moderate risk of bias (*most of the articles included in this meta-analysis), and the* red sign means high risk of bias (*two articles in this meta-analysis*).

4.2.6. Quality of evidence

Table 8. show the quality of evidence in our meta-analysis. Most of the outcomes reached only low evidence, except for 24-hour postoperative cumulative morphine dose with a moderate level of evidence.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Risk difference with transversus abdominis plane block (TAP block) as a part of multimodal analgesia
Pain score 1 hours after surgery assessed with: VAS or NRS	347 (4 RCTs)	⨁⨁◯◯ LOW [a,b]	MD **2.25 fewer** (3.22 lower to 1.28 lower)
Pain score 24 hours after surgery assessed with: VAS or NRS	347 (4 RCTs)	⨁⨁◯◯ LOW [a,b]	MD **0.83 fewer** (1.41 lower to 0.24 lower)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Risk difference with transversus abdominis plane block (TAP block) as a part of multimodal analgesia
24-hour postoperative cumulative morphine dose (mg)	118 (3 RCTs)	⊕⊕⊕◯ MODERATE [c]	MD **7.59 mg fewer** (9.86 lower to 5.32 lower)
Local and systemic complication due to TAP block	525 (8 RCTs)	-	not pooled
Time to ambulate (hours)	347 (4 RCTs)	⊕⊕◯◯ LOW [a,b]	MD **2.2 h fewer** (3.89 fewer to 0.56 fewer)

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Table 8. Summary of finding Table (meta-analysis)

5. DISCUSSION

In these two analyses, we explored new aspects of pain assessment and management. We expect our results to help integrate these aspects of pain into personalized medicine from a new perspective.

5.1. Pain assessment

Scientific literature examines pain almost solemnly in terms of its intensity. The decrease in pain intensity measures the success of most pain management regimens.[3]

Contrary to this traditional concept, we attempted to evaluate this subjective symptom in a more complex way in our *cohort analysis*. Because of the minimal literature data, we created a new evaluation system. This system was intended to be easily and fast applicable, even in the Emergency Department. We also tried to choose categories and questions already used in everyday clinical practice.

Of course, available literature was also considered when creating this system. The most accepted diagnostic guideline, the revised Atlanta classification, defines acute pancreatic pain as "abdominal pain consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back)". When forming our groups in pain localization, we could only rely on this phrase and other phrases frequently appearing in the AP literature and clinical practice.

Nevertheless, seeing the high number of patients with atypical pain in our cohort, it would be reasonable to reconsider what typical pain in AP means. The localization of pain in AP could be more diverse than we think. Reconsidering the diagnostic criterion may facilitate early recognition of AP in centers where imaging and laboratory examinations are not easily accessible.

Our results on pain characteristics were comparable with previous findings concerning pain intensity and duration. Patients experienced mainly VAS 7–10 pain intensity starting within 24 hours prior to hospitalization.[20,21,80] Importantly, this is the first study to investigate the aspect of pain quality descriptors.

Studies in the *meta-analysis* about TAP block used VAS or NRS scales in the efficacy assessment besides measuring the decrease in additional opioid requirement and satisfaction rate. Especially the latter is an attempt to be appreciated. However, in postoperative care, validated, more complex pain questionnaires are available, e.g. the International Pain

Outcomes Questionnaire. It is advisable to use these validated questionnaires since it makes communication between researchers, patients, and clinicians easier. Another important topic would be whether different pain characteristics react differently to TAP block.

5.2. Prognostic role of pain

New disease activity scores, the so-called PASS scores include patient-reported data such as abdominal pain intensity to follow the disease activity throughout the disease course and also to predict disease severity. Besides pain intensity, other pain-related factors might deserve inclusion.

Interestingly, we discovered an unexpected feature of sharp pain: it was associated with unfavorable disease outcomes, such as higher systemic complications and mortality rates. Previous data suggest that pain type (quality descriptors) might be related to the pain mechanism. Understanding this pain mechanism can aid in choosing the optimal therapeutic approach.[9,81] Unfortunately, the currently available data in AP do not allow us to elucidate the mechanisms behind sharp pain.

We need further investigations to explore this topic through an examination of laboratory samples, histological and imaging findings, and an assessment of pain type in more detail with validated questionnaires.

In our cohort, patients with sharp pain experienced the strongest pain, comparable to findings by Dworkin et al. in neuropathic and non-neuropathic pain.[22]

VAS 1–6 and VAS 7–10 groups did not differ significantly concerning disease outcomes, although some tendency could be observed with a higher rate of severe AP in VAS 7–10 groups. Pain intensity as an ordinal variable correlated with the severity of AP.

Surprisingly, despite the apparently milder disease, VAS 1–6 was associated with a significantly longer LOS. Since various variables can influence LOS, it is hard to explain this conflicting result. The difference between the two groups is clinically not significant since it is less than one day. Nevertheless, after examining the longest hospitalizations, we came to the conclusion that a significant proportion of them is linked to pancreatitis unrelated causes or only indirectly related causes such as nosocomial infections (Clostridium difficile infection, pneumonia, urinary tract infection) or iatrogenic disorders (e.g. bleeding after ERCP, drug side effects).

In VAS 1–6 group, investigations to rule out malignancies appear to be more common since a few patients presented with pain lasting for weeks. Moreover, extremely long LOS could be explained mostly by decompensation of comorbidities.

While in the VAS 7–10 group, recurrent pain due to local complications during hospitalization and the antibiotic or surgical treatment of coexistent cholecystitis seems more prevalent. Also, extremely long LOS was mainly because of AP-related complications in VAS 7-10 group.

While we might think that, as in other acute illnesses,[82,83] prolonged pain prior to hospitalization results in a worse prognosis, this does not seem to be the case. The length of pain before hospitalization did not significantly affect disease outcome. This finding is consistent with previous results.[83,84]

An explanation for this controversy may be that patients with more intense and sharp abdominal pain turned to doctors earlier in our study. Thus, those who may expect a fundamentally worse prognosis turned to the doctor sooner because of their more pronounced and worrying symptoms.

The possible prognostic role of on-admission pain should be further characterized, including adjustment to potential confounding factors of both pain and disease outcomes in the future.

5.3. Patients at a higher risk of pain

We could not confirm gender or age-dependent pain pattern in the cohort analysis. Patients requiring more pain medication on admission could also expect a more prolonged need for pain management.

According to our results, components of metabolic syndrome – which can make people more vulnerable to complications of AP[84,85] – show links to atypical pain of currently unknown significance. We may assume that this is due to diabetic neuropathy. However, this is contradicted by the fact that among the metabolic components, DM was the one that was not associated with atypical pain.

It is already known that individuals with obesity are more prone to have chronic pain, including abdominal pain.[86,87] Certain research suggests that these patients are also more sensitive to acute pain. In summary, patients with obesity might deserve more attention from researchers concerning acute pain management, including both postoperative and acute pancreatic pain.

Unfortunately, the currently available data do not allow us to interpret our findings in more detail. Further studies with a larger sample size could confirm or reject altered pain perception in patients with metabolic syndrome.

5.4. Pain management

In the *cohort analysis*, we briefly reviewed the use of opioid and non-opioid pain medications in our registry.

Opioids were given relatively infrequently considering the very strong pain in AP. Despite the steady rise in opioid consumption, Central and Eastern Europe, from where our data originate, has a more restrictive opioid policy. In fact, according to the analysis of worldwide pain management strategies, only North America had a very high rate of opioid administration in AP (93% vs. 27% in other regions). This extremely high difference worldwide could be explained by the shortcomings of the national and international AP guidelines on pain management.[88]

Unfortunately, not enough information about alternative agents in pain management is available in AP despite the promising results of EDA and local anesthetic strategies.[45] Multimodal analgesia regimen should be developed in AP with reasonable restriction in opioid consumption and with satisfactory pain relief.[89]

Our *meta-analysis* also points to the advantages of multimodal analgesia. TAP block, a local anesthetic technique as part of appropriate multimodal analgesia can significantly improve postoperative pain compared to treatment without TAP block. Besides, it can accelerate patient recovery. It reduces the side effects of opioids, since patients who received TAP block required significantly fewer opioids. Presumably, a reduction in opioid requirement decreased the risk of nausea, vomiting, and respiratory depression.

Our meta-analysis also indicated a shorter time required to ambulate with USG-TAP block. It may support faster recovery and a reduced number of complications of immobilization. Since both obesity and postoperative conditions are risk factors for thromboembolism, patients with bariatric surgery are at exceptionally high risk for these complications.[90] Besides thromboprophylaxis, decreasing the length of bed rest can be an essential factor in thrombosis prevention.

The presence of USG-TAP block did not affect the total length of hospital stay, even if we expected that early ambulation would be associated with faster discharge.[91] Nevertheless,

since the length of hospital stay depends on several factors, and patients spent only about two days in the hospital, minor differences might have remained undetected. Further studies assessing the length of hospital stay as the primary outcome could resolve this issue.

In our *cohort analysis*, cases administered with painkillers, especially with opioids had longer LOS compared to patients without a painkiller and opioids, respectively. Although this might seemingly contradict the pre-assumption that adequate analgesia reduces hospital stay, it is not surprising. Patients in the cohort were not treated with rigorous, predetermined pain management strategies but instead based on physicians' preferences. Besides pain intensity, pain management was likely dependent on the disease severity. For example, patients with more severe diseases tended to be treated with opioids. Of course, a direct toxic effect of opioids cannot be ruled out in this case either.

5.5. Translational approach and personalized medicine

Although there is still no specific therapy in AP, pancreas research decreased between 1965 and 2015.[92] Therefore; it is crucial to make efforts in the translation of research to organize specific care for pancreatic diseases,[93] to use existing knowledge, to identify further research needs and to communicate the results to community benefit.[94] We would highlight the importance of guideline development. Guidelines similar to ERAS might also be advantageous in AP, including proper pain management, nutritional guidance, and physiotherapy.[89,95] To fully elucidate the content of an enhanced recovery guideline in AP, we need to know more about the characteristics and pathomechanism of AP and about the adequate tools to prevent recurrence and chronic pancreatitis[96,97] with abdominal pain as the most distressing symptom.[98] Also, we should investigate the efficacy and safety of all the potential analgesic techniques through both observational and randomized controlled studies. This concept may accelerate healing and reduce the length of hospitalization, protecting patients from the possible complications of long hospitalization and incorrect or excessive therapy and preventing the recurrence of AP. Of course, this concept might also reduce healthcare costs.

In the future, new analgesic modalities must also be tested in AP. Also, future research needs to determine the most adequate pain management strategies for different pain characteristics. Of course, protocols like ERAS protocols should be developed with a multimodal and multidisciplinary approach.

5.6. Strength & limitations

The *cohort study* examines the role of abdominal pain in AP in a unique and detailed fashion. The data came from an international, multicenter collaboration with 1432 consecutive patients with AP, thus improving its external validity. The similar mortality and severity rates to those of published international data serve as confirmation. We took several variables into account, collected and validated them in four steps by trained research staff, including clinical research administrators and clinicians.

This study also has limitations. First, a high percentage of missing data in some variables can lead to selection bias. To evaluate the missing data's influence, we compared the whole cohort to the analyzed cohorts, where complete data on a given pain characteristic was available. We found differences when we compared the pain intensity and pain type cohort to the whole cohort. Namely, a lower proportion of severe AP in the pain intensity and pain type cohort was found. Since the question about pain intensity was only included in 2015, improved management of patients over time may explain this phenomenon. Moreover, complete documentation on pain management was only available in 61.6% of the cases.

Second, much of our data were based on questionnaires; thus, the role of recall bias may arise.

Third, we collected data on pain at a single point in time on the day of hospital admission, which does not consider changes in pre-admission pain, pain trajectories during hospitalization, and the effect of therapy.

Fourth, a registry analysis is not suitable to draw a conclusion on the efficacy and safety of therapies. When choosing a therapy, the decision is influenced by a wide range of factors, including the patient's condition or doctor's personal preference.

In contrast, randomized trials, particularly meta-analyzes of randomized trials, are suitable for answering interventional questions. Therefore, the meta-analysis we conducted represents a higher level of evidence. However, our meta-analysis represented low to moderate evidence on the investigated outcomes for various reasons (Table 8).

Heterogeneity was high between studies included in the *meta-analysis*. Since the low number of analyzed studies did not allow subgroup analyses, we could not explore the cause of heterogeneity—with one exception mentioned above. Theoretically, we can explain heterogeneity by the different types of surgery, anesthetic management, dose and type of anesthetics, USG-TAP approach, or postoperative analgesia regimen.

In addition to high heterogeneity across studies, the poor reporting of important outcomes by relatively few, small, and single-center studies is another significant limitation of our meta-analysis as well as the risk of bias of the included studies. The definition of some outcomes (e.g., operation time) was not precise enough. Conversion of medians to mean could distort our result. Some of the included studies may raise ethical concerns since they worked with an invasive placebo (so-called sham-control). The SHAM (serious harm and morbidity) scale classifies the risk of saline injection as placebo control of TAP block as highest (grade 4). [99]

Further limitation can be that some studies were conducted before the "paradigm shift" in opioid use, which means that these studies might apply non-opioids inadequately. The combination of TAP block with non-opioid pain medication within the framework of opioid-restrictive protocols would be worth further studying. The analgesic regimens were not only outdated in some studies but also very diverse across studies.

6. CONCLUSION

6.1. Implication for practice

According to our registry analysis, an intense and sharp pain on admission was associated with higher odds for severe AP and several systemic and local complications. Therefore, a comprehensive patient interview should include questions about pain characteristics, and patients with intense and sharp pain might need closer monitoring.

According to our meta-analysis, our results support the incorporation of USG-TAP block into multimodal analgesia regimens of ERAS protocols for bariatric surgery, which has happened in the 2021 update.[93]

The development of enhanced recovery guidelines in AP might be worth considering.

6.2. Implications for research

Acute abdominal pain is the leading presenting symptom in acute pancreatitis; however, we currently lack specific guidelines for pain assessment and management. We also need to know more about the pathophysiology of pain type to improve personalized medicine.

7. SUMMARY OF NEW RESULTS

7.1. "Acute pancreatic pain" registry analysis

It is the most thorough study that investigates the role of pain in acute pancreatitis, with the highest case number. Its novelty lies in the fact that it examines pain as a complex phenomenon.

1. Acute pancreatic pain was mostly severe, cramping, epigastric or upper abdominal belt-like that begins within 24 hours prior to hospitalization.
2. Characteristics of pain were not influenced by gender or age.
3. The more intense and sharp pain was associated with worse disease outcome
4. Opioid administration was relatively infrequent compared to the high proportion of patients with very intense pain.

7.2. "Pain after bariatric surgery" meta-analysis

TAP block was associated with lower postoperative pain score and 24-hour cumulative morphine dose, also with shorter time to ambulate. Thus, TAP block could be recommended as an efficient part of multimodal analgesia in the 2021 update of ERAS society guidelines.

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APPENDIX

I.

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ORIGINAL ARTICLE

The characteristics and prognostic role of acute abdominal on-admission pain in acute pancreatitis: A prospective cohort analysis of 1432 cases

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Abstract

Introduction: Pain is the most common symptom in acute pancreatitis (AP) and is among the diagnostic criteria. Therefore, we aimed to characterize acute abdominal pain in AP.

Methods: The Hungarian Pancreatic Study Group prospectively collected multicentre clinical data on 1435 adult AP patients between 2012 and 2017. Pain was characterized by its intensity (mild or intense), duration prior to admission (hours), localization (nine regions of the abdomen) and type (sharp, dull or cramping).

Results: 97.3% of patients ($n = 1394$) had pain on admission. Of the initial population with acute abdominal pain, 727 patients answered questions about pain intensity, 1148 about pain type, 1134 about pain localization and 1202 about pain duration. Pain was mostly intense (70%, $n = 511/727$), characterized by cramping (61%, $n = 705/1148$), mostly starting less than 24 h prior to admission (56.7%, $n = 682/1202$). Interestingly, 50.9% of the patients ($n = 577/1134$) had atypical pain, which means pain other than epigastric or belt-like upper abdominal pain. We observed a higher proportion of peripancreatic fluid collection (19.5% vs. 11.0%; $p = 0.009$) and oedematous pancreas (8.4% vs. 3.1%; $p = 0.016$) with intense pain. Sharp pain was associated with AP severity (OR = 2.481 95% CI: 1.550–3.969) and increased mortality (OR = 2.263, 95% CI: 1.199–4.059) compared to other types. Longstanding pain (>72 h) on admission was not associated

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with outcomes. Pain characteristics showed little association with the patient's baseline characteristics.

Conclusion: A comprehensive patient interview should include questions about pain characteristics, including pain type. Patients with sharp and intense pain might need special monitoring and tailored pain management.

Significance: Acute abdominal pain is the leading presenting symptom in acute pancreatitis; however, we currently lack specific guidelines for pain assessment and management. In our cohort analysis, intense and sharp pain on admission was associated with higher odds for severe AP and several systemic and local complications. Therefore, a comprehensive patient interview should include questions about pain characteristics and patients with intense and sharp pain might need closer monitoring.

1 | INTRODUCTION

Acute pancreatitis (AP) is one of the most common acute gastrointestinal diseases to result in hospital admission (Roberts et al., 2017). Acute abdominal pain is the leading presenting symptom in acute pancreatitis, and it is included among the diagnostic criteria (Banks et al., 2013). Since the pain can be excruciating, adequate pain management is of the utmost importance. However, we currently lack specific guidelines for pain management in AP; instead, general perioperative strategies are recommended (Stigliano et al., 2017). This approach in AP is not based on robust scientific data, since our knowledge is insufficient in both basic science and clinical settings (Barreto & Saccone, 2012; Pezzilli et al., 2010). We also lack studies that evaluate pain characteristics and pain

management in everyday practice (Pezzilli et al., 2007; Phillip et al., 2013). Nor are sufficient data available on the relation between patients' clinical parameters and pain characteristics.

Nevertheless, understanding these factors could help to identify risk groups that require special attention as regards pain management and to choose or even expand the available analgesics for them, thus providing personalized medicine. Obviously, therapy should be tailored to the intensity of pain. The significance of pain type (quality descriptors) in other diseases has also been researched extensively, mostly for chronic pain (Asthana et al., 2020; Dworkin et al., 2007; Erdogan et al., 2019; Galli et al., 2019; Rau et al., 2018; Sharma et al., 2016). Recommendations for acute and chronic pain also suggest pain type-based phenotyping of patients, since pain is a complex phenomenon and pain type may influence the efficacy of certain drug classes (Chou et al., 2016; Dworkin et al., 2005; Edwards et al., 2016). Clarification of these issues could also help to discover new targets for both basic and clinical research.

Early identification of patients at a higher risk of severe AP and mortality is important for proper monitoring and management. The most frequently used prognostic scores, such as the Ranson score and APACHE-II, are difficult to follow, can be evaluated only after 72 h of hospitalization, and are not sufficiently accurate, according to the limited evidence in the literature. These prognostic scores do not address questions concerning pain or other clinical symptoms (Hagjer & Kumar, 2018; Harshit Kumar & Singh Griwan, 2018; Tan et al., 2017). Indeed, the role of pain characteristics in AP prognosis has been suggested by a few studies but without strong supporting evidence (Kapoor et al., 2013; Phillip et al., 2013).

Here, we aimed to elucidate the relationship between the characteristics of pain on admission and the main outcomes of AP and to investigate the possible prognostic role of pain. We also intended to identify clinical parameters that potentially influence pain intensity, type, localization and duration prior to admission in AP and to describe pain management in everyday practice.

2 | METHODS

2.1 | Study design, setting and population

This study is a post hoc cohort analysis of an international prospective registry conducted by the Hungarian Pancreatic Study Group, which collected data on consecutive acute pancreatitis cases between 2012 and 2017. There were 1435 adult (>18 years) patients enrolled from 19 Hungarian and eleven foreign institutions (Figure S1).

Acute pancreatitis was diagnosed when two out of the three criteria were met (typical abdominal pain for acute pancreatitis, pancreas enzymes at least three times greater than the normal upper limit, and abnormal findings on abdominal imaging; Banks et al., 2013; Hritz et al., 2015).

Data on demographics, alcohol consumption, smoking, family and personal medical history and symptoms were collected by physicians and trained clinical administrators through predefined patient questionnaires on admission and each day during the entire hospital stay. Relevant clinical data on diagnostic and therapeutic approaches and main outcomes (severity, mortality, complications, length of hospital stay (LOS) and necessity of analgesia) were also collected during physical examinations and from medical records into standardized forms. The process was approved through a four-level quality check system. As regards on-admission abdominal pain, we had information on 1432 cases. The quality of the data is shown in detail in Table S1.

2.2 | Pain assessment (groups)

Patients were classified into subgroups based on pain assessment.

To our knowledge, there are no specific recommendations for pain assessment in acute pancreatitis; hence, we evaluated pain based on categories commonly used in clinical practice.

Our analysis involved four on-admission pain characteristics: pain intensity, pain type, pain localization and pain duration. Pain-free cases according to a Visual Analog Scale (VAS 0) were considered a separate category. Patients were interviewed on admission to the ward, but they had to recall their pain characteristics in the period immediately before hospital admission. Clinicians were responsible for interviewing patients within a relatively short time on admission. Failure to do so might result in missing data.

All these variables were patient-reported. Of the initial population with acute abdominal pain, 727 patients answered questions on pain intensity (this question was only included in 2015), 1148 on pain type, 1134 on pain localization and 1202 on pain duration, resulting in four different sample sizes for the analyses (Figure 1).

For each pain characteristic, we used the highest possible case numbers where the data investigated were available. The representativeness of the groups can be seen in Table S2.

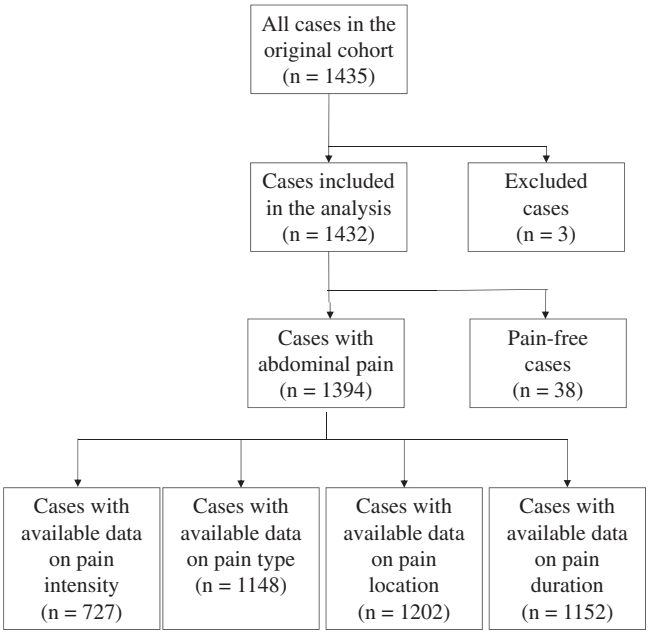

FIGURE 1 Flowchart of included patients

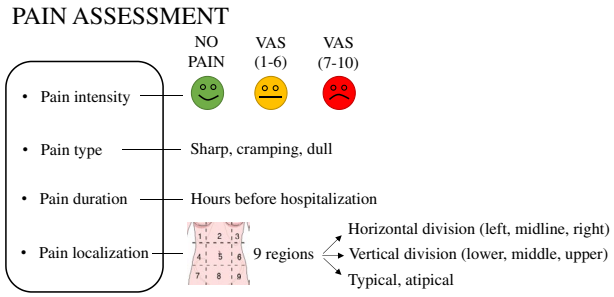

FIGURE 2 Pain characteristics groups (VAS; Visual Analog Scale)

Pain intensity was measured by the VAS on a scale from 1 (one) to 10 (ten). One indicated 'very mild pain' and ten 'the worst pain imaginable" (Phillip et al., 2013). We categorized pain intensity into the following subgroups: VAS 1–6 (mild or moderate) and VAS 7–10 (intense; Figure 2).

Patients assessed *pain type* by three different predefined categories (cramping, dull, or sharp pain; Figure 2). We used these descriptors as collective concepts, sharp pain for 'incisive pressure', cramping pain for 'constructive pressure', and dull pain for dullness categories with multiple possible vocabularies. The original Hungarian version of the questionnaire was then translated into the various relevant languages. Other questionnaires frequently used for different disorders, including the Short-Form McGill Pain Questionnaire (SF MPQ-2) and the Pain Quality Assessment Scale (PQAS; Drewes et al., 2017; Teo et al., 2017) in chronic pancreatitis, contain similar categories.

Pain localization was established by routine physical examination according to the nine abdominal regions (1: right hypochondrium; 2: epigastrium; 3: left hypochondrium; 4: right flank; 5: umbilical; 6: left flank; 7: right groin; 8: pubic; 9: left groin). The localization of pain was analysed according to three divisions (Figure 2).

1. typical/atypical: typical pain means pain in the epigastrium or in the upper abdomen in a belt-like fashion;
2. horizontal division with upper, middle and lower abdominal pain and
3. vertical division with left-sided, midline and right-sided abdominal pain.

Data on *pain duration* prior to hospitalization were primarily collected in the database in terms of hours. We used a division by days (0–24, 25–48, 49–72, >72 h) in the analyses (Figure 2).

2.3 | Other confounding factors

A history of smoking and alcohol consumption was described based on predefined questionnaires, from which we later calculated pack year and daily alcohol consumption in grams. The patients were also asked whether they had a history of acute or chronic pancreatitis.

Weight and height were measured by study nurses or trained clinical administrators, then body mass index (BMI) was calculated. BMI ≥30 kg/m^2 was defined as obesity according to the WHO classification (Obesity: preventing & managing the global epidemic. Report of a WHO consultation, 2000). The presence of abdominal tenderness and guarding was determined by the examining physician.

We considered hypertension if blood pressure was above 140/90 mmHg or the patient was on anti-hypertensive medication. Diabetes mellitus was defined according to the American Diabetes Association Criteria (Chamberlain et al., 2016). The Charlson Comorbidity Index (CCI) was defined by reviewing electronic discharge files as described by Szakács et al. (Charlson et al., 1987; Szakacs et al., 2018).

2.4 | Outcomes

2.4.1 | Primary outcomes

The severity of AP and complications were defined based on the revised Atlanta classification (Banks et al., 2013). The revised classification differentiates between mild (no local or systemic complications), moderate (local complication or organ failure persisting no more than 48 h) and severe AP (organ failure persisting more than 48 h). The definition of each local (acute peripancreatic fluid collections, pancreatic necrosis or pseudocysts) and systemic

(respiratory failure, heart failure or renal failure), complication can be found in Table S3. We studied other outcome measures, such as hospital mortality, LOS and new-onset diabetes.

2.4.2 | Secondary outcomes

To assess on-admission imaging findings, we reviewed the radiological description of ultrasound (US) imaging, computerized tomography (CT) and chest X-rays. We evaluated the following imaging findings: pleural fluid, hypo- or hyperechogenicity of the pancreas, oedematous pancreas, enlarged pancreas, pancreatic duct dilatation, pancreatic calcification, acute peripancreatic fluid collection, on-admission necrosis or on-admission fluid collection.

In-hospital opioid use was defined when there was evidence of opioid administration at least once during hospitalization. We also calculated the number of days with analgesics (non-steroid anti-inflammatory drugs (NSAIDs), paracetamol or opioids) if the details of pain management were available for the whole hospital stay. Where possible, the number of days with opioids was also calculated.

2.5 | Statistical analyses

The analysis was performed with descriptive statistics—median with 25% and 75% quartiles (Q1 and Q3 respectively), and relative frequency—a goodness-of-fit χ^2 test (for categorical data in the representativeness analysis), binominal (for dichotomous data in the representativeness analysis) and one-sample median tests (for continuous data in the representativeness analysis), odds ratio with 95% CI (for dichotomous data in the main analysis), χ^2 test with the Z test (for categorical data in the main analysis), the Mann–Whitney test, the Kruskal–Wallis test with the Mann–Whitney test as a post hoc test and the Bonferroni correction to adjust Spearman's rank correlation (for continuous data in the main analysis). A two-sided p-value of <0.05 was considered statistically significant. The available-case analysis was used for missing data. Statistical analyses were performed with SPSS 25.0 software (IBM Corporation).

2.6 | Ethical approval

The operation of the AP Registry was approved by the Scientific and Research Ethics Committee of the Medical Research Council, Hungary (22254-1/2012/EKU, 17787-8/2020/EÜIG). Informed consent forms were obtained from all participants before enrolment. The study was conducted in accordance with the Helsinki Declaration.

3 | RESULTS

3.1 | Characteristics of the overall cohort

In total, 1432 cases with acute pancreatitis were included in the analysis. All the patients were monitored until discharge. The clinical characteristics for the whole sample are shown in Table 1.

TABLE 1 General characteristics of the study population

	Overall ($n = 1432$)
Age, years, median (Q1–Q3)	57 (43–69)
Gender	
Male, *n* (%)	817 (56.9)
Female, *n* (%)	618 (43.1)
Medication taken regularly[a]	
NSAIDs or paracetamol, *n* (%)	31 (2.9)
Opioid, *n* (%)	5 (0.5)
Benzodiazepines, *n* (%)	96 (9.0)
Antidepressants, *n* (%)	30 (2.8)
Anticonvulsant, *n* (%)	20 (1.9)
Aetiology (pure)	
Biliary, *n* (%)	564 (39.4)
Alcoholic, *n* (%)	305 (21.3)
Hypertriglyceridaemic, *n* (%)	83 (5.8)
Post-ERCP, *n* (%)	41 (2.9)
Idiopathic, *n* (%)	300 (20.9)
Other, *n* (%)	139 (9.7)
Length of hospital stay, median (Q1–Q3)	9 (6–13)
Mortality, *n* (%)	36 (2.5)
Severity of pancreatitis	
Mild, *n* (%)	987 (68.9)
Moderate, *n* (%)	368 (25.7)
Severe, *n* (%)	77 (5.38)
Local complications, *n* (%)	435 (30.5)
Fluid collection, *n* (%)	373 (26.2)
Pseudocyst, *n* (%)	126 (8.8)
Necrosis, *n* (%)	132 (9.3)
Systemic complication, *n* (%)	115 (8.1)
Respiratory failure, *n* (%)	68 (4.8)
Heart failure, *n* (%)	26 (1.8)
Renal failure, *n* (%)	43 (3.0)

[a]Data on medication taken regularly were available in 1069 cases.

More males were affected than females in our cohort (n = 817, 56.9% vs. n = 618, 43.1%). A biliary aetiology (n = 564, 39.4%) was the most common, followed by an alcoholic aetiology (n = 305, 21.3%). Most of the patients had a mild, non-fatal disease; mild AP was observed in 68.9% of the cases (n = 987), moderate AP in 25.7% (n = 368) and severe AP in 5.4% (n = 77), while in-hospital mortality occurred in 2.5% (n = 36).

3.2 | Diagnosis of AP

Of the 1432 patients, 1394 (97.3%) had abdominal pain on admission.

Abnormal pancreas structure was detected in 646 cases by imaging on admission (52.1%). 1149 USs, 235 CTs and 450 chest X-rays were performed on admission. The most common imaging findings were enlarged pancreas (n = 231; 18.7%) and peripancreatic fluid collection (n = 207, 16.7%). Other abnormalities can be seen in Table S4.

Amylase levels were at least three times greater than the normal upper limit in 996 cases (69.6%), while lipase levels were diagnostic in 752 cases (52.4%).

3.3 | Patients without pain

Thirty-six patients reported no pain on admission, of whom 72.2% (n = 26) had mild AP, 19.4% (n = 7) had moderate AP and 8.3% (n = 3) had severe AP. One patient (2.8%) without on-admission pain died. The proportion of systemic (8.3%, n = 3) and local complications (25%, n = 9) did not differ from that of the overall cohort. About one-fifth of the no-pain cases were post-ERCP pancreatitis (19.4%, n = 7). The proportion of other aetiologies (alcoholic, biliary, hypertriglyceridaemic, idiopathic, etc.) was similar to that of the overall cohort.

3.4 | Pain management

Analgesic data were complete for the total LOS in 882 (61.6%) cases.

In summary, 745/882 (85.5%) patients were administered analgesics at least once during the hospital stay, out of whom 678/882 (76.6%) received them on the day of admission. Opioids were administered at least once during the hospital stay in 155 cases (17.6%).

The median duration of pain management was 3 days (IQR 2–6). In the patient group requiring analgesics, the median LOS was 8 days (IQR 6–12) compared to patients without pain management, where LOS was 7 days (IQR 5–11; $p < 0.001$).

The median length of opioid therapy was 2 days (IQR 1–4). In the patient group requiring opioids, the median LOS was 9 days (IQR 5–14) compared to patients without opioid therapy, where LOS was 8 days (IQR 6–13; $p < 0.001$).

To our knowledge, 5 of the patients received epidural analgesia.

3.5 | Individual effect analysis of pain characteristics

Relations between the four pain *characteristics* and demographic and clinical outcomes were analysed.

Most of the patients described their pain as VAS 7–10 (n = 511; 70.3%), characterized as cramping (n = 705; 61.4%), localized in the upper abdomen (n = 525; 46.4%) and starting within 24 h prior to admission (n = 682; 56.7%).

3.5.1 | Pain intensity

We found no statistically significant difference in age, gender, BMI, alcohol consumption, smoking habit, history of pancreatic diseases, other examined comorbidities, aetiology and findings on physical examination in comparing patients with VAS 1–6 and 7–10 (Table S5).

Main outcomes

Pain intensity as an ordinal variable was associated with the disease severity ($p < 0.021$). However, we found no statistically significant difference between the VAS 1–6 and VAS 7–10 groups as regards the main outcomes (severity, mortality, complications and LOS), although we detected a tendency towards a higher proportion of severe AP among patients with VAS 7–10. The AP severity distribution of individuals with VAS 1–6 and VAS 7–10 was as follows: mild AP = 74.5%/74.2%, moderate AP = 23.1%/21.3% and severe AP = 2.3%/4.5%.

Unexpectedly, VAS 1–6 was associated with a longer hospital stay (median 8 days IQR (6–13) in VAS 1–6 vs. median 7.5 days IQR (5–10) in VAS 7–10, p = 0.001; Table S5).

Patients with VAS 7–10 pain on admission were more likely to require opioids during their hospital stay (OR = 2.561, 95% CI: 1.573–4.169) than patients with VAS 1–6. Higher pain intensity on admission was also associated with the duration of the analgesic treatment (median 2 days IQR (1–5) in VAS 1–6 vs. median 3 days IQR (2–5) in VAS 7–10, p = 0.009), but not with the duration of opioid treatment (Table S5).

On-admission imaging

We observed a significantly increased number of acute peripancreatic fluid collection (OR = 1.587, 95% CI: 1.133–2.224) and oedematous pancreas (OR = 1.955 95% CI: 1.178–3.246) via imaging on admission with VAS 7–10 compared to VAS 1–6 (Table S4).

3.5.2 | Pain type

Comparing patients with different types of pain, we found no difference in age, gender, BMI, smoking habit, history of pancreatic diseases, diabetes mellitus or other metabolic diseases or findings on the physical examination (Table S6).

Patients with cramping pain tended to have a biliary aetiology, and they were less likely to have an alcoholic aetiology compared to dull or sharp pain ($p < 0.05$).

Abdominal guarding was more frequent when sharp pain was present compared to cramping and dull pain (26.2% vs. 16.5% and 26.2%, $p < 0.05$).

Main outcomes

Sharp pain was associated with a 2.6-fold increase in mortality odds (OR = 2.632, 95% CI: 1.063–6.514) compared to other types of pain (dull + cramping pain). Sharp pain might also be a risk factor for severe disease (OR = 2.206, 95% CI: 1.199–4.059), especially for systemic complications (OR = 2.481, 95% CI: 1.550–3.969), including new-onset diabetes (OR = 2.561, 95% CI: 1.472–4.456) and respiratory (OR = 3.220, 95% CI: 1.806–5.740) and heart failure (OR = 3.222, 95% CI: 1.319–7.869). There were also increased odds for necrosis development with sharp pain (OR = 1.653, 95% CI: 1.060–2.580). Cramping pain was associated with a longer LOS ($p < 0.05$; Figure 3).

Sharp pain was associated with a higher proportion of opioid administration compared to cramping and dull pain (OR = 2.250 95% CI: 1.585–3.194). Cramping and sharp pain were associated with longer analgesic requirement compared to dull pain (median 4 days IQR (2–6) and median 4 days IQR (2–7) vs. median 2 days IQR (2–6), respectively, $p = 0.005$). Pain type was not associated with the length of opioid administration ($p = 0.938$).

On-admission imaging

There was no difference between pain type categories in the presence of on-admission abnormalities on imaging (Table S4).

3.5.3 | Pain localization

An unexpectedly high percentage of patients ($n = 557$, 50.8%) had atypical pain on admission, mostly presenting with umbilical or right rib pain. In addition, we found a greater chance of atypical pain with obesity (OR = 1.320 95% CI: 1.036–1.681), hypertension (OR = 1.303 95% CI: 1.016–1.669) and hyperlipidaemia (OR = 1.889 95% CI: 1.302–2.741; Table S7). Also, pain typical of acute pancreatitis was associated with a higher proportion of peripancreatic fluid collection (Table S4).

There were only a few notable differences as regards pain location in main outcomes.

We were unable to support it statistically, but, apparently, left, lower abdominal pain was associated with a worse prognosis (Table S8). At the same localization, the proportion of idiopathic cases seemed to be higher compared to other localizations. Although these localizations were considered rare in the cohort.

3.5.4 | Pain duration

Median pain duration on admission was 24 h (IQR 10–72 h). Pain duration on admission was not associated with age, gender, smoking habit, history of pancreatic diseases or metabolic diseases, CCI, or findings on physical examination (Table S9).

Main outcomes

Surprisingly, pain duration prior to hospitalization was not associated with severity, mortality, LOS or different systemic or local complications. Patients with pain duration of fewer than 24 h prior to hospitalization required opioid administration more frequently compared to patients with longstanding pain (≥72 h; 22.9% vs. 9.2%, $p < 0.001$).

On-admission imaging

Findings from on-admission imaging were independent of pain duration on admission.

3.6 | Relation between pain characteristics

There was a weak negative correlation between pain intensity and pain duration ($r = -0.168$, $p < 0.001$). In addition, patients with sharp pain had a significantly shorter duration of pain on admission compared to cramping ($p < 0.001$) or dull pain ($p = 0.003$). Less intense pain was characterized by dull pain rather than by sharp or cramping pain ($p < 0.001$), while sharp pain was more typical of more intense pain ($p < 0.001$).

Further results are described in detail in the Supporting information.

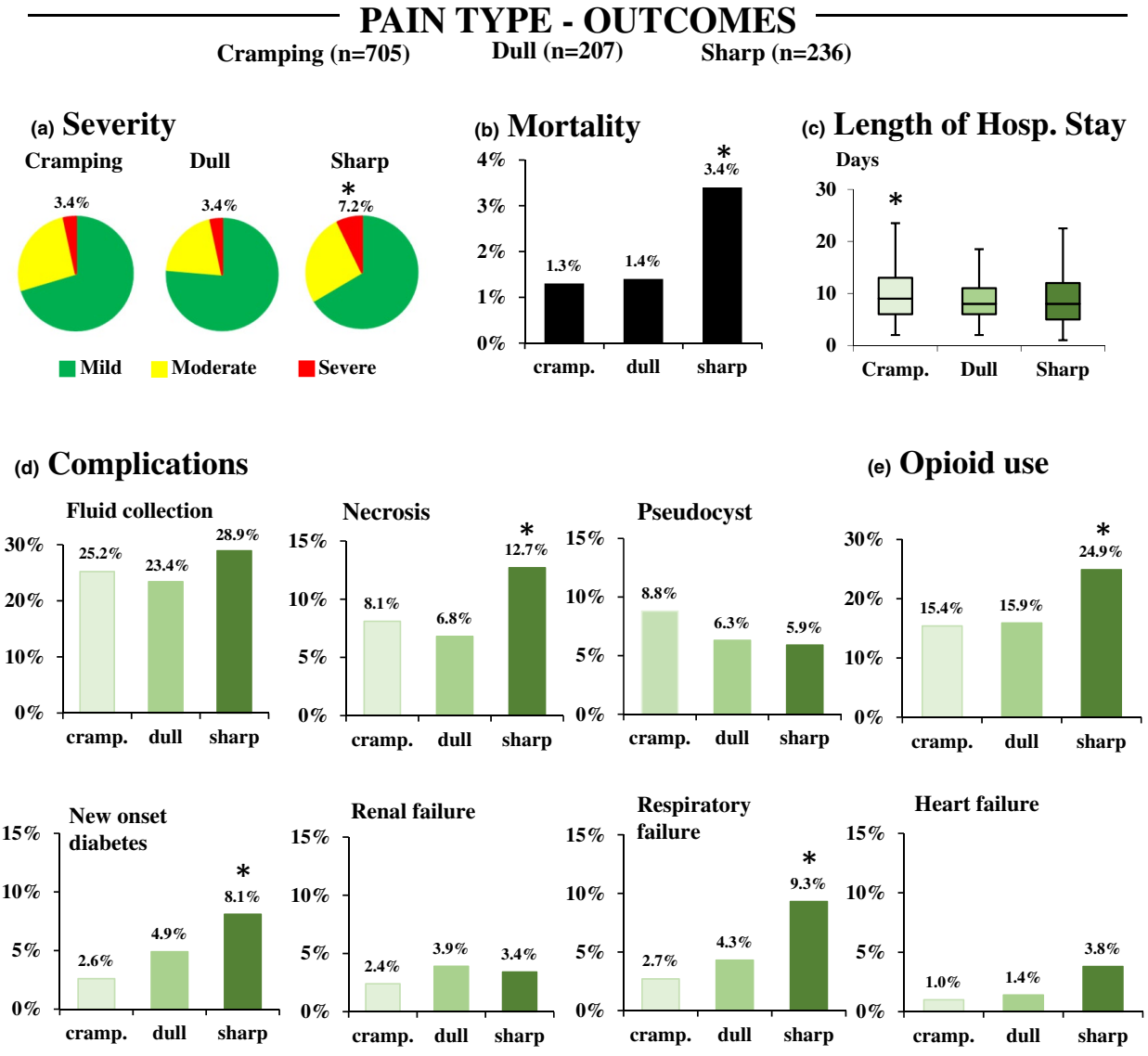

FIGURE 3 Main outcomes of AP in *pain type* groups (cramping and dull vs. sharp). (a) Severity (*OR = 2.206 95%: 1.199–4.059); (b) Mortality (*OR = 2.632 95% CI: 1.063–6.514) Length of hospital stay (*$p < 0.05$); (d) Complications: fluid collection; necrosis (*OR = 1.653 95% CI: 1.060–2.580); pseudocysts; new-onset diabetes (*OR = 2.561 95% CI: 1.472–4.456); respiratory failure (OR = 3.220 95% CI: 1.806–5.740); renal failure; heart failure (*OR = 3.222 95% CI: 1.329–7.869); (e) Opioid use (*OR = 3.250 95% CI: 1.585–3.194)

4 | DISCUSSION

This prospective, multicentre, international cohort study characterizes acute abdominal pain in AP.

4.1 | Generalizability of the registry data

The mortality and severity rates for AP in our study are consistent with the more favourable international data (Brindise et al., 2019; Zhu et al., 2017). This could be explained by the high rates of adherence to international and national guidelines among most of the participating centres, including timely intervention with fluid replacement and early enteral feeding (Hritz et al., 2015; Parniczky et al., 2016; Working Group, 2013).

Our results on pain characteristics were also comparable with previous findings. Patients experienced mostly VAS 7–10 pain intensity starting within 24 h prior to hospitalization (Pai et al., 2017; PanWessex Study et al., 2019; Phillip et al., 2013). Importantly, this is the first study to investigate the aspect of pain quality descriptors, in other words, pain type in AP.

4.2 | Pain characteristics

Interestingly, we discovered an unexpected feature of *sharp pain*: it was associated with unfavourable disease

outcomes, such as higher systemic complications and mortality rates.

Previous data suggest that pain type (quality descriptors) might be related to the mechanism of pain. Understanding the pain mechanism can aid in choosing the optimal therapeutic approach (Asthana et al., 2020; Erdogan et al., 2019). Sharp pain is sometimes interpreted as a sign of neuropathic pain (Mackey et al., 2012). The presence of neuropathic pain is a known phenomenon in pancreas cancer and a novelty in chronic pancreatitis (Demir et al., 2015, 2019). Unfortunately, the currently available data in AP do not allow us to elucidate the mechanisms behind sharp pain. To determine whether neuropathy is present, specifically validated questionnaires, such as the DN4 questionnaire, could be used in the future (VanDenKerkhof et al., 2018).

Nevertheless, it may entail a different mechanism of not only pain but also inflammatory processes in the pancreas since sharp pain was associated with a worse disease course in our study. A different inflammatory process could be further supported by the higher proportion of abdominal guarding among patients with sharp pain, which is usually considered a sign of stronger inflammation in the abdomen. However, we need further investigations to explore this topic through an examination of laboratory samples as well as histological and imaging findings and an assessment of pain type in more detail with validated questionnaires.

In our cohort, patients with sharp pain experienced the strongest pain, which was comparable to findings by Dworkin et al. in both neuropathic and non-neuropathic pain (Dworkin et al., 2007). Furthermore, *pain intensity* correlated with the severity of AP as an ordinal variable, and certain abnormal imaging findings on admission, such as enlarged pancreas and peripancreatic fluid collection, were more common in the case of more intense pain. In chronic pancreatitis, a similar association between pain intensity and morphological changes could not be identified (Madzak et al., 2017). However, VAS 1–6 and VAS 7–10 groups did not differ significantly concerning disease outcomes although some tendency could be observed with an apparently higher rate of severe AP in VAS 7–10 groups. Surprisingly, despite the apparently milder disease, VAS 1–6 was associated with a significantly longer LOS. Since LOS can be influenced by various variables, it is hard to explain this conflicting result. The difference between the two groups is clinically not significant since it is less than 1 day. Nevertheless, after examining the longest hospitalizations, we came to the conclusion that a significant proportion of them is linked to pancreatitis unrelated causes or only indirectly related causes such as nosocomial infections (Clostridium difficile infection, pneumonia, urinary tract infection) or iatrogenic disorders (e.g. bleeding after ERCP, drug side effects). In VAS 1–6 group, investigations to rule out malignancies appear to be more common since a few patients presented with pain lasting for weeks. Moreover, extremely long LOS could be explained mostly by decompensation of comorbidities. While in the VAS 7–10 group, recurrent pain due to local complications and the antibiotic or surgical treatment of coexistent cholecystitis seems to be more prevalent. Also, extremely long LOS was mainly because of AP-related complications.

The possible prognostic role of on-admission pain should be further characterized, including adjustment to potential confounding factors of both pain and disease outcomes.

Typically, the patients with more intense and sharp abdominal pain turned to doctors earlier in our study. Still, the *duration of pain* before hospitalization was not influenced by any other factors under examination, such as age, gender or positive personal or family history with AP, as shown in an earlier study as well. Nor did the authors of the mentioned article noted a link between pain duration and in-hospital outcomes, a finding which is consistent with our own (Phillip et al., 2013).

Earlier studies have suggested that pain assessment in different diseases might depend on the patients' gender because women and men describe and process pain differently (Fillingim et al., 2009; Rau et al., 2018; Unruh, 1996). However, data are not consistent throughout the abdominal pain literature (Fillingim et al., 2009), and we were also unable to confirm a gender difference in patients with AP. As with gender, there are contradictions in the literature about the effect of age on pain perception and analgesic consumption (Banks et al., 2013; Galli et al., 2019). We were also unable to detect an age-dependent pattern of pain in AP. According to our results, components of metabolic syndrome—which can make people more vulnerable to complications of AP (Mosztbacher et al., 2020; Szentesi et al., 2019)—show links to atypical pain of currently unknown significance. We may assume that this is due to diabetic neuropathy. However, this is contradicted by the fact that among the metabolic components, diabetes was the one that was not associated with atypical pain. Unfortunately, the currently available data do not allow us to interpret our findings in more detail. Further studies with a larger sample size could confirm or reject altered pain perception in patients with metabolic syndrome.

Atypical pain was relatively common in our cohort. The most accepted diagnostic guideline, the revised Atlanta classification, defines acute pancreatic pain as 'abdominal pain consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to

the back)'. When forming our groups in pain localization, we were also only able to rely on this phrase and other phrases that appear frequently in the AP literature and in clinical practice. Nevertheless, seeing the high number of patients with atypical pain in our cohort, it would be reasonable to reconsider what typical pain in AP means. The localization of pain in AP could be more diverse than we think. Reconsideration of the diagnostic criterion may facilitate early recognition of AP in centres where imaging and laboratory examinations are not easily accessible.

Lower and left abdominal pain probably caused diagnostic difficulty, suggested by the high proportion of idiopathic cases. However, even in these cases, an effort should be made to determine disease causality (Zadori et al., 2020).

4.3 | Pain management

Pain management in AP is, without a doubt, of particular importance. Unfortunately, according to previous systematic reviews (Basurto Ona et al., 2013; Meng et al., 2013), only a few randomized clinical trials have investigated this topic. In addition, we need further descriptions of analgesic strategy in a real-world setting (Pezzilli et al., 2007). Therefore, we briefly reviewed the use of opioid and non-opioid pain medications in our registry.

Adequate analgesia may improve disease outcome and patient satisfaction by enabling early feeding and mobilization. Non-opioid analgesics may be particularly recommended, since morphine may worsen the severity of AP because of known and hypothesized side effects (Barlass et al., 2018), while NSAIDs can relieve inflammation according to a systematic review of animal and clinical studies (Wu et al., 2020). However, a systematic review found that patients administered with opioids might need fewer supplementary analgesics, but the pain intensity of these patients was similar to that of the controls (including NSAID treatment), pointing to the ongoing debate in this field. Moreover, a recent study comparing pentazocine, an opioid and diclofenac, has found a significantly longer pain-free period, less rescue analgesia, similar side effect profile and disease course in the pentazocine group. Nevertheless, patients in both groups had very fast recovery. The authors have explained it with the proper pain management, resulting in decrease in sympathetic activity and neuroimmune inflammation (Mahapatra et al., 2019).

Contrary to these results, in our cohort, cases administered with painkiller, especially with opioid had longer LOS compared to patients without painkiller and without opioids respectively. However, patients were not treated with rigorous, predetermined pain management strategies in our registry, it was rather based on the preferences of physicians. Besides pain intensity, pain management was likely dependent from the disease severity. For example patients with more severe disease tended to be treated with opioids. Of course, a direct toxic effect of opioids cannot be ruled out in this case either.

So, the question whether opioids or NSAIDs are better has not been decided. Since this is a registry-based analysis, a definitive conclusion on this topic cannot be drawn from our data without the possibility of selection bias. The high percentage of missing data in these parameters should be also considered as limitation. The high proportion of missing data is primarily explained by the temporary or permanent transfer of patients to another ward or department, on which days the paper-based documentation became inaccessible for research personnel.

Nevertheless, it should be highlighted that the percentage of opioid use in our cohort is relatively low. Despite the steady rise in opioid consumption, Central and Eastern Europe, from where most of our data originate, has a more restrictive opioid policy. In fact, according to the analysis of worldwide pain management strategies, only North America had a very high rate of opioid administration (93% vs. 27% in other regions). This extremely high difference might be explained by the shortcomings of AP guidelines on pain management (Matta et al., 2020). To fully elucidate this question and to compare pain relief achieved by opioids and non-opioids, carefully designed randomized controlled trials (RCT) are needed in AP. The already existing RCTs provide limited data with relatively low patient numbers (16 to 50); therefore, more evidence is warranted.

In essence, the use of an enhanced recovery strategy applied in postoperative care may also be recommended in AP (Dong et al., 2019). Tailored therapy (besides pain intensity, therapy that is also tailored to pain type) would facilitate the development of enhanced recovery strategies (Wu et al., 2020). Nevertheless, proper pain assessment must precede pain management (Vivian et al., 2019).

In our cohort, the characteristics of on-admission pain were associated with the frequency of opioid administration and the duration of analgesic requirement, possibly suggesting that these pain characteristics may persist.

Unfortunately, any association with analgesics is highly dubious since analgesic administration might depend on several factors, including pain intensity, patient's age, comorbidities and the severity of AP. Moreover, we were not able to perform analyses on active substances and dosages because of poorly reported data.

4.4 | Strength and limitations

This study examines the role of abdominal pain in AP in a unique and detailed fashion. The data came from

an international, multicentre collaboration with 1432 consecutive patients with AP, thus improving its external validity. The similar mortality and severity rates to those of published international data serve as confirmation. We took several variables into account collected and validated in four steps by trained research staff, including clinical research administrators and clinicians.

This study also has limitations. First, a high percentage of missing data in some variables can lead to selection bias. To evaluate the influential power of missing data, we compared the whole cohort to the analysed cohorts, where complete data on a given pain characteristic was available. We found differences when we compared the pain intensity and pain type cohort to the whole cohort. Namely, a lower proportion of severe AP in the pain intensity and pain type cohort was found. Since the question about pain intensity was only included in 2015, improved management of patients over time may explain this phenomenon. Moreover, complete documentation on pain management was only available in 61.6% of the cases. Second, much of our data were based on questionnaires; thus, the role of recall bias may arise. Third, we collected data on pain at a single point in time on the day of hospital admission, which does not consider changes in pre-admission pain, pain trajectories during hospitalization, and the effect of therapy.

4.5 | Implications for practice

Our research pointed out that a comprehensive patient interview should include questions about pain characteristics. However, there is a pressing need for validated pain quality assessment tools in AP translated into various languages to improve clinical trials and practice.

Patients with sharp and intense pain might require special monitoring and tailored pain management.

4.6 | Implications for research

Since pain in AP can be very severe and difficult to manage, it is essential to explore the mechanism of pain and to understand its relationship with the disease course and patients' characteristics to optimize pain management.

The pathophysiology of pain should be further investigated, for example to explore the possibility of neuropathy. Studies should also focus on the association between pain characteristics and inflammatory parameters. Furthermore, future studies should investigate pain trajectories in AP as well as the transition from acute to chronic pain and the influence of pain trajectories on long-term quality of life.

5 | CONCLUSION

Intense and sharp pain on admission was associated with higher odds for severe AP and several systemic and local complications. VAS 7–10 was linked to peripancreatic fluid and oedematous pancreas. Therefore, the question arises whether patients with more intense pain require closer monitoring and whether pain relief could improve AP outcome.

Sharp pain was associated with the highest pain intensity. The mechanism of pain type is currently unknown but should be further investigated to clarify whether these patients require different pain management strategies besides closer monitoring due to a more severe disease course.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

AUTHORS' CONTRIBUTIONS

All the authors critically revised the final version of the manuscript and approved it. FM, AS, SK, AP and PH participated in drafting the concept, interpreting the data and writing the manuscript. FM also participated in patient enrollment and data collection. Besides reviewing the manuscript, the following authors also provided substantial assistance in patient enrollment and study design:

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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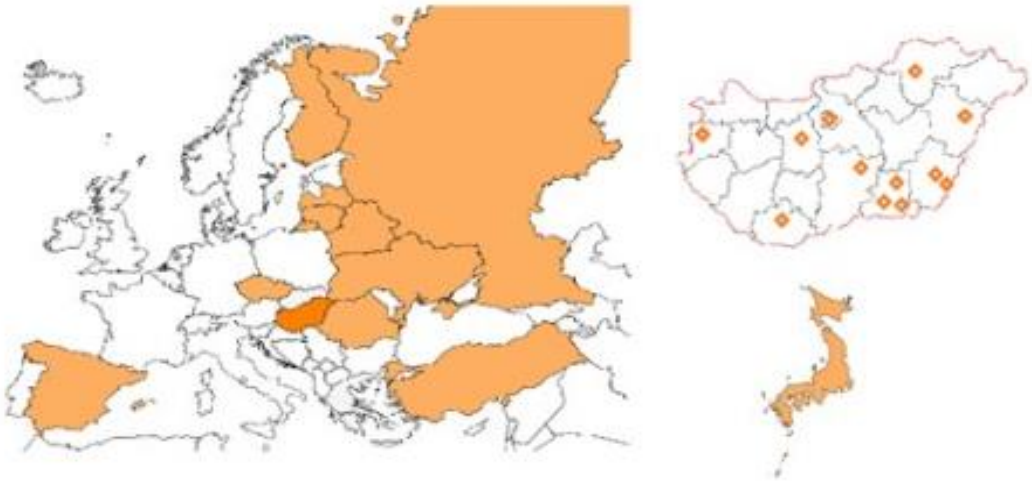
Supplementary Figure 1 – Centre distribution



Acute Pancreatitis Registry Centers			
Country	City	Institute	No. of patients
Hungary	Pécs	First Department of Medicine, Medical School, University of Pécs	363
	Szeged	First Department of Medicine, University of Szeged	247
		Second Department of Medicine, University of Szeged	36
		Department of Emergency, University of Szeged	10
		Department of Surgery, University of Szeged	4
	Székesfehérvár	Szent György Teaching Hospital of County Fejér	199
	Budapest	Bajcsy-Zsilinszky Hospital	138
		Polyclinic of Hospitaller Brothers of Saint John of God	5
		Heim Pál National Institute of Pediatrics	1
		Military Hospital	1
	Debrecen	Department of Internal Medicine, University of Debrecen	76
		Institute of Surgery, University of Debrecen	7
	Békéscsaba	Dr. Réthy Pál Hospital	54
	Gyula	Pándy Kálmán Hospital	27
	Szentes	Dr. Bugyi István Hospital	16
	Miskolc	Borsod-Abaúj-Zemplén County Hospital and University Teaching Hospital	14
	Kecskemét	Bács-Kiskun County Hospital	11
	Makó	Healtcare Center of County Csongrád	10
	Szombathely	Markusovszky University Teaching Hospital	9
Romania	Targu Mures	Mures County Emergency Hospital	41
Lithuania	Vilnius	Vilnius University Hospital Santariskiu Klinikos	31
Spain	Barcelona	Consorci Sanitari del Garraf, sant Pere de Ribes	30
Finland	Helsinki	Helsinki University Hospital	27
Turkey	Istanbul	Hospital of Bezmialem Vakif University	20
Russia	St. Petersburg	Saint Luke Clinical Hospital	18
Czech Republic	Ostrava	Vítkovická Hospital a.s.	11
Belarus	Gomel	Gomel Regional Clinical Hospital	8
Latvia	Riga	Pauls Stradius Clinical University Hospital	8
Ukraine	Kiev	Bogomolets National Medical University	8
Japan	Tokyo	Keio University	2

Supplementary Table 1. Data quality (%)

Variable	Overall (n=1432)	Pain Intensity group (n=727)	Pain Type group (n=1148)	Pain Localization group (n=1134)	Pain Duration (n=1202)
Age at the time of admission	100	100	100	100	100
Sex	100	100	100	100	100
BMI (kg/m2)	87.7	96.8	90.4	87.7	89.1
Etiology	100	100	100	100	100
Length of hospital stay	100	100	100	100	100
Mortality	100	100	100	100	100
Severity of pancreatitis	100	100	100	100	100
Local complications	95.5	95.5	99.5	99.4	99.7
Fluid collection	95.5	95.5	99.5	99.4	99.7
Pseudocyst	99.6	99.6	99.6	99.5	99.8
Necrosis	99.6	99.6	99.6	99.5	99.8
Systemic complication	99.3	100	99.4	99.3	99.3
Respiratory failure	99.2	100	99.3	99.2	99.2
Heart failure	99.3	100	99.4	99.3	99.3
Renal failure	99.3	100	99.4	99.3	99.3
AP in the personal history	94.1	99.8	95.9	94.9	95.6
CP in the personal history	94.1	99.9	95.9	94.9	95.6
DM in the personal history	98.8	100	99	98.9	99.3
Current smoking (Y/N)	99.6	99.2	99.7	98.8	99.7
Cigarettes/day	91.7	98.2	92.1	90.8	92.6
Pack year	65.1	91.4	70.3	65.1	69.1
Current alcohol (Y/N)	99.7	100	99.7	99.7	99.8
Amount of alcohol consumption (g/occasion)	73.4	92.8	85.1	75.2	77.1
Amount of alcohol consumption (g/day)	76.7	90.7	81.8	77.1	78.7
Pleural fluid	82	89.1	84.1	82.6	84.8
Lung infiltrate	81.6	89.0	83.7	82.2	84.3
Ascites	86.5	92.0	88.1	87	88.7
Abnormal pancreas structure	86.5	92.0	88.1	87	88.7
Hypoechogenecity	86.5	92.0	88.1	87	88.7
Hyperechogenecity	86.5	92.0	88.1	87	88.7
Edematous pancreas	86.5	92.0	88.1	87	88.7
Irregular blurred contours	86.5	92.0	88.1	87	88.7
Wirsung-dilatation	86.5	92.0	88.1	87	88.7
Pancreatic calcification	86.5	92.0	88.1	87	88.7
Fatty tissue infiltration	86.5	92.0	88.1	87	88.7
Peripancreatic fluid collection	86.5	92.0	88.1	87	88.7
On-admission necrosis	87.9	92.4	89.6	88.4	82.5
On-admission pseudocyst	87.4	92.2	89.1	87.8	89.8
On-admission fluid collection	87.4	92.2	89.1	87.9	89.7

II.

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ORIGINAL CONTRIBUTIONS

Transversus Abdominis Plane Block Appears to Be Effective and Safe as a Part of Multimodal Analgesia in Bariatric Surgery: a Meta-analysis and Systematic Review of Randomized Controlled Trials

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Abstract

Purpose Pain after bariatric surgery can prolong recovery. This patient group is highly susceptible to opioid-related side effects. Enhanced Recovery After Surgery guidelines strongly recommend the administration of multimodal medications to reduce narcotic consumption. However, the role of ultrasound-guided transversus abdominis plane (USG-TAP) block in multimodal analgesia of weight loss surgeries remains controversial.

Materials and Methods A systematic search was performed in four databases for studies published up to September 2019. We considered randomized controlled trials that assessed the efficacy of perioperative USG-TAP block as a part of multimodal analgesia in patients with laparoscopic bariatric surgery.

Results Eight studies (525 patients) were included in the meta-analysis. Pooled analysis showed lower pain scores with USG-TAP block at every evaluated time point and lower opioid requirement in the USG-TAP block group (weighted mean difference (WMD) = − 7.59 mg; 95% CI − 9.86, − 5.39; $p < 0.001$). Time to ambulate was shorter with USG-TAP block (WMD = − 2.22 h; 95% CI − 3.89, − 0.56; $p = 0.009$). This intervention also seemed to be safe: only three non-severe complications with USG-TAP block were reported in the included studies.

Conclusion Our results may support the incorporation of USG-TAP block into multimodal analgesia regimens of ERAS protocols for bariatric surgery.

Keywords Pain · Bariatric surgery · TAP block · Meta-analysis

Introduction

Pain in the postoperative period can cause serious suffering to patients, prolong recovery, and increase healthcare costs [1]. However, postoperative pain management can be a major challenge as previous studies demonstrated that it is frequently suboptimal [2–4].

Laparoscopic bariatric surgeries are considered minimally invasive, but they can cause severe pain [5, 6]. Opioids are excellent analgesics, but they have several side effects such as respiratory depression, which may further complicate pain management in weight loss surgeries, particularly in cases with obstructive sleep apnea [7]. Other comorbidities such as diabetes mellitus and cardiovascular diseases that are common in patients with obesity can also lead to difficulties with pain management [8]. This complexity highlights the

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importance and the challenges of the optimal choice of analgesia in bariatric surgery.

Enhanced Recovery After Surgery (ERAS) protocols are created to facilitate faster recovery after surgery multimodal analgesia [9]. Although growing evidence supports multimodal analgesic techniques in clinical practice, opioids still remain among the first choice of postoperative pain management [10].

Postoperative opioid overuse could be particularly worrisome. For example, in the USA, the opioid epidemic causes a serious health crisis. According to a recent study, persistent opioid use is a common problem after surgery [11]. In the opioid epidemic era, recognizing the issue of opioid overuse with its associated complications could be of particular importance [12]. Several alternative options can be used including other pain medications such as paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), ketamine, or gabapentin [13].

Besides pharmacological analgesia, locoregional analgesic techniques are also among the alternatives. After decades of being the "gold standard," large meta-analyses and trials reported controversial effects of epidural analgesia on mortality and morbidity associated with frequent technical failures [14, 15]. As an alternative to epidural analgesia, infiltrative techniques—including transversus abdominis plane block (TAP block)—has gained increasing attention in recent years as they can be safely and easily applied [16]. During TAP block, a local anesthetic solution is injected between planes of abdominal muscles to anesthetize the anterior abdominal wall [17]. As ultrasound guidance (USG) becomes more widely available, the popularity of TAP block has further increased. USG facilitates the performance of TAP block in cases where anatomic landmarks are poorly defined, e.g., in patients with obesity [18].

Recent meta-analyses showed that USG-TAP block is effective in reducing pain and opioid consumption in different abdominal surgeries [19], including open appendectomy [20], hysterectomy [21], or colorectal resection [15] to control pain and decrease opioid consumption. Randomized controlled studies (RCTs) investigating the use of TAP block in weight loss surgeries have also been published, but its impact on different outcomes remained controversial. To our knowledge, no meta-analysis has examined TAP block during laparoscopic bariatric surgery. Therefore, we aimed to assess the effects of USG-TAP block as a part of multimodal analgesia for postoperative pain management in patients undergoing laparoscopic bariatric surgery.

Methods and Materials

We report this systematic review and meta-analysis following the Preferred Reporting in Systematic Reviews and Meta-analyses (PRISMA) (Supplementary Material) [22]. We registered the protocol on PROSPERO under registration number CRD42020154384.

Eligibility Criteria

We included full-text RCTs that assessed the efficacy of perioperative USG-TAP block in postoperative analgesia compared with no treatment or sham intervention in patients who underwent laparoscopic bariatric surgery.

The following outcomes were analyzed: pain scores measured by the Visual Analog Scale (VAS) or the Numbering Rating Scale (NRS) on a scale from 0 to 10 within the first 24 postoperative hours, morphine requirement (mg) within the first 24 postoperative hours, rate of nausea during phase I recovery, time to ambulate (hours), length of hospital stay (hours), operation time (hours).

Search Strategy

A systematic search was carried out in the following databases for studies published up to September 2019: CENTRAL, MEDLINE, Web of Science, and Embase. We designed a search key with synonyms to bariatric surgery (population) and TAP (intervention) linked with Boolean operators. We did not use any filters (e.g., language, full-text, human) (Supplementary Material). The reference lists of included studies and previous systematic reviews and meta-analyses have also been screened for additional articles. Gray literature was not included in our meta-analyses.

Selection Strategy and Data Extraction

Two authors independently (SK and MF) removed all duplicate records, then checked titles and abstracts to remove irrelevant articles, and evaluated full-text articles, whether they were eligible for inclusion. All disagreements were resolved by consensus.

Two authors independently (MF and SK) extracted data into a standardized data collection sheet. We resolved any disagreement by consensus. From the individual studies, we extracted the raw data (mean and standard deviation or standard error) in case of cumulative morphine dose, time to ambulate, length of hospital stay, operation time, and pain level in rest and at movement if it was given. In the case of nausea, the number of patients and event rates in the two groups were extracted from the individual studies.

Risk of Bias Assessment

Two independent authors (MF and SK) used the revised Cochrane risk-of-bias 2 (RoB 2) tool to assess the risk of bias

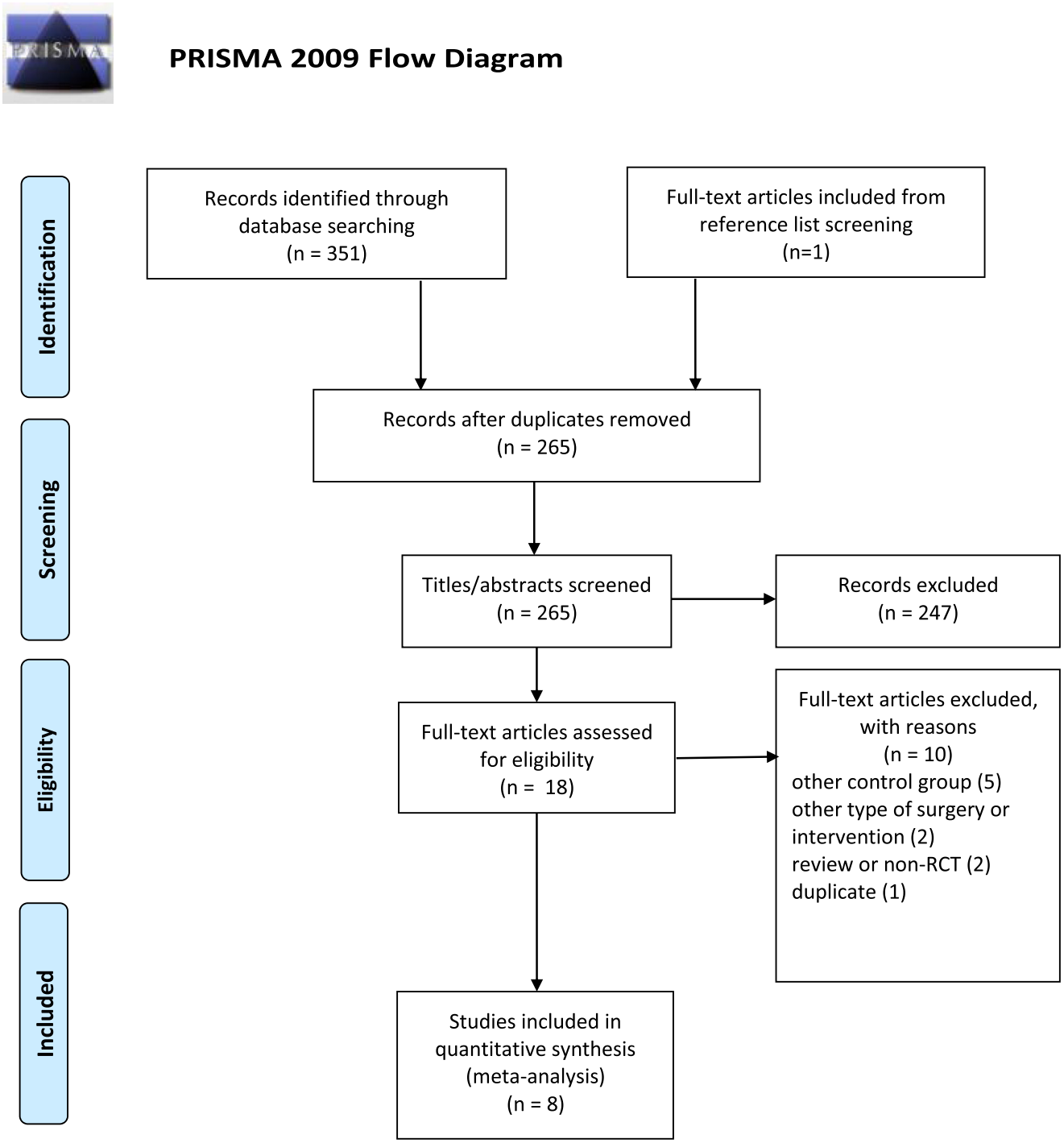


Fig. 1 Flow chart of study selection and inclusion process

of studies in the following categories [23]. Disagreements were resolved by consensus.

Statistical Analysis

We calculated mean differences with 95% CI between the control and USG-TAP groups. In the case of nausea, we calculated risk ratio with 95% CI. A p value < 0.05 was considered statistically significant. Pooled estimates were calculated with a random effects model by using the DerSimonian-Laird method [24]. If mean with standard deviation was not reported, we estimated them from median, interquartile, and range [25]. Results of the meta-analysis were displayed graphically using forest plots. Due to methodological characteristics

Table 1 The "Characteristics of included studies" table

Study name	Country/ setting	Allocation	Participants	Characteristics of participants	Type of surgery	Type and dose of local anesthetic agent	TAP approach	Outcomes	Postoperative analgesia regimen (PACU)
Albrecht 2013	Single center in Canada	USG-TAP	27	Mean age 44.8 (95% CI, 40.8–48.8), 74% female, mean BMI 49.3 (95% CI 45.6–52.9)	Lap. gastric bypass surgery	20 mL of 0.25% bupivacaine	Preop. oblique subcostal	24-h cumulative opioid consumption, length of hospitalization, rate of nausea and vomiting	As needed with incremental doses of fentanyl 25–50 μg iv and morphine 1–2 mg iv or hydromorphone 0.2–0.4 mg iv in order to achieve a clinical target of 4/10 or lower on a Numbering Rating Scale (NRS) for pain
		No USG-TAP*	30	Mean age 38.8 (95% CI, 34.9–42.8), 87% female, mean BMI 48.9 (95% CI, 49.5–51.8)					
De Oliveira 2014	Single center in the USA	USG-TAP	9	Median age 47.0 (39–53), 80% female, median BMI 44.2 (39.0–45.7)	Lap. gastric band surgery	20 mL of 0.5% ropivacaine	Preop. posterior	24-h cumulative opioid consumption, length of hospitalization, rate of nausea and vomiting, operation time	As needed with hydromorphone 0.4 mg iv to achieve 4/10 or lower on a Numbering Rating Scale (NRS) for pain. When oral medications were tolerated, hydrocodone 10 mg plus acetaminophen 325 mg
		Sham	10	Median age 50.0 (36–54), 78% female, median BMI 40.1 (39.0–45.7)					
Emile 2019	Single center in Egypt	USG-TAP	46	Mean age 35.8 ± 8.9, 94% female, mean BMI 50.4 ± 7.9	Lap. bariatric surgery	20 mL of 0.25% bupivacaine	Postop. mid--axillary	Pain scores at 1, 6, 12, and 24 h at rest, time to ambulate, length of hospitalization	Paracetamol (1 g every 8 h) iv. As needed with 0.2 mg/kg pethidine iv in order to achieve a clinical target of 4/10 or lower on a Visual Analog Scale (VAS) for pain
		No USG-TAP*	46	Mean age 33.6 ± 9.8, 91% female, mean 48.6 ± 5.3					
Ibrahim 2014	Single center in Egypt	USG-TAP	21	Mean age 38.3 ± 10.2, 76% female, mean BMI 48.5 ± 10.4	Lap. gastrectomy	30 mL of 0.25% bupivacaine	Preop. oblique subcostal	24-h cumulative opioid dose, operation time	As needed with fentanyl 25–50 μg iv or morphine 1–2 mg iv or pethidine 20–40 mg iv if patient had moderate or severe pain
		Sham	21	Mean age 37.4 ± 11.3, 68% female, mean BMI 46.4 ± 8.7					
Mittal 2018	Single center in India	USG-TAP	30	Mean BMI 46.2 ± 6.7	Lap. sleeve gastrectomy	40 mL of 0.375% ropivacaine	Preop. mid--axillary	Pain scores at 1, 3, 6, 12, and 24 h at rest, time to ambulate	Diclofenac (75 mg every 8 h) iv. As needed with 1 g diclofenac iv in order to achieve a clinical target of 4/10 or lower on a Visual Analog Scale (VAS) for pain
		No USG-TAP*	30	Mean BMI 44.9 ± 7.2					
Saber 2018	Single center in Canada	USG-TAP	30	Mean age 37.0 ± 10.7, 87% female, mean BMI 44.0 ± 4.8	LAP. sleeve gastrectomy	20 mL of 0.25% bupivacaine	Preop. oblique subcostal	Pain scores at 3 h at rest, operation time	Acetaminophen 600 mg q6, gabapentin 100 mg. As needed with morphine and hydromorphone
		Sham	30	Mean age 40.0 ± 11.2, 94% female, mean BMI 44.0 ± 7.1					

Table 1 (continued)

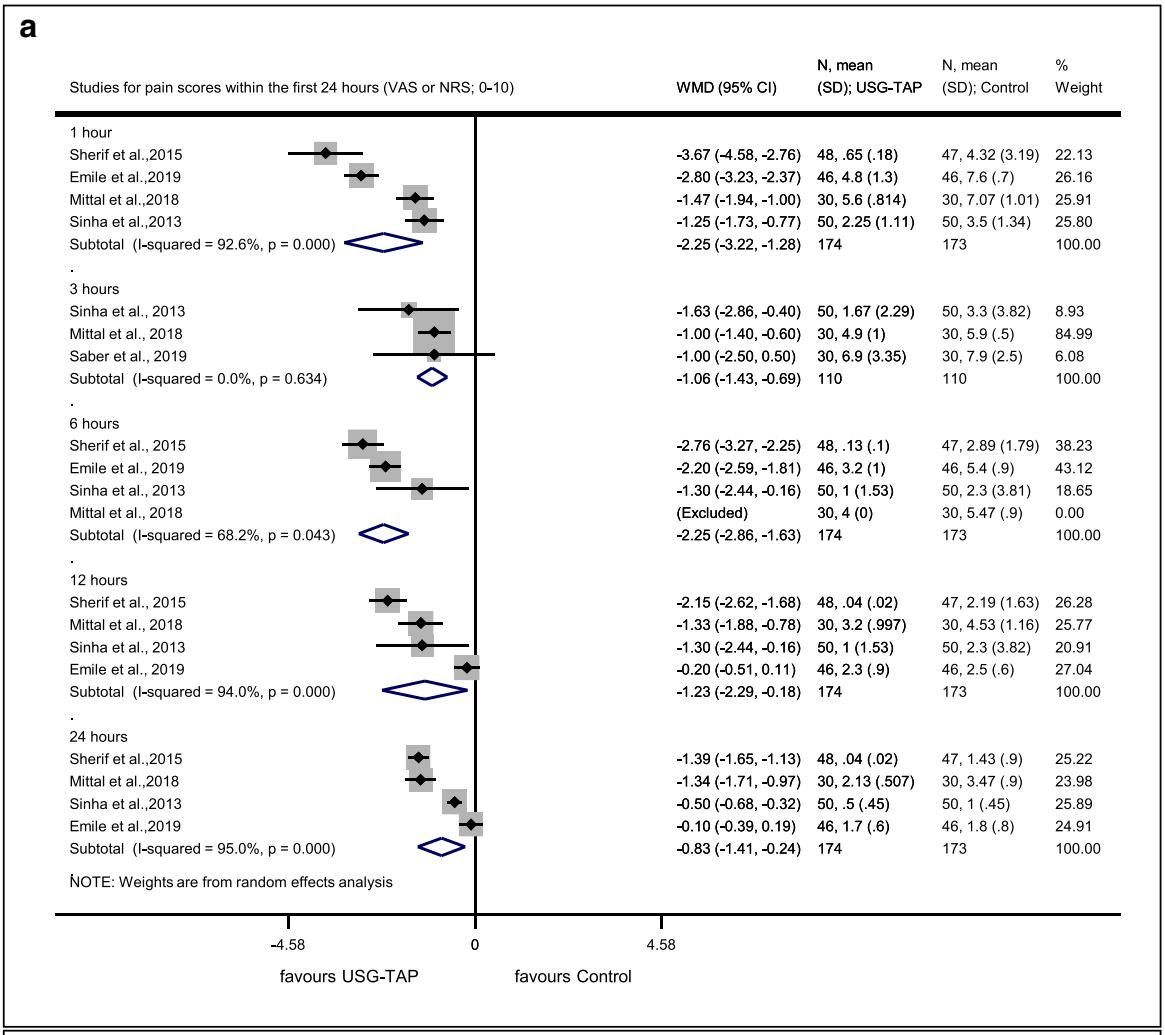
Study name	Country/ setting	Allocation	Participants	Characteristics of participants	Type of surgery	Type and dose of local anesthetic agent	TAP approach	Outcomes	Postoperative analgesia regimen (PACU)
Sherif 2015	Single center in Egypt	USG-TAP	48	Mean age 40.9 ± 8.75, 21% female, mean BMI 38.7 + 2.2	Lap. gastric bypass	20 mL of 0.5% bupivacaine	Postop. anterior axillary	Pain scores at 1, 6, 12, and 24 h at rest, 24-h cumulative opioid dose, time to ambulate, rate of nausea and vomiting	Intravenous patient-controlled analgesia (PCA) system, which provided 1 mg of morphine on demand with a block-out interval of 20 min and a maximum 6 h dose of 10 mg in both groups. All patients received regular postoperative analgesia comprising paracetamol 1 g, intravenous, four times daily
		Sham	47	Mean age 40.4 ± 8.71, 26% female, mean BMI 38.9 ± 2.2					
Sinha 2013	Single center in India	USG-TAP	50	Mean age 39.9 ± 13.3, mean BMI 48.1 ± 6.3	Lap. gastric bypass	20 mL of 0.375% bupivacaine	Postop. oblique subcostal	Pain scores at 1, 3, 6, 12, and 24 h at rest, time to ambulate	Tramadol
		Sham	50	Mean age 39.1 ± 10.6, mean BMI 45.6 ± 6.6					

no USG-TAP* indicates no sham-control was applied

USG-TAP ultrasound-guided transversus abdominis plane, *lap.* laparoscopic, *preop.* pre-operative, *postop.* postoperative

Comments: Patients always received standard medical therapy, including pain management (non-opioids and opioids), antiemetics, antibiotics, thromboprophylaxis, if necessary

Data are expressed either as mean ± SE/SD, as median (interquartile range), or as mean (95% confidence interval)


a
Studies for pain scores within the first 24 hours (VAS or NRS; 0-10)
WMD (95% CI)
N, mean (SD); USG-TAP
N, mean (SD); Control
% Weight
1 hour
Sherif et al.,2015 -3.67 (-4.58, -2.76) 48, .65 (.18) 47, 4.32 (3.19) 22.13
Emile et al.,2019 -2.80 (-3.23, -2.37) 46, 4.8 (1.3) 46, 7.6 (.7) 26.16
Mittal et al.,2018 -1.47 (-1.94, -1.00) 30, 5.6 (.814) 30, 7.07 (1.01) 25.91
Sinha et al.,2013 -1.25 (-1.73, -0.77) 50, 2.25 (1.11) 50, 3.5 (1.34) 25.80
Subtotal (I-squared = 92.6%, p = 0.000) -2.25 (-3.22, -1.28) 174 173 100.00
3 hours
Sinha et al., 2013 -1.63 (-2.86, -0.40) 50, 1.67 (2.29) 50, 3.3 (3.82) 8.93
Mittal et al., 2018 -1.00 (-1.40, -0.60) 30, 4.9 (1) 30, 5.9 (.5) 84.99
Saber et al., 2019 -1.00 (-2.50, 0.50) 30, 6.9 (3.35) 30, 7.9 (2.5) 6.08
Subtotal (I-squared = 0.0%, p = 0.634) -1.06 (-1.43, -0.69) 110 110 100.00
6 hours
Sherif et al., 2015 -2.76 (-3.27, -2.25) 48, .13 (.1) 47, 2.89 (1.79) 38.23
Emile et al., 2019 -2.20 (-2.59, -1.81) 46, 3.2 (1) 46, 5.4 (.9) 43.12
Sinha et al., 2013 -1.30 (-2.44, -0.16) 50, 1 (1.53) 50, 2.3 (3.81) 18.65
Mittal et al., 2018 (Excluded) 30, 4 (0) 30, 5.47 (.9) 0.00
Subtotal (I-squared = 68.2%, p = 0.043) -2.25 (-2.86, -1.63) 174 173 100.00
12 hours
Sherif et al., 2015 -2.15 (-2.62, -1.68) 48, .04 (.02) 47, 2.19 (1.63) 26.28
Mittal et al., 2018 -1.33 (-1.88, -0.78) 30, 3.2 (.997) 30, 4.53 (1.16) 25.77
Sinha et al., 2013 -1.30 (-2.44, -0.16) 50, 1 (1.53) 50, 2.3 (3.82) 20.91
Emile et al., 2019 -0.20 (-0.51, 0.11) 46, 2.3 (.9) 46, 2.5 (.6) 27.04
Subtotal (I-squared = 94.0%, p = 0.000) -1.23 (-2.29, -0.18) 174 173 100.00
24 hours
Sherif et al.,2015 -1.39 (-1.65, -1.13) 48, .04 (.02) 47, 1.43 (.9) 25.22
Mittal et al.,2018 -1.34 (-1.71, -0.97) 30, 2.13 (.507) 30, 3.47 (.9) 23.98
Sinha et al.,2013 -0.50 (-0.68, -0.32) 50, .5 (.45) 50, 1 (.45) 25.89
Emile et al.,2019 -0.10 (-0.39, 0.19) 46, 1.7 (.6) 46, 1.8 (.8) 24.91
Subtotal (I-squared = 95.0%, p = 0.000) -0.83 (-1.41, -0.24) 174 173 100.00
NOTE: Weights are from random effects analysis
-4.58
0
4.58
favours USG-TAP
favours Control
b
Studies for 24-hour morphine requirement (mg)
WMD (95% CI)
N, mean (SD); USG-TAP
N, mean (SD); Control
% Weight
Ibrahim et al.,2013 -8.00 (-10.43, -5.57) 21, 16.8 (2.7) 21, 24.8 (5) 87.06
De Oliveira et al.,2014 -6.66 (-16.23, 2.91) 10, 7.17 (7.74) 9, 13.8 (12.7) 5.61
Albrecht et al.,2013 -3.40 (-11.78, 4.98) 27, 32.2 (12.2) 30, 35.6 (19.6) 7.33
Overall (I-squared = 0.0%, p = 0.575) -7.59 (-9.86, -5.32) 58 60 100.00
NOTE: Weights are from random effects analysis
-20
-10
0
10
favours USG-TAP
favours Control
c
Studies for time to ambulate (hours)
WMD (95% CI)
N, mean (SD); USG-TAP
N, mean (SD); Control
% Weight
Sherif et al.,2015 -4.94 (-5.84, -4.04) 48, 6.85 (1.8) 47, 11.8 (2.6) 24.82
Sinha et al.,2013 -1.72 (-2.43, -1.01) 50, 6.3 (1.8) 50, 8.02 (1.8) 25.53
Mittal et al.,2018 -1.27 (-2.49, -0.05) 30, 8.2 (2.3) 30, 9.47 (2.52) 23.41
Emile et al.,2019 -1.00 (-1.45, -0.55) 46, 6.3 (1) 46, 7.3 (1.2) 26.24
Overall (I-squared = 94.9%, p = 0.000) -2.22 (-3.89, -0.56) 174 173 100.00
NOTE: Weights are from random effects analysis
-10
0
10
favours USG-TAP
favours Control

◀ **Fig. 2** Forest plots that show efficacy endpoints for the comparison of "USG-TAP" and "control". **a** Forest plot for pain score within the first 24 postoperative hours (VAS or NRS, 0–10). **b** Forest plot showing 24-h postoperative morphine requirement (mg). **c** Forest plot showing time to ambulate (h). USG-TAP, ultrasound-guided transversus abdominis plane block; VAS, Visual Analog Scale; NRS, Numbering Rating Scale

of the analysis, we could not indicate pooled means for each group on the forest plots; however, study-level data in each study can be seen in Supplementary Material (for 24-h cumulative morphine requirement, time to ambulate, length of hospital stay, and operation time).

Heterogeneity was tested by using the Cochrane's Q and the I^2 statistics, where $I^2 = 100\% \times (Q - \mathrm{df}) / Q$, and represents the magnitude of the heterogeneity (moderate: 30–60%, substantial: 50–90%, considerable: 75–100%) [16]. A p value < 0.10 was considered statistically significant heterogeneity. All meta-analytical calculations were performed by Stata 11 data analysis and statistical software (Stata Corp LLC, College Station, TX, USA).

We performed trial sequential analysis (TSA) for each outcome if it was possible. We used the TSA tool to estimate the required number of patients in future studies and to quantify the statistical reliability of data if the condition of the tests were met. With this test, we assessed whether the intervention arm is effective applying adjusted significance tests and determined the necessity of conducting more studies in the topic to show significant differences [26].

We planned to conduct the following subgroup analyses: gender, age, type of bariatric surgery, type and dose of local anesthetics, TAP approach. Because of the limited number of studies, we were unable to conduct any of the planned subgroup analyses.

Quality of Evidence

We assessed the overall quality of evidence using the GRADE profiler (GRADEpro). Since data come from only RCTs, we downgraded the evidence from "high quality" by one level for serious (or by two levels for very serious) risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates, or potential publication bias.

We included the critical and important outcomes in the "Summary of findings table" (Table 2).

Results

Results of Search and Selection

The selection process is described in detail in the PRISMA flow diagram (Fig. 1). A total of 351 records were identified through electronic database search (CENTRAL: 89; MEDLINE: 36; Web of Science: 99; Embase 127), eight of which were included in this meta-analysis ($n = 525$; 262 in the "USG-TAP block" group and 263 in the "control" group). Beyond the eight analyzed articles, two studies with active control groups were excluded [27, 28], and in one excluded study, USG-TAP was not performed perioperatively [29].

Characteristics of the Studies Included

All included studies were single-center RCTs (Table 1). From the eight studies, five used sham-control (normal saline infiltration) [30–34]. In three studies, the control group did not receive sham-control [35–37]. One study used port-site infiltration in both intervention and control groups [37].

Studies reported data of patient group numbers ranging from 19 to 100. Studies enrolled predominantly women with a mean BMI over 40 [33]. Four studies reported data of patients undergoing laparoscopic sleeve gastrectomy [31–33, 36]. Two studies recruited patients who underwent laparoscopic gastric bypass surgery [34, 37]. One trial studied patients with gastric band surgery [30] and one with several different types of laparoscopic bariatric surgery [35].

The type and dose of local anesthetic agents and those of USG-TAP approaches were different among studies. In four of the studies, USG-TAP block was performed immediately after completion of surgery [30–32, 37]; the remaining studies carried out surgeries with preoperative USG-TAP block after anesthesia induction [33–36].

Postoperative analgesia regimens were also quite diverse among studies (see in detail in Table 1); most of the studies used regular or as-needed non-opioids supplemented with narcotics on demand. However, some studies—carried out in the early 2010—applied opioids exclusively [31, 34].

Effects of Intervention

Primary Endpoints

Pain Scores Within the First 48 h Pooled analysis showed that USG-TAP block lowered postoperative pain scores (rated on a scale between 0 and 10) at rest by 2.25 ($p < 0.001$) at 1 h, by 1.08 ($p < 0.001$) at 3 h, by 2.25 ($p < 0.001$) at 6 h, by 1.23 ($p < 0.022$) at 12 h, and by 0.83 ($p = 0.006$) at 24 h (Fig. 2a). Heterogeneity was considerable in these analyses (Fig. 2a).

Two studies also examined pain scores at rest 48 h after surgery: they found significantly lower pain scores in the USG-TAP block group [33, 36].

In two included studies [33, 36], pain scores at movement were also significantly lower at each evaluated time point (0.5, 3, 6, 12, 24, and 48 h postoperatively; $p < 0.001$ for all comparisons).

Postoperative Cumulative Morphine Dose Four studies with 213 patients (106 in the intervention group and 107 in the control group) examined the postoperative cumulative morphine dose within the first 24 h [30, 31, 33, 37]. Morphine requirement did not differ significantly between the intervention and control groups (− 12 mg; 95% CI − 26.88, 2.89; $p = 0.114$). However, we observed high heterogeneity in this analysis ($p_{heterogeneity} < 0.001$ and $I^2 = 99.0\%$). We identified and removed the influential study with sensitivity analysis, which reduced heterogeneity to 0% and changed a direction of the main association to favoring TAP (Fig. 2b) [33]. Results of each study can be seen in Supplementary Material.

Secondary Endpoints

Time to Postoperative Bowel Recovery One trial with 46 patients in each arm reported recovery of bowel functions assessed by time to first flatus, and they found a statistically significant difference favoring the USG-TAP block group (9.5 ± 1.9 vs 10.5 ± 2.2 h; $p < 0.001$) [35]. Mittal and coworkers also found earlier resumption of bowel activity in the intervention group [36].

Nausea and Vomiting Pooled analyses of three studies with 171 patients (85 in the intervention and 86 in the control groups) indicated a lower risk of nausea in the USG-TAP block groups compared with control patients (95% CI, RR = 0.24, $p < 0.001$) (Supplementary Material) [30, 31, 33, 37].

Emile and coworkers applied the Apfel score for postoperative nausea and vomiting: they also found a significant improvement with USG-TAP block for this outcome (2.1 ± 0.9 points in the USG-TAP group vs 3.0 ± 0.9 points, $p < 0.001$ in the control group) [35]. Mittal and coworkers reported a pooled number of events of nausea and/or vomiting and found 8/30 and 24/30 cases in the USG-TAP and control groups, respectively [36].

However, both Emile et al. and Saber et al. found that the need for antiemetic use was similar between intervention and control groups [32, 35].

Sedation In the study of Sherif et al., four patients of 47 in the control group required postoperative biphasic intermittent positive airway pressure (BIPAP) ventilation support [33]. According to the study of Sinha et al., four of 50 patients needed BIPAP in the control group [34]. None of these studies detected any need for BIPAP in the USG-TAP group.

Sinha and coworkers also reported significantly lower Richmond Agitation and Sedation Score in the first 6 hours in the USG-TAP block group [34].

Time to Ambulate Pooled analysis of four trials with 347 patients (174 in the intervention group and 173 in the control group) demonstrated that the time to ambulate was shorter by 2.2 h in patients who underwent USG-TAP block ($p = 0.009$) (Fig. 2c) [33–36]. We observed high heterogeneity for this meta-analysis (Fig. 2c). After sensitivity analysis, we identified an influential study [34]. Removal of this study changed the result to non-significant; however, heterogeneity remained high (weighted mean difference (WMD) = − 2.40; 95% CI − 4.98, 0.18; $p < 0.001$ ($p_{heterogeneity} < 0.001$ and $I^2 = 96.6\%$)). (Results of each study are shown in Supplementary Material.)

Length of Hospital Stay A meta-analysis of three studies with 168 patients (83 in the intervention group and 85 in the control group) failed to identify a shorter length of hospital stay following USG-TAP block performance compared with that of controls ($p = 0.102$) (Supplementary Material) [30, 35, 37]. (Results of each study are shown in Supplementary Material.)

Length of Operation Three studies with 121 patients (61 in the intervention group and 60 in the control group) using preoperative USG-TAP block evaluated the length of operation. We found similar operative times in the intervention and control groups ($p = 0.951$) (Supplementary Material) [30–32]. (Results of each study are shown in Supplementary Material.)

Satisfaction Rate Two studies investigated the patient satisfaction rate with different methods. In the study of Mittal and coworkers, it was assessed by the Capuzzo composite score (score range 0–10) in 60 patients: the authors reported significantly higher scores in the USG-TAP block group compared with the control group (8.2 ± 0.7 vs 7.1 ± 0.7; $p < 0.001$) [36]. Sinha and coworkers also observed significantly higher satisfaction scores in the USG-TAP block group at the end of the first postoperative day [34].

USG-TAP Block–Related Complications Only three occurrences of local complications (two cases with hematoma formation, one case with severe pain at the site of injection) due to USG-TAP block were reported in only one study [35].

Trial Sequential Analysis

The cumulative Z curve crossed trial sequential significance boundary with regard to the outcomes: time to ambulate, nausea and vomiting, pain at 1 and 24 h. In addition, nausea and vomiting and pain at 1 h exceeded the required meta-analysis sample size, from which it can be inferred that inclusion of further clinical trials would not change these results (Fig. S5). TSA for morphine requirement and operation time could not be performed due to insufficient availability of data.

Risk of Bias in the Studies Included

We summarized the results of the risk of bias assessment for each included study in Fig. 3 and Fig. S6.

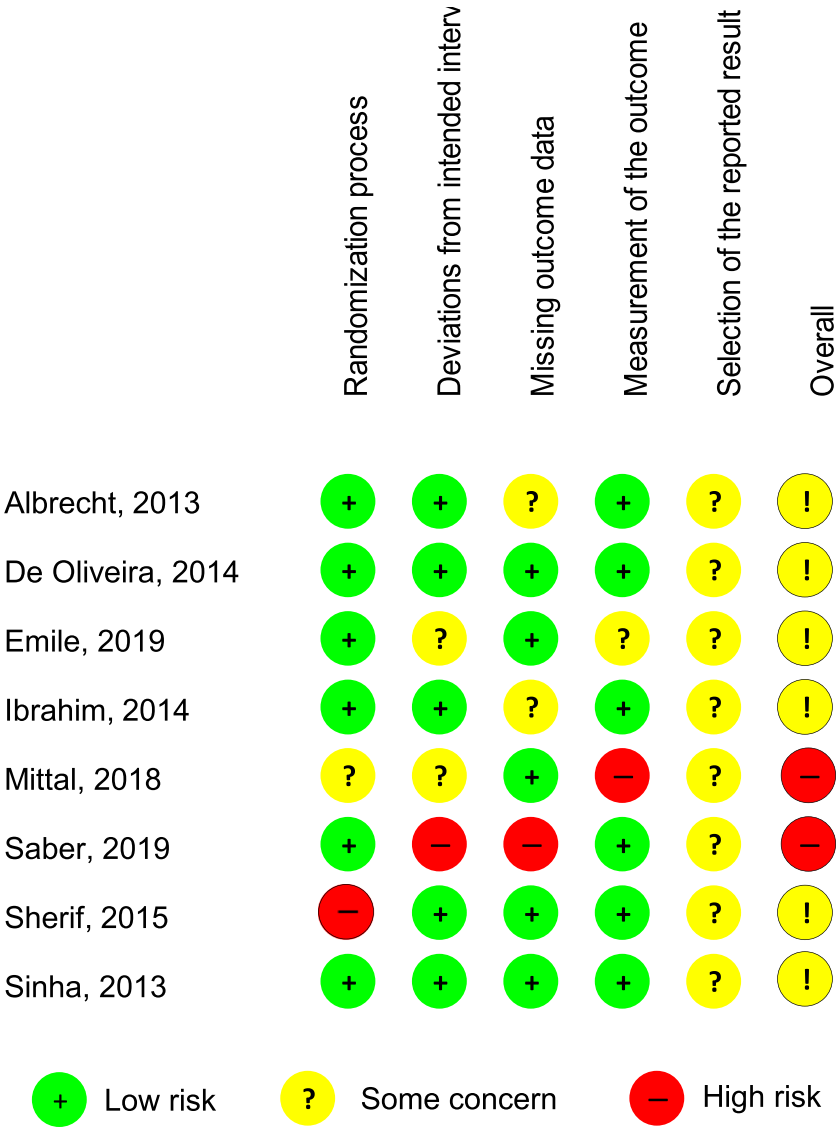


Fig. 3 Risk of bias summary: review authors' judgments about each risk of bias item for each included study

Discussion

This meta-analysis and systematic review investigates the efficacy and safety of USG-TAP block compared with systemic analgesia alone in patients undergoing laparoscopic bariatric surgery. Our analyses suggest various beneficial effects, including a reduction in pain scores, in opioid requirement, and in risk for adverse events associated with opioids in the first 24 postoperative hours, without any reported major adverse events.

We detected a statistically significant decrease in resting pain scores at each evaluated time point during the first 24 postoperative hours. Included studies assessed pain intensity by Visual Analog Scale (VAS) or Numbering Rating Scale (NRS) on a scale from 0 to 10. Previously, Kelly and coworkers reported that the minimum clinically significant difference in VAS score is 0.9 [38]. Accordingly, our results may also demonstrate clinically significant improvement, except for the 24th-hour postoperative pain scores, where we found only 0.83 lower WMD in the USG-TAP block group. Two studies also reported a beneficial effect of USG-TAP block on pain 48 h after surgery: the difference between groups was still statistically significant, but it gradually decreased with time [33, 36].

Interestingly, although the mean elimination half-life of bupivacaine is around 8–10 h after USG-TAP block [39], our results hint at a somewhat longer analgesic effectiveness in agreement with previous studies [21, 40], USG-TAP block appears to be effective in late pain as well but to a lesser extent. We evaluated our findings with some reservations because of the low quality of evidence due to inconsistency and the moderate/high risk of bias in individual studies (Table 2).

Meta-analysis of four RCTs on cumulative morphine requirement in the first 24 h showed a tendency favoring USG-

Table 2 Summary of findings table. *Patient or population*: postoperative pain management in obese patients undergoing laparoscopic bariatric surgery; *Setting*: inpatient; *Intervention*: transversus abdominis plane block (TAP block) as a part of multimodal analgesia; *Comparison*: systemic analgesia alone (no intervention or sham-control)

Outcomes	№ of participants (studies) follow-up	Certainty of the evidence (GRADE)	Risk difference with transversus abdominis plane block (TAP block) as a part of multimodal analgesia
Pain score 1 h after surgery assessed with VAS or NRS	347 (4 RCTs)	⊕⊕○○ Low[a,b]	MD *2.25 lower* (3.22 lower to 1.28 lower)
Pain score 24 h after surgery assessed with VAS or NRS	347 (4 RCTs)	⊕⊕○○ Low[a,b]	MD *0.83 lower* (1.41 lower to 0.24 lower)
24-h postoperative cumulative morphine dose (mg)	118 (3 RCTs)	⊕⊕⊕○ Moderate[c]	MD *7.59 mg lower* (9.86 lower to 5.32 lower)
Local and systemic complication due to TAP block	525 (8 RCTs)	-	Not pooled
Time to ambulate (h)	347 (4 RCTs)	⊕⊕○○ Low[a,b]	MD *2.2 h fewer* (3.89 fewer to 0.56 fewer)

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI)

CI confidence interval, *MD* mean difference

GRADE Working Group grades of evidence:

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[a] In a single study, there was no information of allocation concealment. In two studies, lack of blinding could lead to bias

[b] Heterogeneity was high for this analysis

[c] Optimal information size is not met calculated by trial sequential analysis

TAP block, albeit with a high heterogeneity. After removing the influential study verified by sensitivity analysis, heterogeneity disappeared, and the difference became significant.

We speculate that this phenomenon can be due to the much larger intergroup difference in morphine consumption in the influential study compared with the other studies [33]. This might result from the dissimilar study population (predominantly male and leaner patients) and the use of patient-controlled analgesia, unlike in the other trials. It is important to note that although ERAS guidelines recommend patient-controlled administration of opioids, only one study used patient-controlled analgesia (PCA) [9, 33]. We downgraded this outcome to moderate quality of evidence because it was not supported by a large enough data pool (Table 2).

Previous findings in the literature are controversial with regard to the effect of USG-TAP block on morphine requirement. Most studies agree that TAP block reduces opioid requirement in lower [24] and upper abdominal surgeries (as compared with placebo or no intervention) [40]. However, when TAP block was compared with or added to epidural analgesia [41], intrathecal analgesia [42], or wound infiltration in abdominal surgeries [43], there was usually no difference between groups. These findings may suggest that TAP block has no superior or added effect to these techniques in different types of abdominal surgeries. However, some studies have demonstrated the benefits of adding TAP block to infiltration of port sites [44], or even the superiority of TAP block over wound infiltration in general surgery [45].

One of the analyzed studies performed port-site infiltration in both USG-TAP and control groups; this is the only study which did not find significantly reduced morphine consumption in the USG-TAP block group [37]. In contrast, when Ruiz-Tovar and coworkers compared laparoscopic-guided TAP block directly with port-site infiltration in Roux-en-Y gastric bypass surgery, they could demonstrate the superiority of USG-TAP block over port-site infiltration [27]. Based on these findings, it appears that TAP block may lack an added effect to local infiltration anesthesia in bariatric surgery, but it appears to be preferable over local infiltration techniques. Since a definitive conclusion on the comparison of these two methods has not been reached, this topic in both bariatric and other abdominal surgeries would warrant further studies [46].

Enhanced Recovery After Surgery (ERAS) guidelines strongly recommend the administration of multimodal intravenous medication accompanied by local anesthetic infiltration in order to spare or avoid narcotic consumption in a patient group which is highly susceptible to the adverse events of opioids [9]. Nausea, vomiting, constipation, excessive sedation, and respiratory depression may prolong recovery, cause additional complications, and impair satisfaction rate of

patients. Previous studies showed that multimodal analgesia reduces the rate of side effects and the time to recovery [47].

Our review discusses thoroughly the effects of USG-TAP block on opioid-related harms; USG-TAP block seems to be beneficial in each evaluated aspect (time to postoperative bowel recovery, nausea and vomiting, sedation). However, we could not reach a strong conclusion based on these results, because the pooled analysis was only possible in the case of nausea and vomiting indicating 76% relative risk reduction, and the 1-h reduction in time to first flatus was on the one hand reported by only one study, and on the other, its clinical relevance is questionable despite the statistically significant result [35].

Our meta-analysis indicates shorter time required to ambulate with USG-TAP block. This may support faster recovery and a reduced number of complications of immobilization. Since both obesity and postoperative conditions are risk factors of thromboembolism, patients with bariatric surgery are at a particularly high risk for these complications [48]. Besides thromboprophylaxis, decreasing length of bed rest can be an important factor in thrombosis prevention. We downgraded this outcome to low quality of evidence because of inconsistency and risk of bias (Table 2).

The presence of USG-TAP block did not affect the total length of hospital stay, even if we would expect that early ambulation would be associated with faster discharge [49]. Nevertheless, since the length of hospital stay depends on several factors, and patients spent only about 2 days in hospital, minor differences might have remained undetected. Further studies assessing the length of hospital stay as the primary outcome could resolve this issue.

TAP block is usually considered safe, but rare complications such as puncture of the liver may occur [50]. Among studies included in this review, only Emile and coworkers reported two cases of abdominal wall hematoma and one case of severe pain at the site of injection [35]. Of course, there are more appropriate study designs to detect rare side effects than RCTs, which could not be included in the current meta-analysis as they did not fit in the inclusion criteria. In the future, it would be important to record complications more thoroughly in RCTs.

Despite the previous concerns regarding challenges to TAP block administration in patients with obesity [51], only two studies mentioned minor difficulties that were successfully eliminated [31, 34]. In addition, we incorporated only those trials that operated under ultrasound guidance, which facilitates better visualization. However, most of the included studies failed to report success rates.

Heterogeneity was high between studies. Since the low number of analyzed studies did not allow subgroup analyses, we were not able to explore the cause of heterogeneity—with one exception mentioned above. Theoretically, we can explain heterogeneity by the different types of surgery, anesthetic management, dose and type of anesthetics, USG-TAP approach, or postoperative analgesia regimen.

It is well known that USG-TAP block relieves somatic but not visceral pain. The ratio of pain types can differ depending on the types of bariatric surgery, affecting the extent of USG-TAP block efficacy, as well. A cadaver study has suggested that the subcostal approach is superior to the mid-axillary approach as indicated by the size of dye spread [52]. In addition, Khan et al. and coworkers achieved better postoperative analgesia with the subcostal approach in patients with cholecystectomy compared with the posterior approach [53]. Thus, the subcostal approach may be better when compared with other techniques in upper abdominal surgeries. It has been also suggested that the pre-incisional application of TAP block may be more potent than post-incisional application, because of the preemptive analgesia that spares patients from the development of altered processing of afferent input [54]. Since we could not perform subgroup analyses to address these questions, further well-designed clinical trials would be required.

In addition to high heterogeneity across studies, the poor reporting of important outcomes by relatively few, small, and single-center studies is another important limitation of our meta-analysis as well as the risk of bias of the included studies. The definition of some outcomes (e.g., operation time) was not precise enough. Conversion of medians to mean could distort our result. Some of the included studies may raise ethical concerns since they worked with invasive placebo (so-called sham-control). The SHAM (serious harm and morbidity) scale classifies the risk of saline injection as placebo control of TAP block as highest (grade 4) [55].

Further limitation can be that some studies were conducted before the “paradigm shift” in opioid use, which means that these studies might apply non-opioids inadequately. The combination of TAP block with non-opioid pain medication within the framework of opioid-restrictive protocols would worth further studying. The analgesic regimens were not only outdated in some studies but also very diverse across studies. For instance, pethidine was used as an opioid in one of the studies, which has become obsolete in several countries for more than two decades [35]. It is, therefore, challenging to compare “old fashioned” single-agent techniques to up-to-date multimodal approaches.

Further studies are also necessary to elucidate the optimal use of USG-TAP block in bariatric surgery, including the ideal timing, technique, dose, or type of local anesthetic injection. We also need to know more about its efficacy when it is added to or compared with other analgesic agents in order to find its place in multimodal analgesia. There are further promising fields in TAP block research as the use of continuous infusion of local anesthetics or liposomal bupivacaine.

Conclusion

In summary, USG-TAP block reduces pain intensity, morphine requirement, rate of opioid-related side effects, and the time to ambulate. It is likely to help the faster recovery of patients, even if this meta-analysis could not detect significantly shorter length of hospital stay with USG-TAP block. Our results may support its incorporation into multimodal analgesia regimens of ERAS protocols for patients undergoing laparoscopic bariatric surgery, but further studies are needed to evaluate its co-administration with non-opioid medication in opioid-restrictive protocols.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval Statement This article does not contain any studies with human participants or animals performed by any of the authors.

Informed Consent Statement Informed consent does not apply.

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