The Anesthesiologist’s Perspective Regarding Non-intubated Thoracic Surgery: A Scoping Review

Giulio Luca Rosboch1*, Paraskevas Lyberis2, Edoardo Ceraolo1, Eleonora Balzani3, Martina Cedrone3, Federico Piccioni4, Enrico Ruffini2,3, Luca Brazzi1,3 and Francesco Guerrera2,3

1 Department of Anesthesia, Intensive Care and Emergency, “Città della Salute e della Scienza di Torino” Hospital, Torino, Italy
2 Department of Cardiovascular and Thoracic Surgery, “Città della Salute e della Scienza di Torino” Hospital, Torino, Italy
3 Department of Surgical Science, University of Turin, Torino, Italy
4 Anesthesia and Intensive Care Unit, General and Specialistic Surgical Department, Arcispedale Santa Maria Nuova, Azienda USL – IRCCS di Reggio Emilia, Reggio Emilia, Italy

Non-intubated thoracic surgery (NITS) is a growing practice, alongside minimally invasive thoracic surgery. To date, only a consensus of experts provided opinions on NITS leaving a number of questions unresolved. We then conducted a scoping review to clarify the state of the art regarding NITS. The systematic review of all randomized and non-randomized clinical trials dealing with NITS, based on Pubmed, EMBASE, and Scopus, retrieved 665 articles. After the exclusion of ineligible studies, 53 were assessed examining: study type, Country of origin, surgical procedure, age, body mass index, American Society of Anesthesiologist’s physical status, airway management device, conversion to orotracheal intubation and pulmonary complications rates and length of hospital stay. It emerged that NITS is a procedure performed predominantly in Asia, and certain European Countries. In China, NITS is more frequently performed for parenchymal resection surgery, whereas in Europe, it is mainly employed for pleural pathologies. The most commonly used device for airway management is the laryngeal mask. The conversion rate to orotracheal intubation is ∼3%. The results of the scoping review seem to suggest that NITS procedures are becoming increasingly popular, but its role needs to be better defined. Further randomized clinical trials are needed to better define the role of the clinical variables possibly impacting on the technique effectiveness.

INTRODUCTION

Parallel to the growth of minimally invasive surgical thoracic techniques, non-intubated thoracic surgery (NITS) has been increasingly used (1, 2). NITS procedures appear to avoid either the adverse effects of mechanical ventilation in patients with already impaired pulmonary functional capacity before surgery, and the residual effects of neuromuscular blockers, providing more rapid recovery of respiratory muscle function and less perioperative morbidity (1, 3).

While NITS technique is becoming increasingly popular, there is still no clarity in how it is defined and performed. For example, the procedure is reported in the literature as non-intubated thoracic surgery, but also referred to as tubeless video-assisted thoracoscopic surgery (VATS) or awake thoracic surgery.
Although an expert consensus recently attempted to clarify and establish the critical points of NITS, some perioperative surgical and anesthesiological evaluation variables remained undefined (4).

In order to better clarify the background of NITS, surgical indications, type of patient to be proposed for the procedure, airway management, postoperative complications, and length of stay (LOS) a scoping review based on a systematic literature review was conducted.

**Protocol and Registration**

The study protocol was developed using the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines (5) revised by the members of the thoracic surgery research team of “Città della Salute e della Scienza” university hospital (Turin – Italy). The final protocol was registered prospectively with the Open Science Framework on 26th September 2021 (https://osf.io/mfyp3/).

**Eligibility Criteria**

Peer-reviewed articles dealing with NITS with the following characteristics were identified as potentially eligible: (1) randomized controlled trials (RCTs) and non-RCTs (NRCTs); (2) published in English; (3) involving adult participants (>18 years old).

**Information Sources and Search Strategy**

Potentially relevant studies were searched through September 2021 in Pubmed, EMBASE and Scopus using the search strategies reported in the Supplementary Materials (Supplementary File 1). The results were exported to EndNote V.X9 (Clarivate Analytics, PA, USA), and the duplicates were automatically removed.

**Studies Evaluation and Selection of Sources of Evidence**

The review process was carried out in two steps consisting of evaluating the titles, abstracts, and then full text of all publications identified by our searches for potentially relevant manuscripts. For both levels, four authors worked in pairs (GLR, EC, EB, and MC) and screened the articles with conflicts resolved by consensus and discussion with other reviewers.

**Data Charting Process and Data Items and Synthesis of Results**

A planned Excel spreadsheet was developed by reviewers to determine which variables to extract used (study characteristics, patient characteristics, surgical procedures, country, age, number of patients, body mass index (BMI), Forced Expiratory Volume in the 1st second (FEV1), diffusing capacity for carbon monoxide (DLCO), American Society of Anesthesiologists (ASA) physical status classification, intraoperative drugs used, type of anesthesia, type of regional analgesia, bispectral index (BIS) utilization, airway management device, conversion to oro/tracheal intubation (OTI), conversion to thoracotomy, postoperative pain, postoperative pulmonary complications, and postoperative days of hospitalization). The reviewers independently charted the data in pairs. If not available, any ongoing study was contacted to include unpublished data if applicable. We grouped the studies by the type of study (with or without a comparison group). Where we identified a systematic review, we counted the number of studies included in the review that potentially met our inclusion criteria and noted how many studies had been missed by our search.

**RESULTS**

**Selection of Sources of Evidence PRISMA**

We followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines (5). The systematic literature search performed in September 2021 retrieved 665 results. After deduplication, 283 studies were evaluated. Three hundred eighty-two and 234 were, respectively excluded following the first and second evaluation process bringing the number of studies included in the scoping review to 49. To these, four more articles (6–9) previously reported in systematic reviews were added leading the total number of articles included to 53, all published after 2011.

**General Characteristics of Included Studies**

Among the 53 included studies, 30 were cohort studies comparing NITS and intubated-patient thoracic surgery, whereas 22 were single-cohort studies of patients undergoing NITS. Seventeen were conducted in Taiwan, 15 in China, nine in Italy, four in South Korea, two in Germany and one in Turkey, United Kingdom, Russia, Switzerland, and Hungary (Figure 1). Patients’ characteristics are summarized in Table 1.

Regarding the described surgical procedures: 17.9% were lobectomies, 10.7% endoscopic thoracic sympathectomies, 10.7% bullectomies, 8.9% lung biopsies, 7.1% mediastinal tumor resections, wedge resections, segmentectomies, and lung resections, respectively. In 5.4% of cases the procedure was classified as minor thoracic surgery, without reporting a precise surgical technique. 3.6% were mastectomy and lung resections, mediastinal or pleural tumors, and major thoracic surgeries. Pleural effusions, pneumothorax, lung abscess, pleural biopsies, and decortications were reported in the 1.8% of cases. Surgical procedures as used in different Country are reported in Figure 2.

**Anesthesiological and Intraoperative Management**

Not all studies reported information on how the airways were managed. Laryngeal mask (LMA) was used in 37.5% of cases, facemask in 31.3% of cases, Venturi mask in 22.9% of cases, high-flow nasal cannulas (HFNC) in 6.3%, and nasal cannulas in 2.0%. The type of device used in different Countries is reported in Figure 3.

Average conversion rate to intubation was 0.9% in China, 3.9% in Taiwan, 2.3% in Italy, 1% in Turkey, 5% in Germany and 3.7% in South Korea. The conversion rate to thoracotomy was estimated to be 0.1% in China, 0.3% in Taiwan, 2.3% in Italy, and 3.5% in South Korea. Not all studies reported these data.
Main Outcomes
Length of hospital stay and postoperative pulmonary complications rate, as collected in studies comparing the cohort of patients treated with NITS and intubated VATS, are shown in Table 2.

Same data as collected from single cohort studies are instead shown in Figure 4. In Figure 4 are also presented the data relating to pulmonary complications by type of procedure as taken from single cohort studies.

Perioperative Analgesia
Analgesia performed in the perioperative period was not reported in all studies. Of the studies analyzed, 42.4% used intercostal nerve block, 40.7% thoracic epidural analgesia, 6.8% paravertebral block, 5.1% infiltration with local anesthetic of the wound, 3.4% erector spinae plane block, and 1.6% placed a catheter at the paravertebral site for continuous analgesia. Evaluating NITS vs. non-NITS cohort studies the postoperative pain was significantly lower in the NITS group in five studies (3, 6, 14, 15, 22), whereas the findings were not statistically significant in six studies (19, 21, 25, 28, 31, 32).

Meta-analyzing the available data from observational studies (Figure 5) with a continuous random-effects model showed that the mean postoperative pain rate (VAS) is 1.842 (95% C.I. 1.451–2.233) with a heterogeneity of 96.6%, p < 0.001.

DISCUSSION
In this scoping review, we analyzed 53 primary studies regarding NITS published between 2011 and 2021. The studies are all fairly recent confirming that NITS procedures have gained acceptance quite recently.

One of the objectives of this analysis was to evaluate the clinical context in which NITS is performed. Since the consensus of experts we referred to did not investigate this particular aspect in detail (4), we decided to assess whether there is a type of surgical procedure or airway management on which there is consensus among different Countries. What seems to emerge is that NITS is a procedure performed predominantly in Asia, and in some European countries, first Italy. We did not find any studies conducted in the United States. The trials conducted are mostly focused on selected populations, allowing direct comparison between intubated and non-intubated thoracic surgery. The shortage of clinical trials justifies the lack of consensus and guidelines on its management.

We evaluated the type of surgery performed during NITS by Country: while in China it was mainly used in lung parenchymal surgery, and in sympathectomies for hyperhidrosis, in Italy, it was mainly adopted for minor thoracic operations, such as lung biopsies or pleural effusions, confirming what Pompeo et al. reported in their European survey (56). In Taiwan instead, NITS procedures were used in a more heterogeneous manner, including both major parenchymal procedures, such as lobectomies, and minor procedures.

When assessing the anthropometric characteristics of the population, we found that there was a considerable heterogeneity, and this was probably due to a lack of specific guidelines indicating the population in which NITS procedures is most correctly applied. Even considering the NITS expert consensus, we noted that only ASA I and II stage patients, aged between
| Author                | Year | Country         | Type of study | Surgical procedure | N of patients | Age group A | Age group B | BMI Group A | BMI Group B | ASA I/II/III/IV (%) |
|-----------------------|------|-----------------|---------------|-------------------|---------------|-------------|-------------|-------------|-------------|---------------------|
| AlGhamdi et al. (10)  | 2018 | Korea           | Retrospective | Lobectomy         | 62            | 64.9 ± 10.5 | 66.1 ± 9.5  | 23.8 ± 3.2  | 23.5 ± 2.9   |                     |
| Ambrogi et al. (11)   | 2017 | Italy           | Retrospective | Metastasectomy    | 58            | 62 (46–71)  | 66 (51–73)  |             |             |                     |
| Caviezel et al. (12)  | 2019 | Switzerland     | Retrospective | Endoscopic thoracic sympathectomy | 20 | 28.6 (17–46) | 28.5 (20–55) | 23.6 (17–30.4) | 21.8 (19.1–26.3) |                     |
| Chen et al. (13)      | 2011 | Taiwan          | Retrospective | Lobectomy         | 30            | 57.9 ± 10.4 | 56.5 ± 9.5  | 24.0 ± 3.2  | 23.4 ± 3.3  | 3/3/70/26.7/0       |
| Chen et al. (14)      | 2016 | China           | RCT           | Endoscopic thoracic sympathectomy | 168 | 23.3 ± 6.8 | 21.8 ± 6.1 |             |             |                     |
| Chen et al. (15)      | 2016 | China           | RCT           | Endoscopic thoracic sympathectomy | 221 | 22.9 ± 6.6 | 21.5 ± 5.4 |             |             |                     |
| Cui et al. (3)        | 2016 | China           | Retrospective | Bullectomy        | 90            | 24.6 ± 5.6 | 25.2 ± 11.6 | <25         | <25         | Only ASA I and II   |
| Cui et al. (3)        | 2016 | China           | Retrospective | Endoscopic thoracic sympathectomy | 89 | 22.1 ± 7.2 | 26.5 ± 9.5 | <25         | <25         | Only ASA I and II   |
| Cui et al. (3)        | 2016 | China           | Retrospective | Mediastinal tumor resection | 91 | 38.3 ± 11.0 | 32.7 ± 9.0 | <25         | <25         | Only ASA I and II   |
| Furák et al. (16)     | 2020 | Hungary         | Retrospective | Lobectomy         | 38            | 64 (63) | 63.03 (83) | 24.83 ± 3.07 | 24.31 ± 4.17 |                     |
| Guererra et al. (6)   | 2020 | Italy           | Prospective   | Lung biopsies     | 94            | 60.4 ± 2.0 | 62.1 ± 12.5 | 26.8 ± 4.8  | 26.4 ± 4.6  | 1.5/12.1/80.3/9.1   |
| Guo et al. (17)       | 2016 | China           | Retrospective | Segmentectomy     | 140           | 49.10 ± 12.78 | 56.63 ± 12.7 | 21.59 ± 2.26 | 22.49 ± 3.10 | 25/68.8/6.2/0           |
| Guo et al. (18)       | 2016 | China           | Retrospective | Bilateral bullectomy | 37 | 21.9 ± 5.2 | 26.2 ± 11.4 | 18.6 ± 2.7 | 18.9 ± 2.3 | Only ASA I and II   |
| Hsiao et al. (19)     | 2017 | Taiwan          | Retrospective | Decortication     | 33            | 76.4 ± 6.0 | 76 ± 11.5 |             |             |                     |
| Huang et al. (20)     | 2020 | China           | Retrospective | Mediastinal tumor resection | 32 | 63.90 ± 11.76 | 67.43 ± 14.40 | 22.01 ± 3.67 | 23.43 ± 2.25 | 0/93/7/0             |
| Hwang et al. (21)     | 2018 | Korea           | Retrospective | Lobectomy         | 41            |             |             |             |             |                     |
| Irons et al. (22)     | 2017 | United Kingdom  | Retrospective | Elective minor VATS procedure | 73 | 54.9 ± 19.3 | 50.8 ± 19.2 | 26.2 ± 6.5 | 25.8 ± 5.8 |                     |
| Jung et al. (23)      | 2018 | Korea           | Retrospective | Lobectomy         | 183           | 20.4 ± 7.0 | 22.9 ± 9.2 | 19.7 ± 2.5 | 19.8 ± 2.3 |                     |
| Ke et al. (24)        | 2020 | Taiwan          | Retrospective | Lung resections    | 160           | 56.5 ± 16.8 | 52.3 ± 16.8 | 23.5 ± 3.3 | 23.9 ± 3.2 | 6/63/21/0           |
| Kocatürk et al. (25)  | 2019 | Turkey          | Prospective   | Pleural biopsies   | 293           | 55.1 ± 17.2 | 52.2 ± 15.7 |             |             | 21.4/44.1/29/5.5    |
| Lan et al. (26)       | 2018 | China           | Retrospective | Lobectomy         | 119           | 55.34 ± 13.83 | 56.98 ± 11.05 | 22.40 ± 2.85 | 22.51 ± 2.57 | 82.4/16.8/0.8/0      |
| Liang et al. (27)     | 2019 | China           | Retrospective | Mediastinal tumor resection | 198 | 45.61 ± 14.08 | 48.48 ± 14.64 | 22.93 ± 2.58 | 23.2 ± 3.62 | 8/91/1/0           |
| Liu et al. (28)       | 2021 | Taiwan          | Retrospective | Segmentectomy     | 86            | 60.5 ± 12.1 | 58.2 ± 13.0 | 22.1 ± 2.0 | 22.4 ± 2.7 | 16.3/58.1/23.3/2.3   |
| Liu et al. (29)       | 2014 | China           | RCT           | Bullectomy        | 354           | 32.7 | 28.7 |             |             |                     |
| Liu et al. (29)       | 2014 | China           | RCT           | Lobectomy         | 356           | 56.2 | 56.2 |             |             |                     |
| Liu et al. (29)       | 2014 | China           | RCT           | Wedge resections   | 355           | 55.7 | 50.6 |             |             |                     |
| Liu et al. (30)       | 2016 | China           | Retrospective | Lobectomy         | 339           | 56.0 ± 10.3 | 57.3 ± 10.5 | 22.4 ± 2.5 | 22.5 ± 3.43 |                     |
| Liu et al. (30)       | 2021 | China           | Retrospective | Segmentectomy     | 339           | 51.2 ± 13.0 | 56.0 ± 12.8 | 22.2 ± 2.2 | 22.4 ± 3.1 |                     |

(Continued)
| Author       | Year | Country | Type of study | Surgical procedure | N of patients | Age group A (median ± IQR) | Age Group B (median ± IQR) | BMI Group A (median ± IQR) | BMI group B (%) | ASA I/II/III/IV (%) |
|--------------|------|---------|---------------|--------------------|---------------|---------------------------|---------------------------|---------------------------|----------------|-----------------|
| Liu et al.   | 2019 | China   | Retrospective | Mediastinal tumor resection | 225           | 59.4 (33–67)              | 57.3 (37–76)              | 22.7 (17.1–33.5)          | 23.2           | Only ASA I and II |
| Mao et al.   | 2021 | China   | Retrospective | Mediastinal tumor resection | 40            | 43.90 ± 15.18             | 54.26 ± 11.64             | 23.01 ± 3.64              | 23.49 ± 2.52    | 47.62/52.38     |
| Metelmann et al. | 2021 | Germany | Retrospective | Elective minor VATS procedure | 104           | 55.43 ± 18.71             | 57.83 ± 18.12             | 25.13 ± 4.566             | 26.37 ± 4.38    | 13.04/47.82/34.78/4.35 |
| Mineo et al. | 2014 | Italy   | Retrospective | Pleural effusions | 231           | 66.0 ± 10.5               | 64.7 ± 12.7               | 23.2 ± 4.36              | 23 ± 3          | No ASA IV       |
| Pompeo et al. | 2012 | Italy   | RCT           | Lung resections | 63            | 64 ± 9                    | 65 ± 7                    | 24 ± 4                   | 23 ± 3          | No ASA IV       |
| Pompeo et al. | 2007 | Italy   | Retrospective | Pneumothorax | 49            | 28 ± 14                   | 26 ± 11                   | 24.3 ± 4.566             | 26.37 ± 4.38    | 13.04/47.82/34.78/4.35 |
| Wang et al.  | 2021 | Taiwan  | Retrospective | Lobectomy | 194           | 59.6 ± 11.3               | 61.9 ± 11.5               | 103.9 ± 7.1              | 114.1 ± 6.4     | No ASA IV       |
| Akopov et al. | 2015 | Russia  | Prospective   | Lung abscess | 65            | 58.4 (24 to 78)           | 26.2 (17–38)              | 24.3 ± 4.566             | 26.37 ± 4.38    | 13.04/47.82/34.78/4.35 |
| Ambrogi et al. | 2014 | Italy   | Cohort study  | Wedge resection | 20            | 57 (36–76)                | 24.3 (17–48)              | 25.13 ± 4.566             | 26.37 ± 4.38    | 13.04/47.82/34.78/4.35 |
| Chen et al.  | 2016 | China   | Cohort study  | Endoscopic thoracic sympathectomy | 58          | 23 (16–45)                | 11.8/61.7/26.5             | 24.3 ± 4.566             | 26.37 ± 4.38    | 13.04/47.82/34.78/4.35 |
| Starke et al. | 2020 | Germany | Retrospective | Mediastinal or pleural tumors | 109           | 60.1 ± 14.0               | 22.8 ± 3.6                | 22.8 ± 3.6               | 22.6 ± 2.7      | Only ASA I and II |
| LI et al. (47) | 2020 | China   | Prospective trial | Lung resections or sympathectomy | 57            | 42.3 ± 19.5               | 22.9 ± 2.6                | 22.8 ± 3.6               | 22.6 ± 2.7      | Only ASA I and II |
| Liu et al.   | 2018 | Taiwan  | Retrospective | Lung nodules | 32            | 52.8 ± 11.3               | 22.0 ± 2.4                | 22.8 ± 3.6               | 22.6 ± 2.7      | Only ASA I and II |
| Liu et al.   | 2020 | Taiwan  | Retrospective | Mediastinal or pleural tumors | 109           | 56.4 ± 14.0               | 22.8 ± 3.6                | 22.8 ± 3.6               | 22.6 ± 2.7      | Only ASA I and II |
| Liu et al.   | 2020 | Taiwan  | Retrospective | Lobectomy | 21            | 61.0 ± 15.2               | 22.8 ± 3.6                | 22.8 ± 3.6               | 22.6 ± 2.7      | Only ASA I and II |
| Moon et al.  | 2018 | Korea   | Retrospective | Lung resections, mediastinal or pleural tumors | 115           | 61.8 (± 13.3)             | 23.8 (± 3.0)              | 24.05 ± 4.42             | 24.05 ± 4.42    | 0/5/75/0       |
| Pompeo et al. | 2019 | Italy   | Retrospective | Lung biopsies | 112           | 60 ± 12                   | 26 ± 3                    | 26.37 ± 4.38             | 26.37 ± 4.38    | 13.04/47.82/34.78/4.35 |
| Pompeo et al. | 2011 | Italy   | Retrospective | Bullectomy | 35            | 60 (55–65)                | 23.9 (22–27)              | 26.37 ± 4.38             | 26.37 ± 4.38    | 13.04/47.82/34.78/4.35 |
| Starke et al. | 2020 | Germany | Retrospective | Minor thoracic surgery | 88            | 60.1 ± 14.0               | 25.94 ± 4.95              | 25.94 ± 4.95             | 26.37 ± 4.38    | 13.04/47.82/34.78/4.35 |
| Starke et al. | 2020 | Germany | Retrospective | Major thoracic surgery | 89            | 67.94 ± 12.28             | 24.05 ± 4.42              | 24.05 ± 4.42             | 24.05 ± 4.42    | 0/5/75/0       |

(Continued)
16 and 60 years, were included. This, in our opinion, hardly represents the average patient who ordinarily undergoes thoracic surgery. Moreover, we believe that such procedures would be rather helpful in frail patients with ASA III and IV status to avoid the stress related to intubation and positive pressure mechanical ventilation in patients with compromised respiratory function (3). There are cases in literature where this technique is used in patients with severe comorbidities, including obesity (57, 58) whereas other groups considered them as contraindications (59).

Regarding airway management, we noted that there was a difference among the Countries considered. The facemask was the most widespread device across the board. In China the LMA was used in most cases, as well as in Germany and in Hungary. This can easily be related to the fact that these Countries mainly performed major thoracic surgery. Although the LMA support during NITS has been described in the literature, it certainly does not allow lighter sedation. To date, there is no recommendation on which device to preferentially use for airway management (60, 61) even if He et al. suggest the use of LMA, nasal cannulas, or face mask as alternatives (4). From our review, the type of device for airway management is highly dependent on the background of the study and the practices of individual centers.

In this regard, a fundamental issue on NITS definition arises, as three studies conducted in China used LMA with extemporaneous curarization, and 22 studies reported during...
surgery, BIS values below 60, as under general anesthesia. There is still a lack of definition on the depth of sedation in the context of NITS, and this has resulted in the development of other terminologies we refer to, for example, awake thoracic surgery. However, it is confusing and does not allow focusing on the NITS technique in a univocal way: the expert consensus should aim to provide more information on the depth of sedation in NITS contexts.

The rate of conversion to intubation was highly variable from Nation to Nation, as it was the rate of thoracotomy. Considering the percentages reported in these articles, the average conversion rate to orotracheal intubation was about 3%. The lower rate of intubation found in China could be related to its prevalent use of the LMA. It is worth noting the unexpectedly high conversion rate observed in Germany despite the diffuse use of LMA.

Referring to outcome, we found that in 83% of cases there were no significant differences between the two cohorts, whereas in 27% NITS was proven to reduce pulmonary complications. Also, regarding the effectiveness in limiting the LOS, in 63% of cases NITS was considered more effective while 37% found no statistically significant difference between the two groups (Table 2).

When evaluating single cohort studies, pulmonary complications predominantly developed after parenchymal surgery, whereas for the LOS we did not see a clear correlation with the type of surgical procedure (Figure 4). According to Lan et al. (26) patients who underwent NITS had a higher incidence of atelectasis, pleural effusion, or pulmonary exudation in the face of a better LOS and general postoperative comorbidities compared with intubated patients. From the perspective of NITS and pulmonary complications, this issue remains controversial. In four recent meta-analyses, it is confirmed that NITS would appear to reduce the LOS, providing further validation for our analysis (62–65).

From a pain perspective, our findings were inconclusive: there was no evidence to prove the superiority of NITS in terms of postoperative pain over intubated thoracic surgery. About half of the cases had nonsignificant postoperative pain between the two groups; no regional anesthesia was performed but only sedation. Therefore, this fact might have impacted the final result. In contrast, regional anesthesia had been performed in all studies in which there was a statistically significant difference between the two groups. When evaluating postoperative pain among observational studies, although there was high heterogeneity ($I^2 = 96.6\%$) a very low score of pain at postoperative day 1 was found (Figure 5). The NITS technique, accompanied by regional anesthesia, might be a good way to reduce postoperative pain in surgery at high risk of developing persistent postoperative pain and prone to high acute postoperative pain (66, 67). Reducing opioid consumption in commonly frail patients, such as those undergoing NITS, could affect postoperative hospitalization and complication outcomes (6).
| Author                | Country       | Type of study | Surgical procedure                  | N of patients | Postoperative pulmonary complications group A vs. group B | LOS group A vs. group B |
|----------------------|---------------|---------------|-------------------------------------|---------------|----------------------------------------------------------|------------------------|
| AlGhamdi et al. (10) | Korea         | Retrospective | Lobectomy                           | 62            | Not significant                                          | Not significant        |
| Ambrogi et al. (11)  | Italy         | Retrospective | Metastasectomy                      | 58            | Not significant                                          | Significant, favors NITS|
| Caviezel et al. (12) | Switzerland   | Retrospective | Endoscopic thoracic sympathectomy   | 20            | Not significant                                          | Not significant        |
| Chen et al. (13)     | Taiwan        | Retrospective | Lobectomy                           | 30            | Not significant                                          | Significant, favors NITS|
| Chen et al. (14)     | China         | RCT           | Endoscopic thoracic sympathectomy   | 168           | Not significant                                          | Not significant        |
| Chen et al. (15)     | China         | RCT           | Endoscopic thoracic sympathectomy   | 221           | Not significant                                          | Not significant        |
| Cui et al. (3)       | China         | Retrospective | Bullectomy                          | 90            | Not significant                                          | Significant, favors NITS|
| Cui et al. (3)       |               |               | Endoscopic thoracic sympathectomy   | 89            | Not significant                                          | Significant, favors NITS|
| Cui et al. (3)       |               |               | Mediastinal tumor resection         | 91            | Not significant                                          | Significant, favors NITS|
| Furák et al. (16)    | Hungary       | Retrospective | Lobectomy                           | 38            | Significant, favors NITS                                | Not significant        |
| Guerrero et al. (6)  | Italy         | Prospective   | Lung biopsies                        | 94            | Significant, favors NITS                                | Significant, favors NITS|
| Guo et al. (17)      | China         | Retrospective | Segmentectomy                       | 140           | Not significant                                          | Significant, favors NITS|
| Guo et al. (18)      | China         | Retrospective | Bilateral bullectomy                | 37            | Not significant                                          | Not significant        |
| Hsiao et al. (19)    | Taiwan        | Retrospective | Decortication                       | 33            | Significant, favors NITS                                | Significant, favors NITS|
| Huang et al. (20)    | China         | Retrospective | Mediastinal tumor resection         | 32            | Not significant                                          | Not significant        |
| Hwang et al. (21)    | Korea         | Retrospective | Bullectomy                          | 41            | Not significant                                          | Significant, favors NITS|
| Irons et al. (22)    | United Kingdom| Retrospective | Elective minor VATS procedure        | 73            | Not significant                                          | Not significant        |
| Jung et al. (23)     | Korea         | Retrospective | Bullectomy                          | 183           | Not significant                                          | Significant, favors NITS|
| Ke et al. (24)       | Taiwan        | Retrospective | Lung resections                      | 160           | Not significant                                          | Significant, favors NITS|
| Kocatürk et al. (25) | Turkey        | Prospective   | Pleural biopsies                     | 293           | Not significant                                          | Significant, favors NITS|
| Lan et al. (26)      | China         | Retrospective | Lobectomy                           | 119           | Not significant                                          | Significant, favors NITS|
| Liang et al. (27)    | China         | Retrospective | Mediastinal tumor resection         | 198           | Not significant                                          | Significant, favors NITS|
| Liu et al. (28)      | Taiwan        | Retrospective | Segmentectomy                       | 86            | Not significant                                          | Not significant        |
| Liu et al. (29)      | China         | RCT           | Bullectomy                          | 354           | Significant, favors NITS                                | Significant, favors NITS|
| Liu et al. (29)      | China         | RCT           | Lobectomy                           | 356           | Significant, favors NITS                                | Significant, favors NITS|
| Liu et al. (29)      | China         | RCT           | Wedge resections                    | 355           | Not significant                                          | Not significant        |
| Liu et al. (30)      | China         | Retrospective | Lobectomy                           | 340           | Not significant                                          | Not significant        |
| Liu et al. (30)      | China         | Retrospective | Segmentectomy                       | 339           | Not significant                                          | Significant, favors NITS|
| Liu et al. (31)      | China         | Retrospective | Mediastinal tumor resection         | 225           | Not significant                                          | Not significant        |
| Mao et al. (32)      | China         | Retrospective | Mediastinal tumor resection         | 40            | Not significant                                          | Not significant        |
| Metelmann et al. (33) | Germany      | Retrospective | Elective minor VATS procedure        | 104           | Not significant                                          | Not significant        |
| Mineo et al. (34)    | Italy         | Retrospective | Pleural effusions                   | 231           | Not significant                                          | Not significant        |
| Pompeo et al. (6)    | Italy         | RCT           | Lung resections                      | 63            | Not significant                                          | Significant, favors NITS|
| Pompeo et al. (7)    | Italy         | Retrospective | Pneumothorax                        | 49            | Not significant                                          | Significant, favors NITS|
| Wang et al. (35)     | Taiwan        | Retrospective | Lobectomy                           | 194           | Not significant                                          | Not significant        |

This study has limitations. The major is that it is based on mostly retrospective studies. Results therefore should always consider the low quality due to bias from retrospective studies.

**CONCLUSION**

NITS procedures are becoming increasingly popular, but they need more definition, especially the setting in which they are
performed. It would be necessary, for example, to reach an agreement on the patient sedation, and airway management devices to perform NITS techniques in the same way across the countries. The choice of surgical procedure, as well as that of the patient, have not been well-defined in the literature yet. It is our opinion that frail patients have fewer complications during NITS than during intubated thoracic surgery (6). From a postoperative patient management perspective, the impact of NITS techniques on LOS remains unknown as the existing evidence available in the literature is conflicting. A regional anesthesia approach might be recommended in NITS procedures to reduce acute postoperative pain. Future studies should be directed to evaluate the benefits of NITS in patients with impaired lung function or other comorbidities (e.g., obesity, ASA III, ASA IV). Moreover, other randomized controlled trials are needed to establish more robust evidence.

DATA AVAILABILITY STATEMENT
The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS
GR: conceptualization, formal analysis, investigation, methodology, project administration, supervision, validation, visualization, writing—original draft, and writing—review & editing. PL: data curation, software, visualization,
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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.