

SYSTEMATIC REVIEW

Serious complications associated with nasogastric, orogastric or enteral tube misplacement over the decades: a systematic review

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Abstract

Background: Gastrointestinal tube (GIT) insertion is common in surgical, medical and intensive care unit settings, with approximately 170,000 annual insertions in the UK alone. Despite its apparent simplicity, GIT placement can lead to acute complications, ranging from mucosal lesions to life-threatening conditions. **Methods:** We conducted a systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, searching on PubMed, Cochrane, EMBASE and Scopus, all case reports and series describing harm from nasogastric, orogastric, or enteral tube placement. **Results:** A total of 148 studies reported acute GIT complications in 168 patients (70 patients received an enteral feeding tube). The number of publications increased over time. Half (91 patients, 52%) of the displacements involved the respiratory tract, but other organs were also affected, including the brain (33 patients, 20%), gastrointestinal tract (23 patients, 14%) and intravascular system (6 patients, 4%). Brain misplacement had the highest mortality (60.6%), while for respiratory tract misplacement mortality was 20.9%. Mortality was high in emergency department procedures and acute trauma, while it was low when enteral feeding tubes were involved. Only 30% of the manuscripts reported adherence to guidelines, which was associated with a trend towards decreased mortality. **Conclusions:** Our findings identify an increasing reporting of GIT misplacement complications and emphasize a variety of involved anatomical sites, from the well-known brain, respiratory tract, and pleural space mispositioning, to gastrointestinal and abdomen perforation, to the extremely uncommon spleen and intravascular mispositioning. The importance of implementing standardized protocols and maintaining heightened clinical vigilance is crucial to mitigate complications related to GIT misplacement. **The PROSPERO Registration:** PROSPERO CRD42024491074.

Keywords

Anaesthesia; Enteral feeding tube; Nasogastric tube; NGT misplacement; Gastrointestinal tube

1. Introduction

Gastrointestinal tube (GIT) is commonly used for both surgical and non-surgical patients, with approximately 170,000 GIT s placed annually in the UK [1, 2]. The most common indications for GIT placement include gastrointestinal decompression, enteral nutrition for patients unable to swallow, medication delivery when oral intake is not feasible, facilitate gastric lavage in poisoning or overdose cases, and aspiration prevention in high-risk patients. While GIT placement is generally considered a bedside procedure with low risk, misplacement can occur. Misplacement occurs when a GIT is inserted incorrectly into an unintended tract, commonly within the respiratory or gastrointestinal system. This can cause a series

of complications, ranging from mucosal lesions to potentially life-threatening conditions such as pneumothorax or cardiac arrhythmias [3, 4].

The incidence of GITs misplacement varies depending on the study and the type of device placed, ranging from 7% for nasogastric tubes (NGT) to 40% for enteral tubes [5]. Gastrointestinal tube misplacement can occur due to several factors, including errors in the placement technique. Adequate training and education are crucial to mitigate this risk [2, 6]. Symptoms of misplacement, such as difficulty in breathing, chest pain, coughing or abdominal pain, may not always be evident. It is important to note that GITs are often placed in patients with a diminished level of consciousness or under anaesthesia, making these symptoms less noticeable. Ap-

proved confirmation methods should be employed, as clinical symptoms alone may not be sufficient. Guidelines recommend x-ray as an accurate method to determine the placement of a GIT in either the stomach or respiratory tract [7]. Aspirate pH can distinguish between gastric and respiratory samples and is a good alternative to x-ray, although it is limited by relatively low sensitivity and specificity. Thus, based on available evidence [8], x-ray and aspirate pH are effective methods to confirm GIT placement. They help to identify the exact position of the device but can be used only at the end of the procedure. Even if this may help to prevent subsequent complications, they do not have the capacity to mitigate the risk of placement-related injury. Auscultation of stomach or gastric fluid aspiration as confirmation tests should be avoided. These methods are neither sensitive nor reproducible. Studies show that a tube tip in the pleural cavity can produce sounds similar to those in the stomach, leading to false confirmations [7, 9].

GIT misplacement is particularly dangerous and more common in specific patient populations, including those with altered anatomy of the head and neck, facial trauma, basilar skull fractures, oesophageal trauma, caustic ingestion and oesophageal obstruction. In these cases, careful consideration, and avoiding GIT placement can reduce the risk of intracranial misplacement and associated mortality [10].

The aim of this review was to systematically summarize documented instances of harm associated with nasogastric, orogastric or enteral tube reported in the scientific literature, identifying common features that warrant improvement.

2. Materials and methods

2.1 Search strategy

We performed a systematic review following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and adhering to the recommendations of the Cochrane Collaboration [11, 12]. This systematic review was registered in International Prospective Register of Systematic Reviews (PROSPERO) (Registration number: CRD42024491074).

In accordance with the PRISMA checklist (**Supplementary Table 1**), two trained investigators independently searched PubMed, Cochrane Central Register, EMBASE and Scopus to identify all reported cases of nasogastric, orogastric or enteral tube misplacement resulting in patient harm. The latest search was performed on 06 April 2024. The search strings included terms such as “nasogastric tube” and its synonyms, as well as “case report” or “case series” as study design, combined with appropriate Boolean operators. More detailed information about the search strategy and the research string used are included in the **Supplementary material (Supplementary material 1)**. Only publications in English were considered for potential inclusion.

2.2 Study selection

Two stages of screening were performed. Two investigators independently screened each identified document title and abstract for potential relevance. Full text analysis of pertinent documents was performed for inclusion. Then, the references

of selected articles were scrutinized to identify additional studies to be included in this systematic review. Disagreements were resolved through discussion involving a senior co-author.

2.2.1 Inclusion criteria

Case reports and case series reporting nasogastric, orogastric or enteral tube (including both drainage and feeding tubes) misplacement or immediate use resulting in patient harm were included. Human patients of any age (paediatric, adult or elderly patients) and in any setting were included. We defined misplacement when the tip was in an incorrect anatomical position: this included tubes that ended up in the wrong site as well as those that followed an improper route. We only considered complications that occurred during the tube insertion procedure when misplacement happened. Any damage caused using the feeding tube or after its placement, such as chemical pneumonia or decubitus, was excluded. The inclusion criteria adhered to the Patient/Population/Problem, Intervention, Comparison/Control, Outcome (PICO) approach. Details of the inclusion criteria are provided in Table 1.

2.2.2 Exclusion criteria

Abstracts were excluded. Publications lacking original experiences (*e.g.*, reviews and editorials) were excluded to prevent duplication. All papers written in languages other than English were excluded. We only analyzed adverse events that occurred during the placement procedure. Therefore, we did not consider whether the tubes were subsequently used for feeding or drainage and we did not collect complications such as chemical pneumonia or decubitus. We included all instances and complications regardless of GIT intended use. No restrictions were imposed based on the publication date and we did not exclude patients based on age. No further restrictions were imposed. Exclusion criteria are detailed in Table 1.

2.3 Data extraction and study characteristics

Data on patient characteristics (*e.g.*, sex, age, consciousness status and risk factors for GIT misplacement), study design, tube type (gastric or enteral), setting details (*e.g.*, medical or surgical ward, operating theatre, intensive care unit, emergency department), guidelines approved test performance, injured structures (*e.g.*, pleura, brain, blood vessels or others), need for additional invasive procedures, and relevant clinical outcomes (*e.g.*, survival, *etc.*) were collected for each of the retrieved articles when available. Data were extracted using Microsoft Excel (version 16.92, Microsoft Corp, Seattle, WA, USA). Standardized forms were used to carry out data extraction. All data were extracted by one reviewer and controlled by a second one.

2.4 Data analysis and statistics

Firstly, we compared the two most commonly reported type of misposition, specifically classifying misplacement based on the resulting harm to organs. The proportions of GIT misplacement in each group were reported, allowing for a comparison between the two most prevalent groups: patients

TABLE 1. Inclusion and exclusion criteria.

| Inclusion criteria (all must be present) | Exclusion criteria (one is sufficient) |
|--|---|
| GIT malpositioned | Papers lacking original experience (e.g., reviews) |
| Structure damaged during the GIT placement procedure | No abstract or full text availability |
| Case report or case series | Language other than English |
| Human population | Damages caused after the placement procedure (e.g., chemical pneumonia, decubitus). |

GIT: denotes gastrointestinal tube.

experiencing brain misplacement and those with respiratory tract misplacement. Secondly, we classified all GIT misplacement cases based on mortality. A repeated analysis was performed to identify differences between survivors and non-survivors. Categorical variables were expressed as number and percentage, continuous variables were expressed as median and interquartile range. Categorical variables were compared using chi square or Fisher test when applicable. Continuous variables were compared using Student *T* test. If the data significantly deviated from normality, the non-parametric Mann-Whitney U test was used. Missing data were not imputed throughout this study. A *p*-value of < 0.05 was considered statistically significant. All analyses were run using STATA version 14 (IBM Corp, Armonk, NY, USA).

3. Results

A total of 148 studies were included in the systematic review. The majority were case report (n = 141) each one reporting a single event, while 7 were case series reporting 27 overall cases. The total number of patients included in the final analysis was 168 and references to the 148 studies can be found in **Supplementary Table 2**. Major excluded studies are listed in **Supplementary Table 3**. The study selection flow chart is depicted in Fig. 1.

Reports of damage from GIT misplacement first appeared in 1975, with an increase in publications in the 21st century (Fig. 2).

In 91 cases (54.2%), the site of misplacement was the tracheobronchial tract, particularly the pleural area, reached transfixing the trachea (82 patients, 48.8%). Additionally, 33 cases (19.6%) involved misplacement in the brain and in 23 patients (13.7%) GITs were displaced into other segments of the gastrointestinal tract, resulting in gastrointestinal perforation. Furthermore, in 6 cases (3.6%) the GIT was intravascularly placed (e.g., internal jugular vein, hepatic vein or aorta), in 2 cases (1.2%) GIT traversed multiple structures, perforating the gastrointestinal tract and culminating in the pleural space or spleen, and in 10 cases (6.0%) we found alternative localizations (Table 2). Of note, aspiration pneumonia was poorly represented.

It is important to note that the highest number of incidents (68, 40.5%) during tube placement occurred in the emergency department.

When comparing the two most common type of mispositioning (respiratory tract misplacement versus brain misplacement), we noted that patients were more frequently male (23

patients, 69.7% vs. 36 patients, 39.6%, *p* = 0.009), younger (median age 45 yr, interquartile range (IQR) 28.5–55 yr vs. 71 yr, IQR 59–79 yr, *p* < 0.001), more often involved in traumatic events (24 patients, 72.7% vs. 35 patients, 38.5%, *p* < 0.001), and more likely unconscious (23 patients, 69.7% vs. 28 patients, 30.8%, *p* = 0.002) when respiratory tract mispositioning was involved (Table 3).

Enteral feeding tube represented 41.7% of cases (70/168 patients) and, within the enteral feeding subgroup, the prevalence of brain misplacement (12.1%) was lower compared to respiratory tract misplacement (58.2%), *p* < 0.001.

Respiratory tract misplacements (41/91, 45.1%) were more commonly identified using a guideline approved test when compared to brain misplacements (2/33 patients, 6.1%) (Table 3).

A total of 48 patients (28.7%) died. Mortality rate was higher in patients who experienced brain misplacement compared to those with respiratory tract misplacement (20/33 patients, 60.6% vs. 19/91 patients, 20.9% *p* < 0.001) (Table 4).

Key factors associated with mortality included emergency department settings (29/48 patients, 60.4% vs. 39/109 patients, 35.8%, *p* = 0.02); previous trauma (30/48 patients, 62.5% vs. 43/109 patients, 39.4%, *p* = 0.001); positioning of a nasogastric tube (30/48 patients, 62.5% vs. 54/109 patients, 49.5%, *p* = 0.04) and pre-existing risk factors (30/48 patients, 62.5% vs. 51/109 patients, 46.8%, *p* = 0.02) (Table 5).

4. Discussion

The insertion of a GIT is a routine bedside procedure, often considered straightforward. However, it can occasionally result in severe complications, including patient death. In the scientific literature, 168 instances of damage caused by GIT misplacement are reported, with a mortality rate of 28.7%, likely because only severe cases are documented, suggesting that GIT misplacement is actually much more common than currently documented.

The varied instances of misplacement, particularly within the tracheobronchial tract and the brain, emphasize the complexity and severity of occurrences. Comparisons based on displacement sites reveal distinct demographic and clinical patterns. Patients involved in traumatic events are more susceptible to undergo brain misplacement, which has a significantly higher mortality rate. This observation aligns with existing data and recommended guidelines that establish a strong correlation between intracranial misplacement and severe craniofacial or skull trauma [13]. Alarming, patients

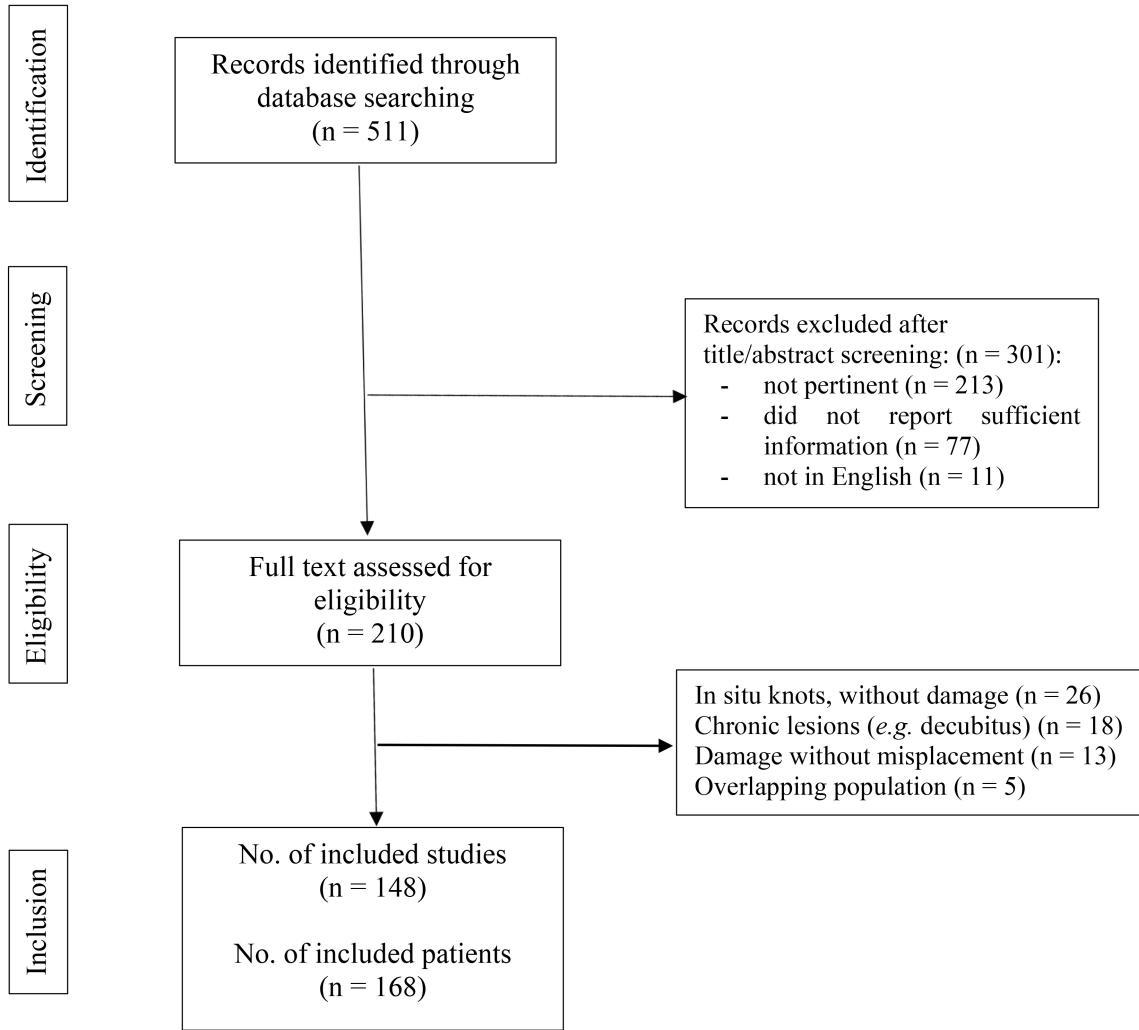


FIGURE 1. Study selection flowchart. Flowchart of the study selection process.

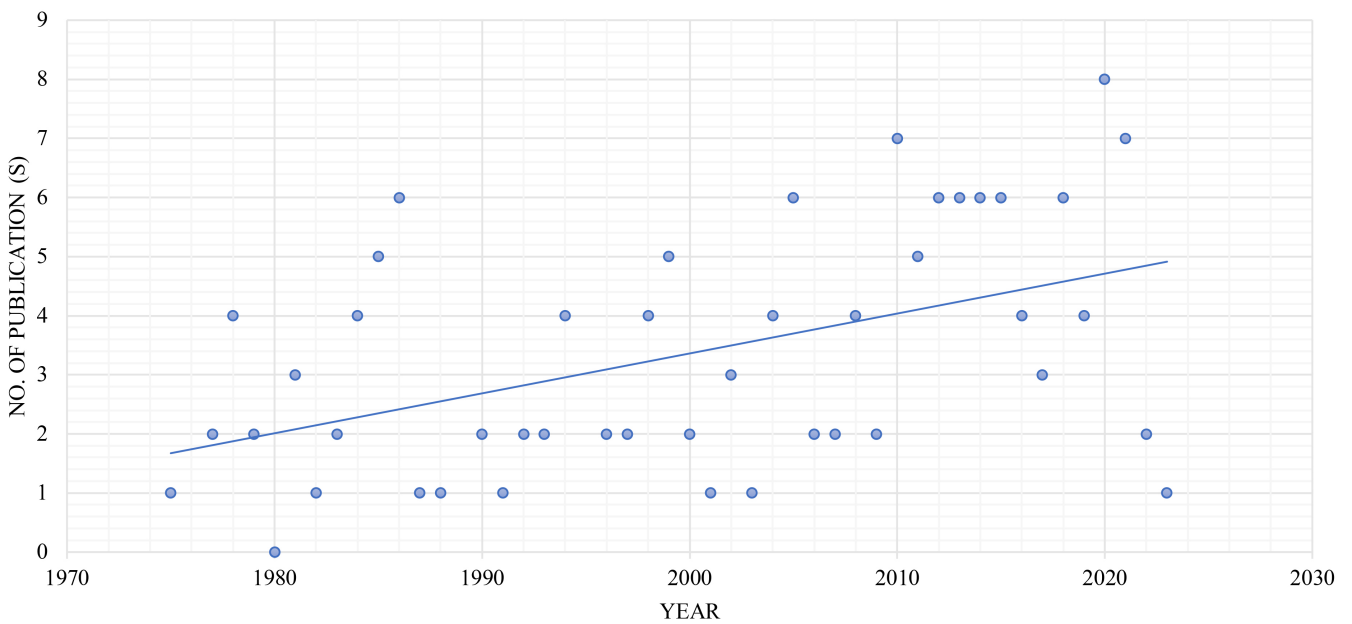


FIGURE 2. Publications trend. Trend in number of publications during the decades.

TABLE 2. Structures injured during nasogastric tube placement.

| Structure injured | Explanation | Number (%) |
|-------------------|--|------------|
| Respiratory tract | Lungs (intra-bronchial or pleura) | 83 (49.4%) |
| Other respiratory | Trachea or larynx | 8 (4.8%) |
| Brain | Intracranial | 33 (19.6%) |
| Gastrointestinal | Pharynx, esophagus, stomach, intestinal | 23 (13.7%) |
| Vessel | Intravascular | 6 (3.6%) |
| Multiple site | Perforation of gastrointestinal ending in other organs | 2 (1.2%) |
| Other | | 10 (6.0%) |
| Missing | | 3 (1.8%) |

Note: Aspiration pneumonias are included in lung complications. Inconsistencies, if any, between the values set out in the table are due to rounding to the first decimal point.

TABLE 3. Characteristics of patients who had nasogastric tube misplacement in the respiratory tract, in the brain and in the overall study population (which also includes intravascular, gastrointestinal misplacement, multiple damages and others).

| | Respiratory (n = 91) | Brain (n = 33) | p-value | Overall (n = 168) |
|---|-------------------------|-------------------|---------|----------------------|
| Male, n (%) | 36 (39.6) | 23 (69.7) | 0.009 | 75/156 (48.1) |
| Age, median (IQR) | 71 (59.0–79.0) | 45 (28.5–55.0) | <0.001 | |
| Setting, n (%) | | | | |
| Medical ward | 18 (19.8) | 3 (9.1) | | 25 (14.9) |
| Operating theatre | 7 (7.7) | 2 (6.1) | | 14 (8.3) |
| Emergency department | 33 (36.3) | 21 (63.6) | 0.03 | 68 (40.5) |
| ICU | 16 (17.6) | 4 (12.1) | | 34 (20.2) |
| Missing | | | | 27 (16.0) |
| Acute Trauma, n (%) | 35 (38.5) | 24 (72.7) | <0.001 | 73/166 (44.0) |
| Unconscious pts, n (%) | 28 (30.8) | 23 (69.7) | 0.002 | 69/133 (51.9) |
| Cranial malformation, n (%) | 5 (5.5) | 5 (15.1) | 0.08 | 14 (8.3) |
| Enteral feeding tube, n (%) | 53 (58.2) | 4 (12.1) | <0.001 | 70 (41.7) |
| Insertion, n (%) | | | | |
| Trough nose | 79 (86.7) | 30 (90.9) | 0.77 | 144 (85.2) |
| Trough mouth | 10 (11.0) | 3 (9.1) | | 20 (11.9) |
| Use of laryngoscope during placement, n (%) | 3 (3.3) | 1 (3.0) | 0.81 | 6 (3.6) |
| Guidelines approved test*, n (%) | 41 (45.0) | 2 (6.1) | <0.001 | 51 (30.3) |
| Misplacement diagnosis, n (%) | | | | |
| Signs and symptoms | 38 (41.7) | 12 (36.4) | 0.16 | 80 (47.6) |
| Radiological examination | 46 (50.1) | 20 (60.6) | | 77 (45.8) |

Abbreviations: ICU: intensive care unit; IQR: Interquartile range. *X-ray or aspiration plus pH tested. Note: Inconsistencies, if any, between the values set out in the table are due to rounding to the first decimal point.

TABLE 4. Patients outcomes after nasogastric tube misplacement in the Respiratory tract, in the brain and in the overall study population (which also includes intravascular, gastrointestinal misplacement, multiple damages and others).

| | Respiratory (n = 91) | Brain (n = 33) | <i>p</i> -value | Overall (n = 167) |
|----------------------------------|-------------------------|-------------------|-----------------|----------------------|
| Invasive procedure needed, n (%) | 52 (57.1) | 9 (27.3) | 0.008 | 87 (52.1) |
| Serious damages, n (%) | 35 (38.5) | 11 (33.3) | 0.35 | 69 (41.3) |
| Death, n (%) | 19 (20.9) | 20 (60.6) | <0.001 | 48 (28.7) |
| Multiple reasons*, n (%) | 9 (9.9) | 14 (42.4) | <0.001 | 27 (16.2) |
| Key reason, n (%) | 5 (5.5) | 3 (9.1) | 0.48 | 11 (6.6) |

*Damages produced by GIT misplacement represented one of the mortality factors. Note: Inconsistencies, if any, between the values set out in the table are due to rounding to the first decimal point.

TABLE 5. Survivors characteristics.

| | Survivors (n = 109) | Did not survive (n = 48) | <i>p</i> -value |
|---|------------------------|-----------------------------|-----------------|
| Male, n (%) | 59 (54.1) | 22 (46.8) | 0.40 |
| Age, median (IQR) | 68 (50–78) | 58.5 (36–76) | 0.25 |
| Setting, n (%) | | | |
| Medical ward | 28 (28.3) | 6 (14.9) | |
| Surgical ward | 20 (20.2) | 5 (11.9) | 0.02 |
| ICU | 12 (12.1) | 2 (4.8) | |
| Emergency department | 39 (35.8) | 29 (60.4) | |
| Trauma, n (%) | 43 (39.4) | 30 (62.5) | <0.001 |
| Unconscious patient, n (%) | 47 (43.1) | 17 (35.4) | 0.30 |
| Cranial malformation, n (%) | 11 (10.1) | 3 (6.3) | 0.31 |
| Procedural characteristics | | | |
| Tube types, n (%) | | | |
| Enteral feeding tube | 55 (50.4) | 14 (29.2) | |
| Nasogastric tube | 54 (49.5) | 30 (62.5) | 0.04 |
| Missing | 0 (0.0) | 4 (8.3) | |
| Insertion, n (%) | | | |
| Trough nose | 102 (93.6) | 43 (89.6) | |
| Through mount | 5 (4.6) | 4 (8.3) | 0.92 |
| Missing | 2 (1.8) | 1 (2.1) | |
| Preexisting risk factor, n (%) | 51 (46.8) | 30 (62.5) | 0.02 |
| Use of laryngoscope during placement, n (%) | 3 (2.8) | 1 (2.1) | 0.64 |
| Placement test used, n (%) | | | |
| Approved guidelines | 39 (35.8) | 12 (25.0) | |
| Others | 38 (34.9) | 17 (35.4) | 0.75 |
| Missing | 32 (29.3) | 19 (39.6) | |
| Misplacement diagnosis, n (%) | | | |
| After symptoms | 55 (50.4) | 21 (43.8) | 0.04 |
| After exams | 54 (49.6) | 24 (50.0) | |
| Additional invasive procedure needed, n (%) | 66 (60.6) | 21 (43.8) | 0.09 |

Abbreviations: IQR: interquartile range; ICU: intensive care unit. Note: Inconsistencies, if any, between the values set out in the table are due to rounding to the first decimal point.

with brain displacement exhibit a significantly higher mortality rate, emphasizing the critical nature of this complication. To mitigate this risk, blind GIT insertion should be avoided following traumatic events involving the facial region, unless direct laryngoscopic or fluoroscopic visualization can be used [14]. Additionally, integrated real-time imaging system (IRIS) tubes, which are guided under direct vision using an integrated real-time imaging system, can be utilized to enhance the safety and accuracy of tube placement. The additional baseline patient characteristics are consistent with the previously mentioned findings, revealing that brain misplacements frequently occur in young male patients, who are also more prone to trauma [15, 16]. In our patient population, strict adherence to guidelines reduced the risk of severe complications, including intracranial misplacement, highlighting the importance of standardized procedures. Standard procedure indicates not to place a nasal tube if nasal anatomy is deemed unsafe unless performed under direct vision (*e.g.*, laryngoscopy). Finally, the use of polyurethane drainage tubes should be considered, since they do not harden and contain 40% barium sulfate. Consequently, they offer better radio-opacity and improve patient management by facilitating accurate placement.

There is controversy over whether GIT placement is a medical or nursing procedure [17–19]. However, in daily clinical practice, both doctors and nurses perform it and are responsible for its correctness, and whoever does it should be trained to an expert level. The GIT placement is a common procedure for anaesthesiologists and intensive care unit (ICU) physicians. As far as we know, this study represents the first comprehensive analysis of the literature on this topic, which examines both nasogastric and enteral feeding tubes dislodged in unexpected anatomical sites, demonstrating the wide range of potential risks. This study highlights a poorly reported yet common and potentially dangerous event with fatal consequences. Its strength lies in the comprehensive systematic review, providing insights into the risks and mechanisms of GIT placement. Our findings contribute to a nuanced understanding of GIT misplacement, highlighting its widespread occurrence and emphasizing the need for ongoing research and standardized protocols to mitigate associated risks [20].

Beyond the assessment of correct placement according to guidelines, which may identify issues after incorrect positioning, several strategies have been proposed to reduce the risk of injury during nasogastric tube placement even if they are not widely adopted. In patients under general anesthesia, safety can be enhanced by direct visualization using laryngoscopy or videolaryngoscopy. In awake patients, fiberoptic, fluoroscopic guidance and electromagnetic tracking systems, offer additional options to further enhance safety [21–24].

Contraindications to GIT insertion should be carefully considered to minimize the risk of placement-related injuries. These include basilar skull fractures, facial trauma, esophageal obstructions, esophageal trauma and ingestion of caustic substances. Additionally, caution is required in patients on anticoagulation due to the increased risk of bleeding and individuals with altered gastrointestinal anatomy, such as those with a history of hiatal hernia repair or gastric bypass surgery, in which endoscopic placement is recommended [25]. A major limitation of our work is that only the most severe cases

were likely published, which may affect the identification of risk factors. Reports of intracranial misplacement have led to guidelines recommending direct visualization of the tube during positioning. Similarly, further instances of GIT misplacement should be reported to assess alternative risk factors and to explore potential additional solution. We acknowledge there is a lack of large observational studies documenting the incidence of direct harm from GIT misplacement. This gap in the literature has been one of the primary motivations for conducting our systematic review. Early diagnosis of mispositioning significantly helps to reduce the consequences of incorrect insertion. This step is crucial to ensure proper placement before feeding or medication administration, and to ensure that all necessary tasks for safe extraction can be properly planned. We also acknowledge that analyzing the differences between various settings was outside the scope of the present review. Furthermore, minor complications (*e.g.*, epistaxis) are frequent but likely not reported in medical literature. Finally, case reviews like this are affected by both the willingness to report unusual complication and the fear of legal or disciplinary consequences. Only a small fraction of complications are published, making it difficult to draw definitive conclusions.

Future guidelines should also indicate the maximum number of attempts at GIT insertion and the number and expertise of operators involved before upgrading insertion technique. Furthermore, since one complication of GIT placement is its accidental removal, securing methods and devices should be addressed as well.

5. Conclusions

Our systematic review revealed 168 severe complications after GIT misplacement including 33 intracranial and 6 intravascular misplacements. Clinicians should carefully evaluate the need for GIT, select patients appropriately and consider techniques aimed at reducing placement-related injury. Considering the widespread adoption of GIT placement in global medical practice, every effort should be made to enhance the safety of this procedure, with the implementation of local protocols to guide units involved in GIT placement, focusing on tube selection, personnel training, competency, verification methods and complications management and reporting. Additionally, given the non-negligible mortality risk, we support the creation of registries to track misplacement incidents.

ABBREVIATIONS

GIT, gastrointestinal tube; NGT, nasogastric tube; ICU, intensive care unit; IQR, interquartile range; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PROSPERO, International Prospective Register of Systematic Reviews; PICO, Patient/Population/Problem, Intervention, Comparison/Control, Outcome.

AVAILABILITY OF DATA AND MATERIALS

The data used to support the findings of this study are available from the corresponding author upon request.

AUTHOR CONTRIBUTIONS

FM, RL, GL and SFr—designed the research study; wrote the manuscript. FM, RL, CC, AY and SFr—performed the research. FM, CC, SFe, AY and SFr—analyzed the data. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at <https://oss.signavitae.com/mre-signavitae/article/1888036014445740032/attachment/Supplementary%20material.docx>.

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