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Nomogram to predict gas-related complications during transoral endoscopic resection of upper gastrointestinal submucosal lesions: Clinical significance

Nomogram to predict gas-related complications

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Abstract

we comment on the article by Yang J [et al.](#) accepted in the recent issue of the *World Journal of Gastrointestinal Endoscopy*. We focus on the research and clinical significance of the four-variable nomograms, namely diabetes, lesion origin, surgical resection method, and surgical duration for predicting gas-related complications in transoral endoscopic resections. Transoral endoscopic resections in treating upper gastrointestinal submucosal lesions have the advantages of maintaining the integrity of the gastrointestinal lumen, avoiding perforation and reducing gastrointestinal fistulae. They are becoming more widely used in clinical practice, but they may also present a variety of complications. Gas-related complications are one of the most common, which can be left untreated if the symptoms are mild, but in severe cases, they can lead to rapid changes in the respiratory and circulatory systems in a short period, which can be life-threatening. Therefore, it is important to predict the occurrence of gas-related complications early and take preventive measures actively. Based on the authors' results in the prepublication of the article "Nomogram to predict gas-related complications during transoral endoscopic resection of upper gastrointestinal submucosal lesions," and in conjunction with our evaluation and additions to the relevant content, radiographs may help screen patients at high risk for gas-related

complications. Controlling blood glucose levels, shortening the duration of surgery, and choosing the most appropriate surgical resection may positively impact the prognosis of patients at high risk for gas-related complications during transoral endoscopic resection of upper gastrointestinal submucosal lesions.

Key Words: Complications; Endoscopy; Upper gastrointestinal tract; Nomogram; Clinical significance

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Core Tip: Transoral endoscopic resection of upper gastrointestinal submucosal lesions is associated with gas-related complications, which are unavoidable and may increase patient burden and prolong the duration of hospitalization. A four-variable nomogram predicts the risk of gas-related complications after transoral endoscopic resection of upper gastrointestinal submucosal lesions, guiding endoscopists during clinical operations.

INTRODUCTION

Upper gastrointestinal submucosal lesions, as a gastrointestinal disorder, are smooth-surfaced elevated lesions and are common in elderly patients^[1]. With the development and maturation of endoscopy and endoscopic ultrasonography examination techniques, as well as the increased health awareness of the population, the detection rate of gastrointestinal submucosal lesions in the digestive tract has increased dramatically^[2, 3]. Gastrointestinal submucosal lesions are often called subepithelial gastrointestinal lesions (SELs). SELs are an elevated lesion originating in the muscularis mucosae, submucosa, or lamina propria, and can also be extraluminal. Endoscopic techniques are the first line of investigation for the diagnosis of SELs. Recently, a rising number of

¹gastrointestinal submucosal lesions were treated at gastroscopy^[4, 5]. The American Society for Gastrointestinal Endoscopy and National Comprehensive Cancer Network guidelines recommend endoscopic surveillance of asymptomatic lesions <2 cm in diameter. However, larger lesions or those causing significant symptoms require immediate intervention^[6].

For endoscopic treatment of SELs, the results of a large epidemiologic study suggested that the difference in disease-specific morbidity and mortality in patients with gastrointestinal stromal tumors <2 cm in diameter was not statistically significant compared with those treated with surgical resection^[7]. Therefore, in conjunction with clinical practice, some patients undergoing endoscopic techniques, an invasive investigation, show poor compliance with follow-up. endoscopic treatment can be performed in such patients who are unable to have regular follow-up and have a strong desire for endoscopic treatment. The techniques of transoral endoscopic resection include ¹high-frequency electrocoagulation, endoscopic mucosal resection (EMR), endoscopic submucosal excavation (ESE), endoscopic submucosal dissection (ESD), submucosal tunneling endoscopic resection (STER), and endoscopic full-thickness resection (EFTR). STER is a new technique developed based on transoral endoscopic esophageal sphincterotomy (peroral endoscopic myotomy, POEM), which is also an extension of the ESD technique. The resection rate of SELs treated by STER is 84.9% to 97.5%^[8, 9].

Irregular tumor morphology, originating from the deep layers of the intrinsic muscular layer, intraoperative air insufflation, and operative time >60 min are independent risk factors for the occurrence of major postoperative complications^[10]. Of the complications that can occur after endoscopic treatment, gas-related complications are more common^[11], but most of these complications are mild and can usually be self-absorbed or improved by conservative therapy, and the application of carbon dioxide (CO₂) gas throughout the operation can effectively reduce the severity of gas-related complications^[12-14].

The main influencing factors leading to gas-related complications are (1) depth of intrinsic myotomy, and (2) intra-tunnel pressure. They are mainly caused by gas entering the lumen outside the esophageal wall, entering the mediastinum to form mediastinal emphysema, infiltrating into the subcutaneous tissues to form subcutaneous emphysema, and entering the abdominal and thoracic cavities to form pneumomediastinum and pneumothorax. Usually, mild symptoms do not require treatment, but severe cases can lead to rapid changes in respiratory circulation for a short period, which can be life-threatening. At present, some progress has been made in domestic and international research on the mechanism and factors affecting the occurrence of gas-related complications during endoscopic operations, which may be related to the duration of the disease, previous treatment history, Eckardt's score, S-type esophagus, Ling's staging, the way of establishing the tunnel entrance, the width of the tunnel, the length of the tunnel, the duration of the operation, and the use of the hybrid knife. Many of these factors are still in disagreement^[15-17]. It is crucial to predict the occurrence of gas-related complications, take proactive precautions, and determine the need for intraoperative emergency treatment, such as closed thoracic drainage and peritoneal puncture deflation.

³ Nomogram, a visual clinical predictive model, provides a scientific basis for clinical decision-making. ³ This nomogram primarily visualizes the results of the regression equation, which is usually used for logistic regression or COX regression to draw multiple line segments in a specific proportion based on the regression results, so that an individual's risk of disease or survival probability can be easily calculated. ¹ Researchers have evaluated, validated, and compared risk factors for gas-related complications in the training cohort using univariate and multivariate analyses. ¹ Diabetes, lesion origin, surgical resection method, and surgical duration were incorporated into the final nomogram^[18].

ACTUALITY OF GAS-RELATED COMPLICATIONS DURING TRANSORAL ENDOSCOPIC RESECTION OF UPPER GASTROINTESTINAL SUBMUCOSAL LESIONS

Gas-related complications were the most common complications, including the mediastinum and subcutaneous emphysema, pneumothorax, pneumoperitoneum, and even gas embolism. Currently, CO₂ is mainly used as a gas source for perfusion, which is a natural product of the organism's metabolism and has the characteristics of easy inhalation from the outside and excretion from the body, which can effectively prevent the occurrence of related complications and reduce the risk of surgery^[19, 20]. During the STER procedure, subcutaneous emphysema is identified by observing and palpating the skin of the patient's neck. Subcutaneous emphysema is often associated with mediastinal emphysema. On a CT scan performed after the POEM procedure, the rate of capnoperitoneum or subcutaneous emphysema was 30%-57%^[20]. A recent review of 19 studies, including approximately 1,300 cases of POEM, found an overall incidence of gas-related complications of 36%. Complications were distributed as follows: pneumoperitoneum 17%, pneumothorax 5%, mediastinal air 4%, and subcutaneous emphysema 10%^[21]. In POEM, sigmoid-type esophagus was identified as an independent risk factor for gas-related complications, possibly due to an esophageal twist increasing the pressure into the tunnel^[22].

Besides, the main influencing factors leading to gas-related complications are (1) depth of intrinsic myotomy, and (2) intra-tunnel pressure. Notably, many patients have multiple concurrent gas-related complications, such as pneumothorax and pneumomediastinum. Although the incidence of gas-related complications is relatively high, most of these complications are minor and do not require therapeutic intervention. Using CO₂ instead of air to reduce the risk of gas embolism and pneumothorax is theoretical, as demonstrating a statistical advantage of carbon dioxide in reducing the incidence of such rare complications is challenging. However, since air aeration can have catastrophic consequences, the use of CO₂ is recommended because transoral endoscopic resection typically destroys large areas of mucous membranes,

which normally acts as a barrier to air. Most studies suggest that prolonged CO₂ inflation should be relatively safe for upper and lower gastrointestinal endoscopy in sedated patients with normal respiratory status^[12, 13, 15, 23]. Based on autopsy findings, forensic experts found an open blood vessel at the base of a gastric ulcer in a patient who died of air embolism after a gastroscopy and recommended using carbon dioxide to inflate it. Improved quality of endoscopic recovery is another advantage of CO₂ infusion, which has been demonstrated in many randomized controlled studies only in patients undergoing colonoscopy^[24] and endoscopic retrograde cholangio pancreatography^[25]. We believe it is reasonable to extrapolate these findings to transoral endoscopic resection of upper gastrointestinal submucosal lesions.

CLINICAL SIGNIFICANCE OF FOUR-VARIABLE NOMOGRAM FOR PREDICTING GAS-RELATED COMPLICATIONS IN TRANSORAL ENDOSCOPIC RESECTIONS

Currently, there are no reliable prediction models for predicting major gas-related complications in patients with transoral endoscopic resections. Although several studies have developed nomograms to predict other complications in patients with transoral endoscopic resections, most are limited to predicting stenosis^[26-28].

Therefore, in this study, the researchers retrospectively analyzed clinical data from 353 patients to identify predictors of gas-related complications in patients undergoing transoral endoscopic resection. The results showed that diabetes, lesion origin, surgical resection method and duration were independent predictors associated with gas-related complications during transoral endoscopic resection of upper gastrointestinal submucosal lesions.

Concerning Patients with diabetes mellitus (DM). DM is a chronic metabolic disorder in which prolonged episodes of hyperglycemia are common. Hyperglycemia can cause impairment and disruption of the normal function of many organs, including the gastrointestinal tract^[29]. The pathogenesis of gas-related complications during transoral endoscopic resection in DM is complex, multi-factorial with motor dysfunction,

glycemic control, autonomic neuropathy, and psychological factors, and is not well understood^[30]. Previous studies have shown that the morphology and biomechanical properties of the gastrointestinal tract change during diabetes, such as increased wall thickness and hardness of the gastrointestinal tract^[31]. The changes in stress distribution and wall stiffness likely alter the stress after the stop the way the mechanosensitive afferents. Consequently, the perception and motility of the intestinal tract will change as well. Therefore, the morphological changes and biomechanical remodeling are likely to affect function of mechanosensitive afferents in the gastrointestinal wall and further affect the motor and sensory function^[32]. Some studies confirms that type 2 diabetes is an independent risk factor for esophageal foreign body perforation^[33]. The underlying mechanism of diabetes-induced esophageal foreign body perforation may lie in impaired wound healing and neuropathy in DM patients. Neuropathy can cause abnormal esophageal movement in most people with diabetes, sometimes similar to diffuse esophageal spasm^[33]. As the disease progresses, some minor injuries caused by foreign bodies tend to be repaired in non-diabetic patients, whereas diabetic patients are more prone to worsening injuries and a tendency to persistent stagnation, which may lead to serious complications such as gas-related complications or perforation and exacerbation of the disease. In part, this is the result of neuropathy. Therefore, future studies target neuropathy associated with diabetes. For example, we may be able to obtain data on the patient's glycosylated hemoglobin before the procedure, which could help determine whether poor glycemic control in diabetic patients increases the risk of gas-related complications or perforation.

Concerning lesion origin. Regarding the overall incidence of adverse complications, the prevalence was higher in esophagoscopy patients than in gastroduodenoscopy patients. Endoscopic procedure-related morbidity (i.e., pneumomediastinum and subcutaneous emphysema) is the main reason for the differences shown, which may be related to anatomical features such as lack of serosa in the esophagus and thin intestinal wall. The development of extended subcutaneous emphysema has been reported to be an enhancing factor for CO₂ retention during laparoscopic surgery and requires

immediate attention to determine the presence of pneumothorax or pneumomediastinum, especially when the endoscopic procedure involves the chest^[34]. In this case, patients with Endoscopic submucosal dissection require more careful attention. Some studies have shown that increases in PaCO₂ and the prevalence of adverse events were greater in patients undergoing esophagoscopy than in those undergoing gastroduodenoscopy^[35]. As things stand, it is uncertain whether the degree of CO₂ retention may be different with different targeted organs for endoscopy.

Concerning surgical resection method. The incidence of gas-related complications during transoral endoscopic resection varies significantly depending on the surgical method. The main influencing factor leading to gas-related complications is the depth of myometrium propria incision. Due to the lack of serosal layer in the esophagus, to reduce the occurrence of gas-related complications, in early POEM, it is recommended to only incise the circular muscles to avoid damaging the longitudinal muscles. However, this method is less effective for some patients with severe symptoms^[36]. To ensure long-term patient outcomes, a clinical study of more than 2,000 POEM surgeries showed that total myotomy, namely total incision of the circular and longitudinal muscles from the stenosis to the subcardia, not only did it not increase the number of gas-related complications, but also significantly shortened the operative time compared with simple circular myotomy^[22]. But subsequent studies have confirmed that the incidence of postoperative gastroesophageal reflux is higher with this method. Another influencing factor is the pressure inside the tunnel. To ensure tunnel expansion during surgery, the gas must be fed continuously. If the gas accumulates excessively in the tunnel, the increased pressure inside the tunnel will cause the gas to flow into the mediastinum through the airspace and lead to the accumulation of gas, which then enters the subcutaneous tissues. At present, the inverted T-shaped tunnel opening method has been established, i.e., the first transverse incision is 0.5-0.8 cm, and then a longitudinal incision of about 1.0 cm is made at the anus side edge of the transverse opening, which on the one hand ensures that there is enough space in the surgical incision for the mirror to be easily accessed and for the gas and liquid to be smoothly

discharged^[37]. On the other hand, with a small transverse span, it is relatively easy to close the incision. on the other hand, the transverse span is small, so it is relatively easy to close the incision^[37, 38]. Simple longitudinal incision of the tunnel entrance will result in the endoscope being tightly encircled by the mucosa at the exit, and prolonged poor gas injection and drainage will keep the gas in the tunnel under high pressure, making it susceptible to gas-related complications^[23]. Besides, during full myotomy, ¹² the integrity of the outer esophageal membrane should be preserved as much as possible.

Concerning surgical duration. The gastrointestinal tract rapidly absorbs CO₂, so prolonged surgical durations can still lead to gas-related complications. The duration of transoral endoscopic resections ¹³ may be affected by various resection devices, traction techniques, and even submucosal injection of materials, which may further affect the results^[39]. In addition, some studies have suggested that lesion fibrosis may alter transoral endoscopic resections duration^[39, 40]. As the duration of surgery increases, the rate of gas-related complications becomes higher and more severe. Second, it is worth considering whether the endoscopist's experience level is related to the duration of transoral endoscopic resections and ultimately, whether it leads to gas-related complications

LIMITATIONS OF FOUR-VARIABLE NOMOGRAM FOR PREDICTING GAS-RELATED COMPLICATIONS IN TRANSORAL ENDOSCOPIC RESECTIONS

We acknowledged the limitations in the present study. First, while their four-variable ¹¹ nomogram showed promise, its performance could potentially be improved by incorporating additional clinical variables, such as presence of previous treatment history, how the tunnel portal is established and narrowness of the tunnel. A history of preoperative treatments such as: dilation, surgery, which can cause adhesions in the submucosal layer and increase the difficulty of tunnel creation. Simple longitudinal incision of the tunnel entrance will result in the endoscope being tightly encircled by the mucosa at the exit, and prolonged poor gas injection and drainage will keep the gas in the tunnel under high pressure, making it susceptible to gas-related complications^[23].

Additionally, the corresponding performance comparison against other well-established models is warranted. In future studies, many experiments are needed to further search for possible biomarkers to better predict the occurrence of gas-related complications in transoral endoscopic resections.

CONCLUSION

In summary, using a ¹ nomogram incorporating surgical duration, method of surgical resection, DM, and the lesion layer of origin to predict gas-related complications in transoral endoscopic resections is recognizable. Theoretically, a ¹⁰ patient's preoperative gas intolerance may be a marker for the development of postoperative gas-related symptoms. Perioperative risk can be reduced through early prevention and intervention. However, there are many factors contributing to the development of gas-related complications during surgery, possibly involving the patient, anesthesia, and surgery, and the influence of these factors can continue to be investigated, and the predictive value can be confirmed by expanding the sample size. Future studies should evaluate the clinical value of preoperative gas provocation tests.

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