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# The influence of body mass index on efficacy and outcomes of percutaneous transforaminal endoscopic surgery (PTES) for the treatment of lumbar degenerative diseases: a retrospective cohort study

Chenyang Zhuang[1,2†], Yun Xu[3†], Hong Lin[1,2*] and Yutong Gu[1*]

## Abstract

**Background** To investigate and quantify the influence of body mass index (BMI) on the efficacy and outcomes of percutaneous transforaminal endoscopic surgery (PTES), a novel minimally invasive surgical technique in the treatment of lumbar disc herniation (LDH).

**Methods** A total of 55 patients suffering from single-level LDH with or without high iliac crest, scoliosis or calcification, who underwent PTES in our department from January 2019 to December 2021 were retrospectively analyzed. Patients were divided into two groups according to BMI. The operative events of two groups including X-ray projection, operation time, blood loss and length of stay were compared. Visual Analogue Scale (VAS) and Oswestry Disability Index (ODI) were used to evaluate the clinical efficacy and outcomes of the surgery. Differences in complications and recurrences between two groups were also analyzed.

**Results** 55 patients were divided into obese and nonobese groups according to their BMI (33.03 vs. 23.07). There was no significant difference in X-ray projection (times), operation time (mins), blood loss (mL) and length of stay (days) between two groups (7/5–11 vs. 5/5–10, 58.17 ± 9.20 vs. 53.65 ± 10.06, 6.41 ± 1.43 vs. 5.50 ± 2.45, 3.17 ± 1.44 vs. 2.96 ± 0.53, $P > 0.05$). Both groups demonstrated a significant decrease in ODI (12.01 ± 3.57% vs. 67.16 ± 9.25%, 13.92 ± 4.24% vs. 68.10 ± 9.27%, $P < 0.05$) and VAS (0.10 ± 0.48 vs. 8.38 ± 0.94, 0.22 ± 0.56 vs. 8.38 ± 0.86) at 24 months after the operation compared with which at the preoperative status. No significant difference in the improvement of the clinical outcomes was found between the two groups in ODI or VAS ($P > 0.05$).

†Chenyang Zhuang and Yun Xu contributed equally to this work.

*Correspondence:
Hong Lin
lin.hong1@zs-hospital.sh.cn
Yutong Gu
447574313@qq.com

Full list of author information is available at the end of the article

**Conclusions** With the simple orientation, easy puncture and reduced steps, PTES is an effective and safe method to both obese and normal patients with LDH.

**Clinical trial number** Not applicable.

**Keywords** Body mass index, Obesity, Percutaneous transforaminal endoscopic surgery, Minimally invasive surgery

## Background

Obesity is one of the major public health problems around the world, especially within the developed countries. The prevalence of obesity has increased steadily in the past 30 years among the adults. It is estimated that nearly 45% of people will reach the standard of obesity (BMI > 30) by 2050 in UK [1]. Almost one third of Chinese adolescents are overweight or obese and the increased trend of obesity is not mitigated [2]. Furthermore, many obesity-associated disorders including diabetes mellitus, cardiovascular diseases, depression, and anxiety have increased huge economic and social burden, jeopardizing the health of people and social stability severely [3, 4]. Another typical syndrome closely related to the obesity is lumbar disc herniation (LDH) [5]. Overload of lumbar disc is more commonly investigated within obese adults than normal ones, which constitutes the major cause of lumbar disc herniation [6]. Additionally, both the decline of exercise and less proportion of lumbodorsal muscle in obese individuals may aggravate the lumbar degeneration [7].

Posterior lumbar interbody fusion (PLIF) or transforaminal lumbar interbody fusion (TLIF) has shown certain therapeutic effects on patients of LDH with neurologic symptoms of lower extremities since the middle of the last century [8, 9]. However, the open surgery was found in many researches inducing more soft tissue trauma, destruction of dorsal musculature, longer hospitalization times and later return to work [10]. In recent years, minimally invasive transforaminal lumbar interbody fusion (MIS-TLIF) has been widely used as the modified and effective methods to LDH, which only requires relatively limited surgical wound to gain access, thereby, offsetting the negative effects of open surgery [11]. Nevertheless, obesity was still considered as the risk factors of higher incidence of long-term complications and failure of MIS-TLIF [12]. As the concept of minimally invasive surgery was universally introduced, the spinal endoscopic surgery has become the most minimally invasive technique to treat LDH patients with neurologic symptoms [13].

In 2017, we first introduced the percutaneous transforaminal endoscopic surgery (PTES) technique with the significantly satisfactory surgical outcomes for the treatment of LDH [14]. Moreover, compared with MIS-TLIF, PTES has the advantages including less damage of paraspinal muscle and bone, less blood loss and X-ray exposure, faster recovery, lower complication rate and shorter operation time under local anesthesia [15, 16]. Besides, it has more indications than the normal spinal endoscopic surgery including L5/S1 level with high iliac crest, herniation with scoliosis or calcification and adjacent disc herniation after decompression and fusion, with a relatively flat learning curve [17]. Compared to the traditional puncture point, Gu's point of PTES is more medial, which significantly shortens the surgical pathway, avoids the need for long surgical instruments, and reduces the difficulty of the surgery especially for the obese patients [18, 19]. Herein, our purpose was to investigate whether obesity affect the clinical outcomes and safety following PTES in patients with single-level LDH compared to their normal BMI counterparts with a retrospective cohort study.

## Methods

### Patients

The clinical study proposal was approved by Zhongshan Hospital Ethical Committee. From January 2019 to December 2021, a total of 55 patients with single-level LDH (from L3-S1) receiving PTES were divided into obese and nonobese groups according to their BMI (BMI ≥ 28 is defined as obesity [20]) and retrospectively analysed. Besides, some special kinds of LDH including high iliac crest, scoliosis or calcification were also recorded. The inclusion criteria were as follows: (1) Radicular symptom of unilateral leg pain resulted from LDH, (2) Image data such as MRI and CT showed a single-level LDH from L1 to S1, which was consistent with the clinical symptoms of corresponding neurologic compression, (3) Poor outcome after regular conservative treatment of at least 3 months. The exclusion criteria were (1) Imaging data showed lumbar spondylolisthesis or intervertebral instability, (2) Lumbar spine inflammation, tumors, vertebral fracture and other lesions. (3) A history of spinal surgery around the affected level.

### Pre- and postoperative imaging

All patients underwent three-dimensional lumbar CT at our hospital (320-row computed tomography, Aquilion One, tube voltage 120 kV; Canon Medical Systems, Japan), and MRI scans (Magnetic Resonance Imaging System, Aera, 1.5T, Siemens, Germany) to determine the involved segment or to determine if there was calcification. Posteroanterior and lateral radiographs were

obtained to detect lumbar instability, scoliosis, lumbarization of S1 or high iliac crest when the lower plate of L4 vertebral body is not higher than the line between highest points of bilateral iliac crest. Images of the lumbar spine were reviewed using the picture archiving and communication system (PACS). Postoperative MRI images were obtained to assess neurological decompression or exclude hematoma, dural tears or spinal fluid leaks, and reherniation.

### Surgical procedure

As illustrated in our previous studies, PTES was performed under local anesthesia with 1% lidocaine. The patient was placed in a prone position with bolsters under the abdomen on a radiolucent table, making the hip joint flexion and keeping the back in a horizontal state. The segment was then determined by posteroanterior C-arm fluoroscopy. The puncture point was located at the corner of flat back turning to lateral side according to "Gu's point". The puncture needle was further inserted at 25°- 85° to the horizontal plane aiming at the vertical line of body surface through the anatomical centre of intervertebral disc. This entrance was easy to determine without the fluoroscopy regardless of different age, gender, and body size (Fig. 1). A successful puncture should have the following features, the needle reached the posterior 1/3 of intervertebral space or around its posterior edge on the lateral film, and close to the lateral edge of pedicle on the posteroanterior film (Fig. 2). Through a nearly 8 mm small incision, the guiding wire was inserted and over which the 6.3-mm guiding rod was introduced into the foramen. Along with the same path, the 8.8-mm protective cannula was inserted, and docked at the facet. Press-down enlargement technique was used to make the angle of cannula to the horizontal plane smaller according to the inclination of puncture needle on the fluoroscopy. A 7.5 mm reamer was further introduced to cut the outer and ventral bone of articular process to enlarge the foramen. When resistant disappeared, the fluoroscopy showed that the top of reamer exceeded the inner edge of pedicle on the posteroanterior film and reached the posterior edge of target intervertebral space on the lateral film. After the 7.5 mm working channel placed along the guiding rod, the ipsilateral traversing and exiting nerve root, contralateral traversing nerve root, or epidural sac were exposed under endoscopic vision. The protruding disc tissue were removed to decompress the nerve root.

### Clinical follow-up

Visual Analogue Scale (VAS) before operation, immediately, one week, one month, two months, three months, six months, 12 months and 24 months after surgery were recorded. Also, Oswestry Disability Index (ODI) before and 24 months after surgery were recorded to evaluate the surgical outcomes. The therapeutic results were further graded 24 months after surgery based on the

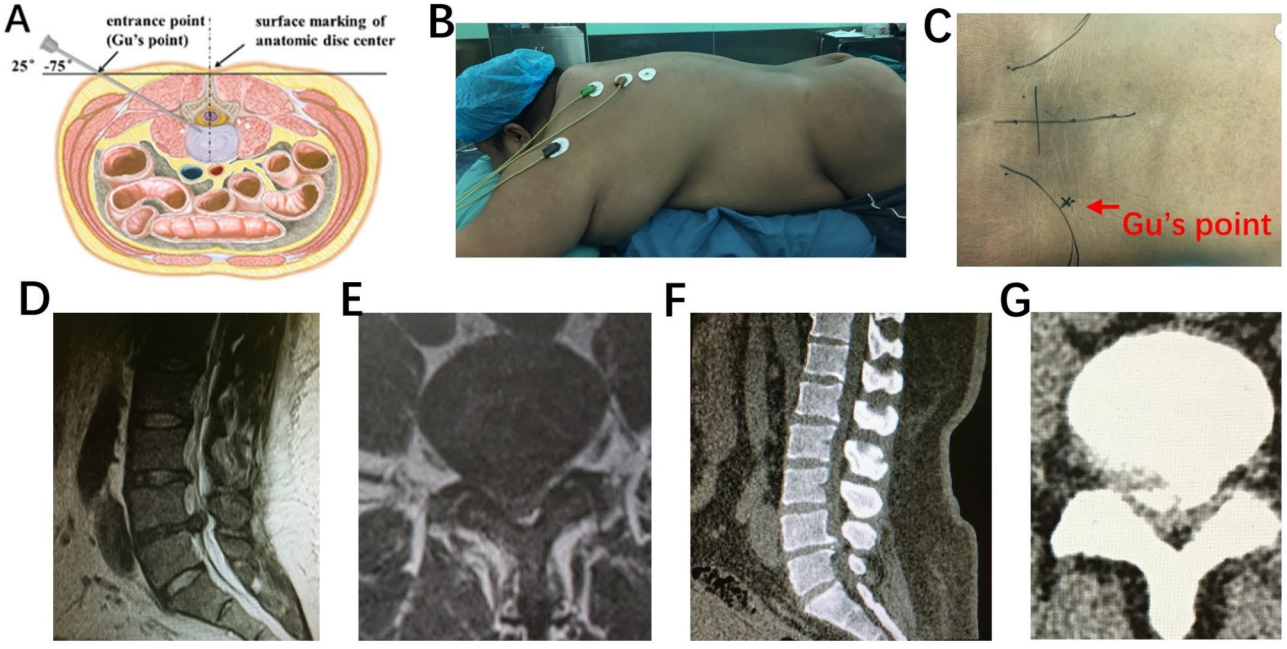


**Fig. 1** Puncture procedure of PTES on a 37-year-pld male patient with BMI 41 kg/m$^2$, with L4/5 disc herniation and calcification. **a** Schematic diagram of the puncture. The entrance point locates at the corner of flat back turning to lateral side at the height of target disc or cranially or slightly caudally. After local anesthesia, an 18-gauge puncture needle was inserted at an angle of about 45° (25°-75°) until reaching the posterior 1/3 of the intervertebral space or intracanal area close to posterior wall of the disc on lateral view and near the medial border of the pedicle on posteroanterior view. **b**, **c** The entrance point on real body surface. **d** Sagittal, **e** axial MR images, and **f** sagittal, **g** axial CT scan showed calcification in L4/5 disc herniation

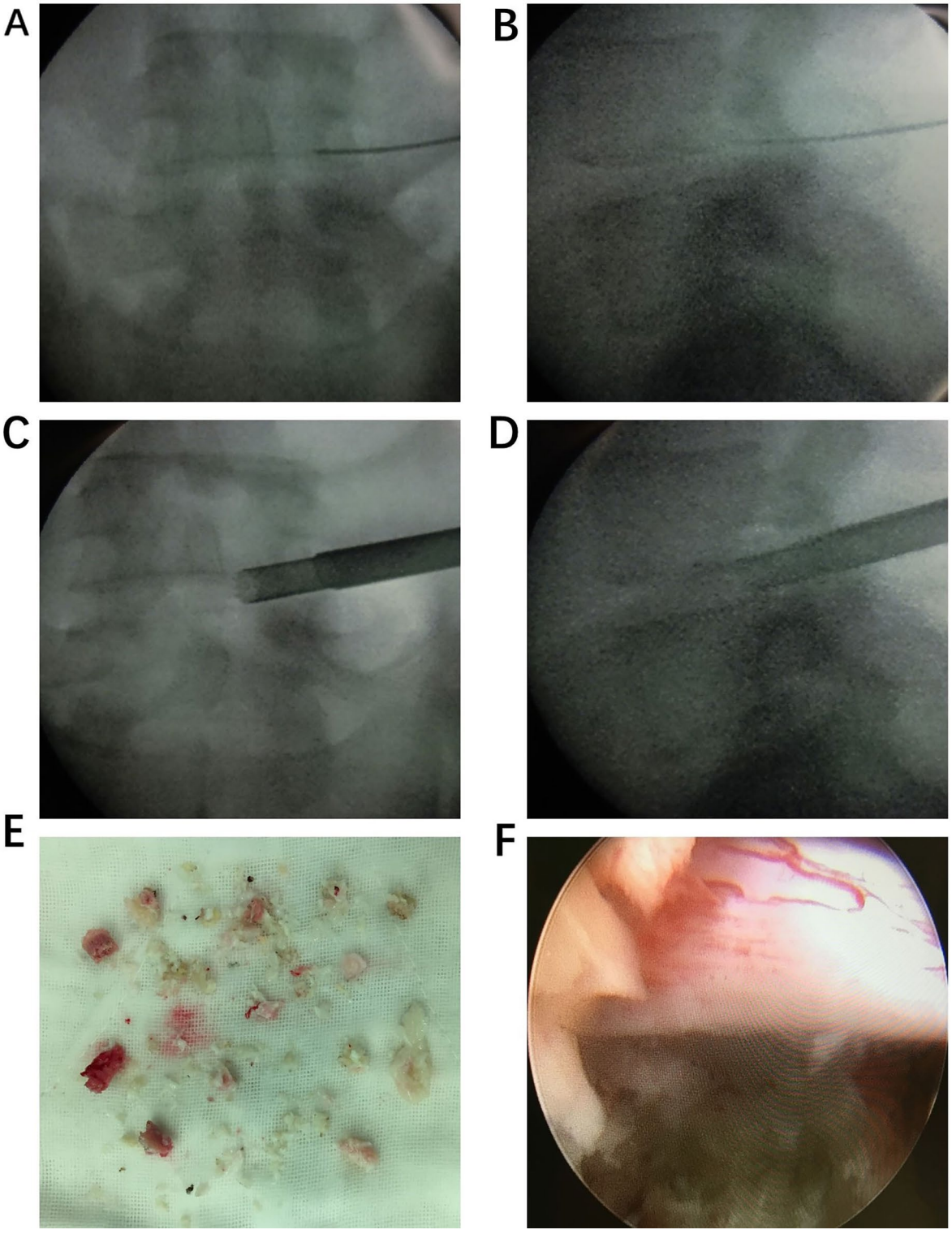


**Fig. 2** During the procedure of PTES, the tip of the puncture needle was beyond the medial border of pedicle on **a** posteroanterior C-arm view, and in the posterior one third of intervertebral space on **b** lateral C-arm view. **c** Posteroanterior and **d** lateral C-arm image confirmed that a 7.5-mm working cannula was advanced directly to the protruding fragment. **e** Endoscopic picture showed that the nerve root was exposed for complete decompression after removal of **f** sequestrated disc fragments

**Table 1** Patient characteristics of the two groups(mean ± SD; $P < 0.05$ was identified with significant difference; n = number)

| Variables | | Obese ($n = 26$) | Nonobese ($n = 29$) | $p$ value |
|---|---|---|---|---|
| Sex (male/female) | | 15/11 | 16/13 | > 0.05 |
| Age (year) | | 46.19 ± 11.01 | 43.69 ± 10.12 | > 0.05 |
| BMI (kg/m$^2$) | | 33.03 ± 2.06 | 23.07 ± 1.34 | < 0.001 |
| Smoking history (Y/N) | | 8/26 10/29 | | > 0.05 |
| Cardiovascular comorbidities (Y/N) | | 3/26 | 2/29 | > 0.05 |
| Diabetes (Y/N) | | 5/26 | 6/29 | > 0.05 |
| VAS-Back, preoperative | | 6.65 ± 1.57 | 6.59 ± 1.45 | > 0.05 |
| VAS-Leg, preoperative | | 8.38 ± 0.94 | 8.38 ± 0.86 | 0.983 |
| The segment of the lumbar disc herniation (n) | L3/4 | 2/26(8%) | 3/29(10%) | |
| | L4/5 | 18/26(69%) | 19/29(66%) | |
| | L5/S1 | 6/26(23%) | 7/29(24%) | |
| ODI, preoperative | | 67.16 ± 9.25 | 68.10 ± 9.27 | 0.710 |

**Table 2** Operative treatments, complications, and events

| Variables | Obese ($n = 26$) | Nonobese ($n = 29$) | $p$ value |
|---|---|---|---|
| X-ray Projection (times) | 7 | 5 | $p > 0.05$ |
| Operation time (min) | 58.17 ± 9.20 | 53.65 ± 10.06 | $p > 0.05$ |
| Blood loss (mL) | 6.41 ± 1.43 | 5.50 ± 2.45 | $p > 0.05$ |
| Length of stay | 3.17 ± 1.44 | 2.96 ± 0.53 | $p > 0.05$ |
| *Complications* | | | |
| Dural tear or spinal fluid leak | 0 | 0 | |
| Nerve root injury | 0 | 0 | |
| Recurrent disc herniation | 1 | 0 | |
| *MacNab Classification* | | | |
| Excellent or good n (%) | 24(92.2) | 27(93.1) | $p > 0.05$ |
| Fair n (%) | 1(3.9) | 2(6.9) | $p > 0.05$ |
| Poor n (%) | 1(3.9) | 0(0) | $p > 0.05$ |

MacNab criteria: Excellent, Good, Moderate or Poor. Clinical follow-up was carried out through outpatient or telephone follow-up. Complications including infection, recurrence, and permanent nerve injury were also recorded.

### Statistical analysis

The SPSS Statistics version 21.0 package (IBM Corp., Armonk, NY, USA) was used for data analysis. The independent samples Student's t-test was applied for continuous variables. A chi-squared test was applied for categorical data analysis. Continuous variables such as age, BMI, VAS, ODI, operation time, blood loss, and length of stay are presented as mean ± standard deviation (SD). $P < 0.05$ was considered as a significant difference.

**Table 3** Treatment effect of nonobese patients compared with obese patients for outcome measures

| Outcome variables | Obese ($n = 26$) | Nonobese ($n = 29$) | $p$ value |
|---|---|---|---|
| *Oswestry Disability Index(ODI)* | | | |
| Pre-operation | 67.16 ± 9.25 | 68.10 ± 9.27 | $p > 0.05$ |
| 24 months post-operation | 12.01 ± 3.57 | 13.92 ± 4.24 | $P = 0.078$ |
| *VAS-Back* | | | |
| Pre-operation | 6.65 ± 1.57 | 6.59 ± 1.45 | $p > 0.05$ |
| Immediately post-operation | 0.50 ± 0.58 | 0.79 ± 0.86 | $p > 0.05$ |
| 6 months post-operation | 0.31 ± 0.54 | 0.12 ± 0.33 | $p > 0.05$ |
| 12 months post-operation | 0.28 ± 0.45 | 0.12 ± 0.33 | $P = 0.143$ |
| 24 months post-operation | 0.23 ± 0.41 | 0.10 ± 0.30 | $P = 0.156$ |
| *VAS-Leg* | | | |
| Pre-operation | 8.38 ± 0.94 | 8.38 ± 0.86 | $P = 0.983$ |
| Immediately post-operation | 1.08 ± 0.93 | 1.03 ± 0.91 | $P = 0.865$ |
| 6 months post-operation | 0.12 ± 0.43 | 0.24 ± 0.58 | $P = 0.368$ |
| 12 months post-operation | 0.11 ± 0.45 | 0.23 ± 0.56 | $P = 0.324$ |
| 24 months post-operation | 0.10 ± 0.48 | 0.22 ± 0.56 | $P = 0.378$ |

## Results

Demographic data was demonstrated in Table 1. There was no significant difference in age, gender, smoking history, cardiovascular comorbidities, surgical level, preoperative symptoms and follow-up duration. The average BMI of obese and nonobese groups were 33.03 ± 2.06 and 23.07 ± 1.34, respectively. The operative events of two groups including X-ray projection, operation time, blood loss, incision length and length of stay were summarized in Table 2. None of these events were found different between obese and nonobese patients. Additionally, surgery-related complications including dural tear or spinal fluid leak, nerve root injury were not found in both groups.

In terms of the postoperative outcomes of the two groups, we found ODI in the both groups at 24 months after treatment decreased compared with that before surgery significantly (Table 3, $P < 0.05$). However, the ODI difference between the two groups were not found significant at 2-year follow-up ($P = 0.078$). The VAS scores were also used to evaluate the surgical effects. Both groups have gained a satisfactory relief in the back pain immediately after surgery and at 6 months, 12 months and 24 months after operation ($P < 0.05$). The similar results were also acquired in the leg pain relief ($P < 0.05$). Nevertheless, obesity was not found as the risk factor that influenced the pain control after PTES ($P > 0.05$). According to MacNab classification, the excellent and good rate was 92.3% (24/26) in the obese group and 93.1% (27/29) in the control group 2 years after surgery. (Table 2) There was no statistical difference in the excellent and good rate between two groups. Only one case in the obese group was found recurrent and rated as poor at the end of follow-up. He was admitted again for PTES and discharged with a satisfactory outcome until now.

## Discussion

According to the statistics from WHO, worldwide obesity has nearly tripled since 1975. In 2016, more than 1.9 billion adults were overweight. Of these over 650 million were obese, indicating a tough challenge to the public health [21]. Many surgeons have found along with the extra pounds, overload on spine especially in lumbar vertebrae increases the risk of the LDH and degenerative lumbar spondylolisthesis through case-control studies and biomechanical analysis in human and animal specimens [22, 23]. Compared with the conventional posterior lumbar surgery, MIS-TLIF has definite effects and fewer complications and has become the routine surgical technique worldwide to treat LDH with severe neurological symptoms [11]. Nevertheless, some studies reported longer surgery time, more blood loss and longer length of hospital stay were observed in obese patients after MIS-TLIF [24]. In addition, the decrease in lumbodorsal muscle strength after MIS-TLIF, especially in overweight patients, may become a latent factor inducing postoperative low back pain.

In 1992, Kambin introduced the innovative method to treat LDH with arthroscopy, taking a significant step to the micro-invasive surgery in the spine field [25]. After subsequent development in the Yeung endoscopic spine system (YESS) by Yeung et al. and transforaminal endoscopic spine system (TESS) by Hoogland et al., the modified percutaneous endoscopic lumbar discectomy (PELD) has become one of the most popular surgical methods that is equivalent to open spine surgery in terms of efficacy and entails less trauma and complication [26, 27]. Additionally, PELD reduced the paraspinal muscle trauma significantly compared with the open surgery, even the MIS-TLIF, which alleviated the low back pain in the normal and obese patients. PELD is favourable for obese patients because it minimizes incision length, which decreases the rate of postoperative unhealed wound and infectious complications. Obese patients are easily exposed to postoperative infection due to the poor blood supply in adipose tissue and fat liquefaction caused by the electrotome during surgery [28]. Furthermore, PELD under local anesthesia can also avoid the adverse events associated with general anesthesia, such as respiratory obstruction, hypotension and arrhythmia [29].

However, some researchers also have investigated the difficult and crucial points of PELD when treating obese patients. The finding of meta-analysis by Yin et al. reconfirmed that the prevalence of recurrent herniation after PELD was significantly higher in obese (BMI ≥ 25) patients [30]. The conclusion is reasonable given that the excess weight with the cyclical increase of the intradiscal pressure could lead to higher shear strains in the posterolateral part of the annulus fibrosus, which would cause disc herniation. It remains complex in the guiding process and navigating for the optimal trajectory especially in the obese patients, which may constitute a steep learning curve. More difficulties in PELD unfolded while these obese patients catch a calcified LDH or high iliac crest for the L5/S1 level. All the limitations above lead to much exposure of X-ray, long duration of operation, and restrict the application of PELD.

After summarizing the pros and cons of all those previous endoscopic techniques and instruments, we introduced percutaneous transforaminal endoscopic surgery (PTES) in 2017 and confirmed it was an effective and safe method to treat almost all kinds of LDH, including L5/S1 level with high iliac crest, herniation with scoliosis or calcification, recurrent herniation, and adjacent disc herniation after decompression and fusion, with a shallow learning curve [14–16, 31]. The present study is the first analysis to date exploring the impact of obesity on surgical and functional outcomes following PTES for single-level LDH with or without high iliac crest, scoliosis or calcification. No significant difference was found in operative events and postoperative outcomes between obese and normal groups, which showed a different consequence from the PELD. Herin, we intend to further introduce and discuss the advantages of this effective technique.

First, PTES innovatively introduced modified entrance point, also named as “Gu’s point”, was located at the corner of the flat back turning to the lateral side, which was more medial than other transforaminal endoscopic techniques. The modified “Gu’s point” has four advantages, (1) Avoid interfering with the exiting nerve root which leaves the foramen from superomedial to inferolateral. If the entrance point locates laterally, the foraminotomy may injure the exiting nerve root more possibly and the patient may complain of pain in lower extremities under the local anesthesia surgery. (2) Avoid blockage by the high iliac crest for the L5/S1 level. Peak of the iliac crest locates at the lateral side of the waist and the height lowers down when getting closer to the midline. Height of the iliac crest at “Gu’s Point” is relatively lower, reducing the difficulty of puncture and subsequent operation. (3) Shorten the surgical path. Routine PELD surgery has a more lateral entrance point from the midline, which makes the path for surgical target longer. Especially in obesity patients, more subcutaneous adipose tissue makes the puncture point more distal from surgical target, which needs very long working channel for transforaminal endoscopic surgery, raising the risk of dead space formation and issue necrosis. Gu’s point of puncture is more medial, which makes the approach short, the surgery easy and there is no need of long surgical instruments for the obesity patients, resulting in the similar surgery time between the two groups. (4) Avoid injuring abdominal viscera and main blood vessels. Puncture

from a lateral entrance point could be dangerous if penetrating into the abdomen. With this simplified entrance point, it was not necessary to take the extra fluoroscopy projection and measuring the distance to the midline for determination. In addition, it is essential to enlarge the foramen through a simple and convenient method, especially in those obese patients who have thicker subcutaneous tissues and more calcified discs. We introduced "press-down enlargement of foramen" technique, which allows the cannula docking at the facet and make the angle of cannula to horizontal plane smaller and a 7.5-mm reamer is performed to remove more ventral bone of articular process for enlarging the intervertebral foramen. For those who had bilateral symptoms, "press-down" technique could decompress not only the ipsilateral nerve root, but also the central dura and the contralateral nerve root. In the present study, we got a satisfactory outcome in both obese group and control group.

We have used PTES technique to treat over 750 patients with lumbar degenerative diseases in nine studies [14–19, 31–33]. The complications we summarized among all these patients were shown as Table 4. Among these complications, we identified transient weakness of quadriceps or foot/toe extensor strength, disc infection, rebound of leg pain, and recurrence by reexaminations after surgery. While intraoperative nerve root sleeves rupture was found during surgery, but no cerebrospinal fluid leakage or other abnormal clinical symptoms were observed. Transient weakness of leg strength is related to the stimulation to exiting root during surgery. To avoid the situation, we suggest stopping the action immediately when the patient feel pain in lower extremities and changing the direction to avoid the exiting root. So far, only one case of postoperative intervertebral disc infection has been found, which was relieved after 3-week continuous antibiotic treatment. We assessed the patients who had rebound pain comprehensively, which may be due to the severe compression to the nerve root and the demyelinating changes before surgery. During the repair of the myelin sheath after the compression was removed, hyperpathia may happen. These patients got pain relief almost 2 months later when the repair of the myelin sheath completed. Therefore, we suggest observing at least for two months after rebound pain happening instead of undergoing surgery again immediately. As for the recurrence, we still firmly hold that the better outcome is closely related to a better postoperative care. We repeatedly remind patients: (1) Avoiding frequent bending; (2) Avoiding lifting heavy objects; (3) Avoiding maintaining the same posture for a long time; (4) Avoid focusing strength on the waist when coughing and sneezing. In this study the only one recurrent case in the obese group was found not following these instructions and resumed his work as a porter only one week after surgery. Therefore, the overall recurrence rate after PTES is low in our studies and even if the recurrence happens, it is feasible to undergo another PTES. All these patients had satisfactory outcomes after surgery.

**Table 4** The complications among all patients undergoing PTES ($n = 750$)

| Complications | Number | Percent |
|---|---|---|
| Transient weakness of quadriceps or foot/toe extensor strength | 3 | 0.4% |
| Disc infection | 1 | 0.1% |
| Intraoperative nerve root sleeves rupture | 9 | 1.2% |
| Rebound of leg pain | 20 | 2.7% |
| Recurrence | 3 | 0.4% |

However, the research has some limitations. First, the sample size of this retrospective cohort study may be slightly small, which could induce bias in the results. Second, the follow-up time is relatively short. A five-year follow-up period should also be included. The low recurrence rate will be more persuasive to reflect the long-term therapeutic effect of PTES especially on obese patients.

## Conclusions

This present retrospective research shows the PTES, an innovative minimally-invasive surgery, has relatively similar satisfactory effects on normal and obese patients with LDH.

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12893-025-02761-8.

Supplementary Material 1

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**Author contributions**
Research design: C Zhuang and Y Gu; Collection and analysis of data: C Zhuang and Y Xu; Drafting and revision of paper: C Zhuang, Y Gu, H Lin, etc. All authors gave final approval of the version to be published, and agree to be accountable for all aspects of the work. All authors read and approved the final manuscript.

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**Data availability**
The datasets generated during and analyzed during the current study are not publicly available due to privacy and ethical restrictions but are available from the corresponding author on reasonable request.

## Declarations

**Ethics approval and consent to participate**
The study methods were conducted in accordance with the Declaration of Helsinki and was approved by the institutional review board and independent ethics committee of Zhongshan Hospital, Fudan University (approval No.2022–130). All eligible participants in the study gave written informed consent.

**Consent for publication**
All the participants involving individual's radiological data gave the consent for publication.

**Competing interests**
The authors declare no competing interests.

**Author details**
[1]Department of Orthopaedic Surgery, Zhongshan Hospital, Fudan University, Shanghai, PR China
[2]Department of Orthopaedic Surgery, Shanghai Geriatrics Centre, Shanghai, PR China
[3]Centre for Rehabilitation Medicine, Department of Pain Management, Zhejiang Provincial People's Hospital, Zhejiang, PR China

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