ORIGINAL RESEARCH

Systemic Inflammatory Markers and Clinical Outcomes of Open versus Biportal Endoscopic Transforaminal Lumbar Interbody Fusion

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Purpose: The purpose of this study is to preliminarily assess the change in perioperative systemic inflammatory markers and clinical outcomes between open TLIF and BE-TLIF procedures.

Patients and Methods: In total, 38 patients who underwent single-level lumbar fusion surgery (L4-5 or L5-S1) were retrospectively reviewed. 19 patients were treated by the BE-TLIF technique, while the other patients were managed using open TLIF. The perioperative serum C-reactive protein (CRP), neutrophil/lymphocyte ratio (NLR), lymphocyte/monocyte ratio (LMR), and platelet/lymphocyte ratio (PLR) of the two groups were compared to determine if there was a statistical difference. Meanwhile, clinical evaluations were conducted to assess various factors including operative duration, estimated blood loss (EBL), drainage catheter stay, length of hospitalization, visual analogue scale (VAS), and Oswestry disability index (ODI) scores.

Results: The perioperative analysis revealed that BE-TLIF cases experienced a longer operative duration than open TLIF cases (open TLIF: 138.63 ± 31.59 min, BE-TLIF: 204.58 ± 49.37 min, p < 0.001). Meanwhile, the EBL showed an increased trend in the BE-TLIF group (260.7 ± 211.9 mL) in comparison with the open TLIF group (200.9 ± 211.9 mL) (p =0.485). In terms of systemic inflammatory markers, the mean postoperative CRP, NLR, LMR, and PLR were lower in the BE-TLIF group than in the open TLIF group, although these differences were not statistically significant (p > 0.05). The VAS and ODI scores in both groups were significantly improved after surgery (p < 0.05).

Conclusion: There was no significant difference found between BE-TLIF and open TLIF in terms of systemic inflammatory markers, and clinical outcomes. Overall, BE-TLIF can be considered a viable choice for lumbar canal decompression and interbody fusion for less invasion. It is worth noting that BE-TLIF does have a longer operation time, indicating that there is still potential for further improvement in this technique.

Keywords: transforaminal lumbar interbody fusion, unilateral biportal endoscope, systemic inflammatory markers

Introduction

Degenerative disease of the lumbar spine, as a common condition among the elderly population, is increasingly affecting younger individuals as well.[1] It is a major contributor to low back pain, leg pain and numbness, and can even result in walking difficulties in severe cases.[2] The two primary conditions associated with this degenerative disease are lumbar spinal stenosis and spondylolisthesis. Lumbar interbody fusion (LIF) has long been regarded as the gold standard treatment for degenerative lumbar diseases by spinal decompression and stability reconstruction. Currently, the mainstream of LIF includes posterior LIF (PLIF), oblique LIF (OLIF), anterior LIF (ALIF), lateral LIF (LLIF), and transforaminal LIF (TLIF).[3,4]

Among these approaches, PLIF and TLIF are widely performed. TLIF has several advantages over PLIF, as it can effectively decompress the spinal canal and release the nerve roots by removing unilateral partial facet joints and lamina.[5] However, TLIF has also been criticized for the extensive destruction of posterior musculoligamentous structures.[6] The inflammatory response is a physiological reaction of the body to tissue injury to promote repair and healing.[7]

Nevertheless, an excessive inflammatory response can also lead to adverse consequences, such as pain, swelling, and further tissue damage.[8] Additionally, the inflammatory response can increase the risk of postoperative infection. Currently, the popularity of minimally invasive spine surgery for treating spine disorders is growing.[9] The unilateral biportal endoscopic technique which uses two incisions that are 3 cm apart, is a good approach (Figure 1A).[10] This technique is not only effective for treating lumbar disc herniation but is also used in lumbar decompression and fusion.[11]

Biportal endoscopic TLIF (BE-TLIF) is a minimally invasive spine surgery, based on conventional arthroscopic systems, using a percutaneous biportal endoscopic approach to perform spinal canal decompression, insert cages and pedicle screws.[12] The goal of BE-TLIF is to reduce blood loss and soft tissue trauma through smaller incisions, which can lessen the inflammatory response in the body caused by trauma, minimize postoperative complications and increase the speed of recovery.[13] Systemic inflammatory markers are biochemical indicators or molecules produced during the systemic inflammatory response, that are used to assess the severity of the systemic inflammatory response and aid in the diagnosis, monitoring, and treatment of inflammation-related diseases.[14] Among these markers, C-reactive protein (CRP), neutrophil/lymphocyte ratio (NLR), lymphocyte/monocyte ratio (LMR), and platelet/lymphocyte ratio (PLR) serve as canonical perspective indexes of cellular immune activation, physical stress and systemic inflammation.[15]

This study aims to preliminarily assess the changes in perioperative systemic inflammatory markers and clinical outcomes between open TLIF and BE-TLIF. To the best of our knowledge, this is the first report on this topic, which will open up a train of thought for the clinical research and generalization of BE-TLIF.

Materials and Methods
Patient Population
The inclusion criteria for participants in this study were as follows: 1) degenerative lumbar spondylolisthesis (Meyerding grades 1–2), isthmic lumbar spondylolisthesis (Meyerding grades 1–2), lumbar spinal stenosis (LSS), lumbar disc herniation (LDH); 2) single-level lumbar lesion; 3) persistent neurological symptoms with no response to conservative treatment for over three months. Those with spine tumors or infections were excluded.

All patients underwent surgery under general anesthesia and were treated with prophylactic antibiotics (cefuroxime) 1 hour before the skin incision and within 24 hours after the operation. In the presence of a penicillin allergy, clindamycin was used instead of cefuroxime. All BE-TLIF cases were performed by a senior spine surgeon (Figure 1B), who was also involved with the open TLIF cases with the other two senior spine surgeons in our department.

Surgical Operation of Open TLIF
Under general anesthesia, the patient is positioned prone on the arched spine stent and the paraspinal muscles are then detached along the periosteum to expose the spinous process, lamina, and facet joints.[16] Anatomical anomalies and the patient's complaints may dictate the need for a laminectomy, facetectomy, or both. Following sufficient neural element decompression, pedicle screws and an interbody device(s) are positioned conventionally.
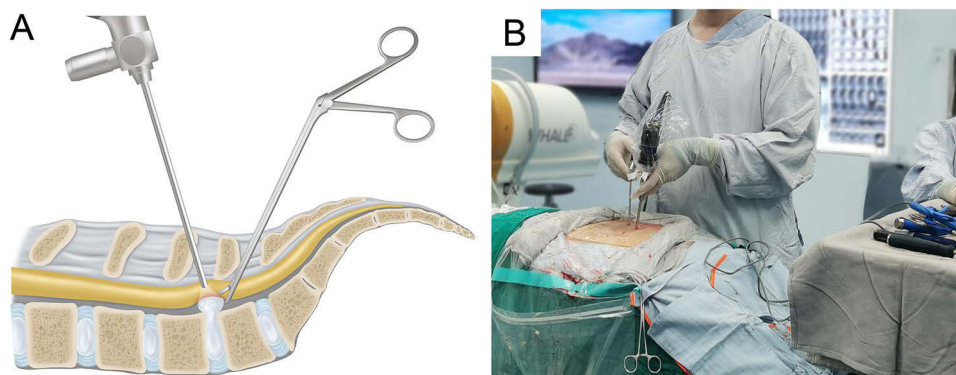

Figure 1 Overview of biportal endoscopic lumbar interbody fusion. (**A**) Illustration of unilateral biportal endoscopic discectomy; (**B**) the dominant hand was used for the working portal and the nondominant hand was used for the endoscopic portal.

Surgical Operation of BE-TLIF

As with open TLIF, the patient is positioned prone on the spine's arch under general anesthesia. Under fluoroscopy, the endoscopic incision on the body surface, and the entry points for the bilateral percutaneous pedicle screws were marked.[13] A 1.5cm distance beside the spinous process of the fusion segment was identified, and oblique incisions with a skin length of about 1.5cm were made on both sides of the head and tail. Observation and operation channels were established accordingly. Decompression and fusion procedures, similar to open TLIF, were carried out under the endoscope. Subsequently, percutaneous placement of the pedicle screws was guided by fluoroscopy.

Outcome Estimates

CRP, NLR, LMR, and PLR were tested respectively on the first day after hospitalization and the first day after the operation. Estimated blood loss (EBL) was calculated by using the methods of Nadler's blood volume formula and Meunier's blood loss formula.[17] The standard for removing the drainage catheter was that the amount of drainage was less than 50 mL in 24 hours. When the patient's preoperative symptoms were relieved, and there were no obvious postoperative complications, they could be discharged from the hospital. We collected the data of VAS and ODI scores starting from the preoperative period and investigated pain scores at 1–13 months postoperative follow-ups.

Statistical Analysis

All statistical analyses were accomplished using the Graphpad Prism software (Graphpad Software, San Diego, California). A Student's t-test (or Fisher's exact test) for independent samples was used to compare continuous variables (age, BMI, operative duration, EBL, length of hospitalization, drainage-tube stay, CRP, NLR, LMR, PLR, VAS, and ODI). The chi-square test was used to analyze whether there was a statistical difference in gender between the two groups. In all analyses, significance was defined as $p < 0.05$.

Results

From July 2022 to July 2023, a total of 38 patients admitted to the Department of Spine, Shandong Provincial Hospital affiliated to the Shandong First Medical University, were enrolled. They included 19 males and 19 females, aged between 34 and 70, with either the L4-5 segment or the L5-S1 segment being considered the cause of most clinical symptoms (Table 1). All patients underwent thorough neurological physical examinations and radiological imaging, which involved digital radiography (DR), computed tomography (CT) and magnetic resonance imaging (MRI).

Among them, 19 patients (11 males and 8 females) were treated by BE-TLIF technique, and the other 19 (8 males and 11 females) were managed by conventional open TLIF. Patients in both groups were not pre-selected, and the type of surgery performed depended on the preferences of surgeons and patients.

Operative Duration and EBL

The mean operative durations were 138.6 ± 31.6 minutes in the open TLIF group and 204.6 ± 49.4 minutes in the BE-TLIF group. The mean operative duration was significantly higher in the BE-TLIF group than in the open TLIF group ($p < 0.001$, Figure 2A, Table 2). The mean amount of EBL was 200.9 ± 211.9 mL in the open TLIF group and 260.7 ±

Table 1 Demographic Information of Enrolled Patients

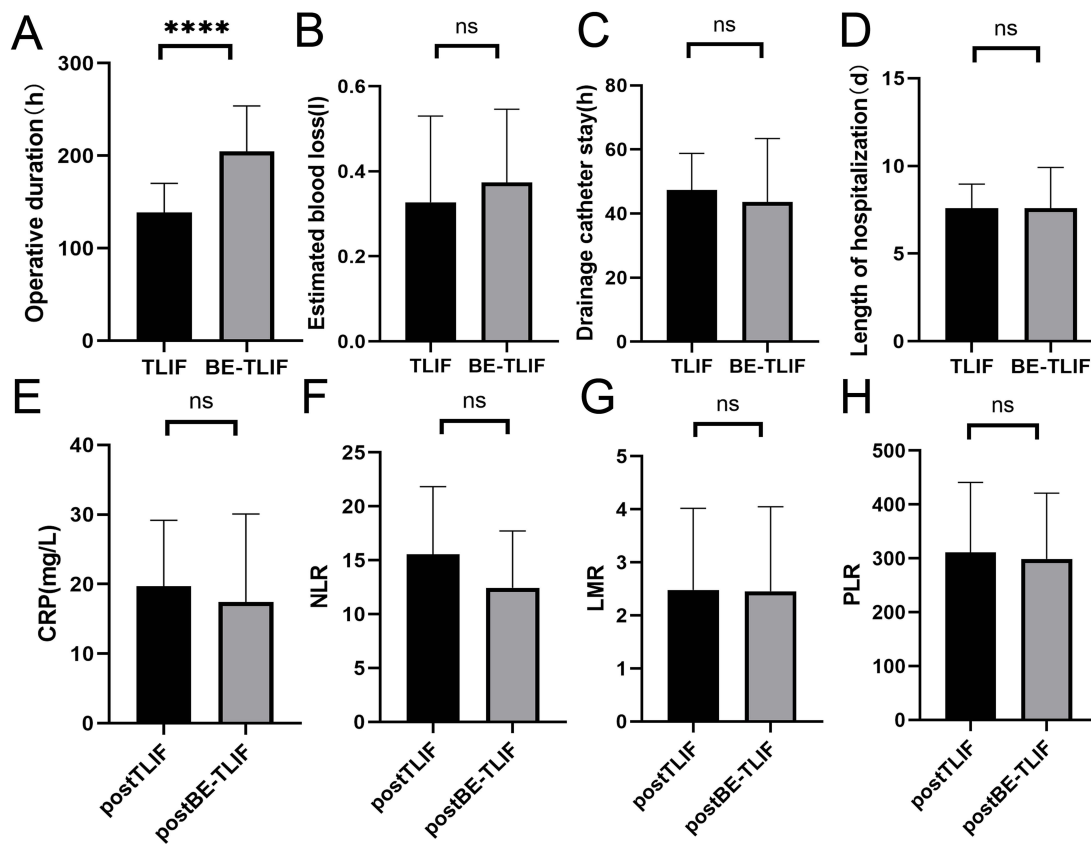|	Open TLIF (n=19)	BE-TLIF (n=19)	p-value
Age (years), range	53.9±11.5, (34–70)	53.2±7.7, (41–65)	0.818
Gender (male/Female)	8/11	11/8	0.517
BMI (kg/m²)	25.04±2.87	26.09±3.87	0.350
Follow-up duration	9.84±3.61	6.84±3.40	0.012
Spinal level fused			
L4-5	12	12	1.000
L5-S1	7	7	

Figure 2 Perioperative parameters and postoperative systemic inflammatory markers between open TLIF and BE-TLIF. (**A**) Operative duration; (**B**) estimated blood loss; (**C**) drainage catheter stay; (**D**) length of hospitalization; (**E**) C-reactive protein; (**F**) neutrophil-to-lymphocyte ratio; (**G**) lymphocyte-to-monocyte ratio; (**H**) platelet-to-lymphocyte ratio.

211.9 mL in the BE-TLIF group. Although there was a trend towards increased blood loss in the BE-TLIF group in comparison with the open TLIF group, the difference was not statistically significant (p = 0.485, Figure 2B, Table 2).

Drainage Catheter Stay and Length of Hospitalization

Drainage catheter stay (47.37 ± 11.41 hours) in the open TLIF group was comparable to that in the BE-TLIF group (43.58 ± 19.86 hours, p = 0.476, Figure 2C, Table 2). Meanwhile, the length of hospitalization (7.58 ± 1.39 days) in the open TLIF group was also similar to that in the BE-TLIF group (7.58 ± 2.34 days, p = 0.999, Figure 2D, Table 2).

Table 2 Perioperative Parameters of Patients Receiving Open TLIF and BE-TLIF

	Open TLIF	BE-TLIF	p-value
Operative duration (min)	138.63±31.59	204.58±49.37	<0.001
Length of hospitalization (d)	7.58±1.39	7.58±2.34	0.999
Drainage catheter stay (h)	47.37±11.41	43.58±19.86	0.476
Estimated blood loss (mL)	320.20±193.04	362.91±168.53	0.485
VAS			
Pre-operative	3.47±1.74	4.42±2.27	0.158
Post-operative	0.58±0.84	0.58±0.69	0.999
ODI			
Pre-operative	23.8±7.89	21.78±8.63	0.456
Post-operative	3.68±6.14	4.64±4.87	0.598

VAS and ODI Scores

The mean preoperative VAS (3.47 ± 1.74) and ODI (23.8 ± 7.89) scores were significantly reduced after open TLIF (VAS: 0.58 ± 0.84, ODI: 3.68 ± 6.14; p < 0.001, Supplementary Table 1). Meanwhile, the mean preoperative VAS (4.42 ± 2.27) and ODI (21.78 ± 8.63) scores were also significantly improved after BE-TLIF (VAS: 0.58 ± 0.69, ODI: 4.64 ± 4.87; p < 0.001, Supplementary Table 2). However, there were no significant differences in the VAS and ODI scores during the perioperative follow-up periods between the two groups (p > 0.05).

CRP, NLR, LMR, and PLR

CRP was significantly increased after both open TLIF (pre-operation, 1.08 ± 0.78 mg/L, post-operation, 19.71 ± 9.49 mg/L; p < 0.001, Figure 3A, Table 3) and BE-TLIF (pre-operation, 1.36 ± 1.46 mg/L, post-operation, 17.44 ± 12.65 mg/L; p < 0.001, Figure 3B, Table 3). Meanwhile, NLR was also significantly increased after both open TLIF (pre-operation, 2.26 ± 1.80, post-operation, 15.55 ± 6.27; p < 0.001, Figure 3C, Table 3) and BE-TLIF (pre-operation, 2.19 ± 1.76, post-operation, 12.44 ± 5.27; p < 0.001, Figure 3D, Table 4). Similar results were obtained for PLR (Figure 3E and 3F, Table 3). Meanwhile, LMR (pre-operation, open TLIF: 6.43 ± 4.33, BE-TLIF: 5.02 ± 1.29, Figure 3G, Table 4) was significantly reduced after surgery (post-operation, open TLIF: 2.48 ± 1.54, BE-TLIF: 2.45 ± 1.59, p < 0.001, Figure 3H, Table 3). Although the mean postoperative CRP, NLR, and PLR seemed lower in the BE-TLIF group than in the open TLIF group, these differences were not statistically significant (p > 0.05, Figure 2E–2H, Table 5).
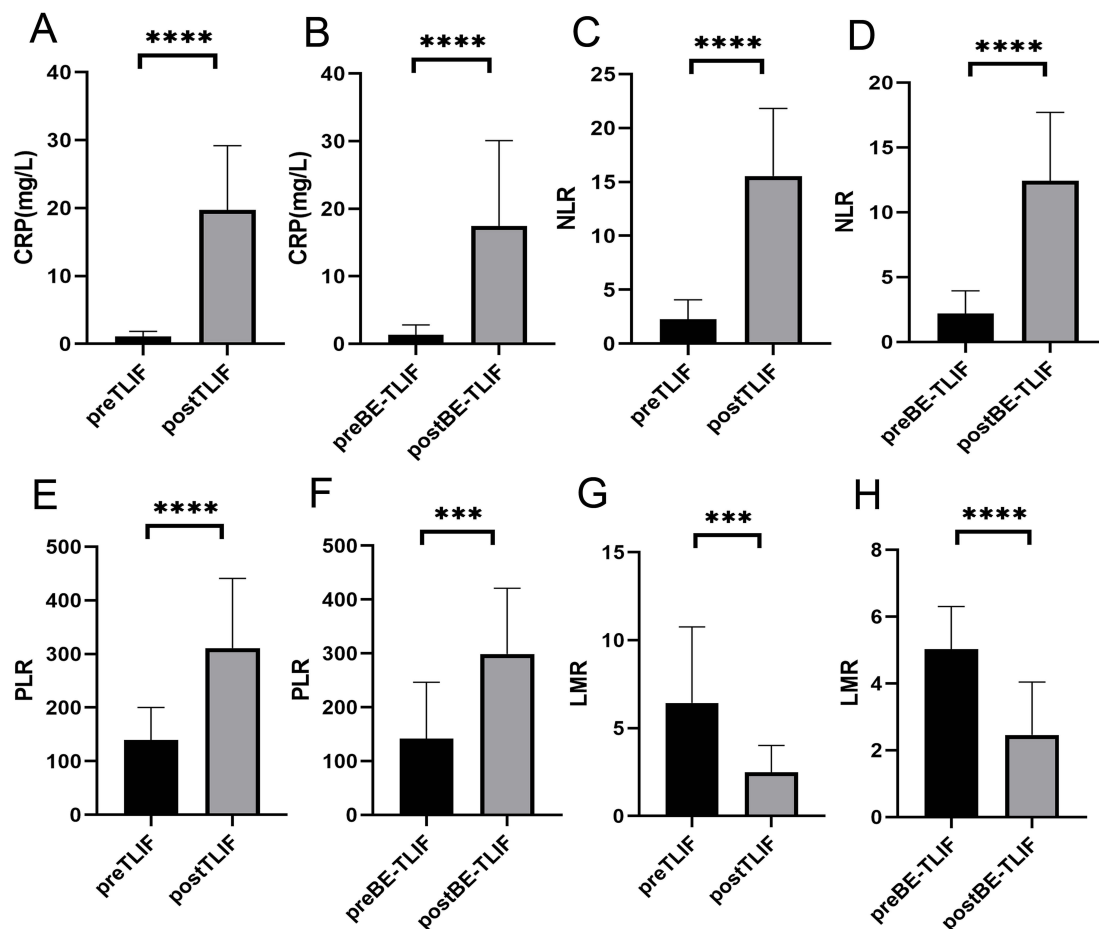

Figure 3 Comparison of the preoperative and postoperative inflammatory markers in open TLIF and BE-TLIF groups. (**A**) CRP in the open TLIF group; (**B**) CRP in the BE-TLIF group; (**C**) NLR in the open TLIF group; (**D**) NLR in the BE-TLIF group; (**E**) PLR in the open TLIF group; (**F**) PLR in the BE-TLIF group; (**G**) LMR in the open TLIF group; and (**H**) LMR in the BE-TLIF group.

Table 3 Perioperative CRP and Systemic Inflammatory Ratios of Patients Receiving Open TLIF

	Pre-open TLIF	**Post-open TLIF**	**p-value**
CRP (mg/L)	1.08±0.78	19.71±9.49	<0.001
NLR	2.26±1.80	15.55±6.27	<0.001
LMR	6.43±4.33	2.48±1.54	<0.001
PLR	139.93±60.22	311.18±130.02	<0.001

Table 4 Perioperative CRP and Systemic Inflammatory Ratios of Patients Receiving BE-TLIF

	Pre-BE-TLIF	**Post-BE-TLIF**	**p-value**
CRP (mg/L)	1.36±1.46	17.44±12.65	<0.001
NLR	2.19±1.76	12.44±5.27	<0.001
LMR	5.02±1.29	2.45±1.59	<0.001
PLR	142.05±104.50	298.76±122.34	<0.001

Table 5 Perioperative CRP and Systemic Inflammatory Ratios of Enrolled Patients

	Open TLIF	**BE-TLIF**	**P-value**
CRP (mg/L)			
Pre-operative	1.08±0.78	1.36±1.46	0.468
Post-operative	19.71±9.49	17.44±12.65	0.536
NLR			
Pre-operative	2.26±1.80	2.19±1.76	0.905
Post-operative	15.55±6.27	12.44±5.27	0.107
LMR			
Pre-operative	6.43±4.33	5.02±1.29	0.183
Post-operative	2.48±1.54	2.45±1.59	0.955
PLR			
Pre-operative	139.93±60.22	139.93±60.22	0.940
Post-operative	311.18±130.02	298.76±122.34	0.764

Case Presentations

Case 1 (isthmic spondylolisthesis)

A 50-year-old female patient suffered from low back pain, pain and numbness of the right leg for five years, and neurological intermittent claudication for two years. There was no obvious remission after medication and physiotherapy. The preoperative CT and MRI demonstrated lumbar isthmic spondylolisthesis with stenosis at the L4-5 level (Figure 4A–4C). First of all, we performed laminectomy and facetectomy on the left side of this level under the biportal endoscope, and then achieved wide decompression of neural structures. Next, a similar decompression was implemented on the right side at the L4-5 level. Thirdly, we conducted interbody fusion under endoscopic vision, similar to open TLIF. Finally, percutaneous pedicle screw fixation was performed. The postoperative DR and CT showed a good reduction in isthmic spondylolisthesis, and the physiological curvature of lumbar vertebrae had been restored to a certain extent (Figure 4D–4F). Postoperatively, the patient's symptoms were significantly improved.

Case 2 (developmental spondylolisthesis)

A 50-year-old female patient presented with low back pain for half a year, and the symptoms worsened 20 days ago. There was no pain or numbness in both lower limbs. After bed rest, medication and physiotherapy, the patient's symptoms were
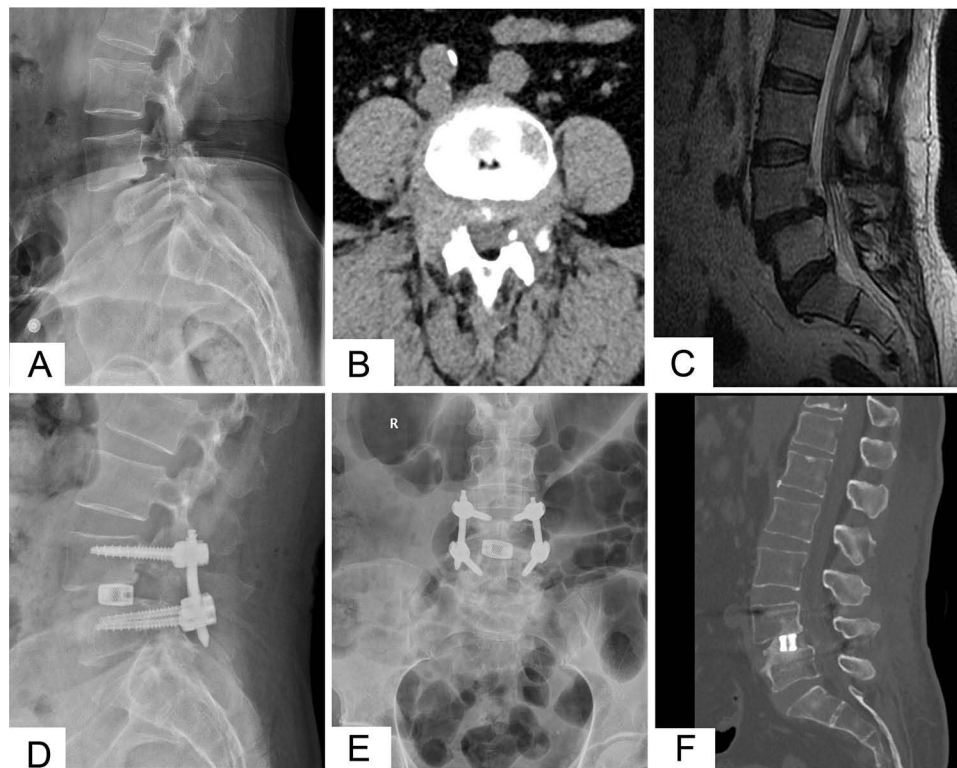
Figure 4 Perioperative imaging examinations in case 1. (**A**) Preoperative lateral DR revealing the 4th lumbar isthmic spondylolisthesis; (**B**) preoperative axial CT showing lumbar spinal stenosis; (**C**) preoperative sagittal MRI showing lumbar spondylolisthesis with stenosis at L4-5 level; (**D**) postoperative lateral DR after BE-TLIF showing a good reduction in isthmic spondylolisthesis; (**E**) postoperative posteroanterior DR showing good pedicle screws fixation and a cage implanted transversely; (**F**) sagittal CT image revealing lumbar interbody fusion with a cage and autologous and allograft bone.

not significantly improved. The preoperative DR, CT and MRI revealed developmental spondylolisthesis at L4-5 (Figure 5A–5C). First of all, we located the surgical target through fluoroscopy and drew the incision marks on the skin of the operative area (Figure 5D–5F). Secondly, spinal canal decompression, nerve roots release, and lumbar interbody fusion were performed under endoscopic vision. With the aid of fluoroscopy, pedicle screws were percutaneously implanted according to the pre-drawn incision marks. The postoperative DR and CT revealed a significant reduction in lumbar developmental spondylolisthesis and the symptom of low back pain was resolved well (Figure 5G–5I).

Discussion

TLIF was first introduced by Harms et al as a safe and effective technique to achieve wide decompression of neural structures and provide stabilization for surgically treated segments since the 1980s.[4] Compared with other types of LIF (eg, PLIF, OLIF, ALIF, and LLIF), TLIF only opens one side of the nerve foramen, which can reduce the damage to important anatomical structures such as nerve roots, spinal dura mater and ligamentum flavum.[3] However, with the rapid development of minimally spine invasive techniques, relatively extensive iatrogenic lumbar soft tissue and muscle injuries associated with open TLIF have made this procedure constantly criticized.[6] BE-TLIF refers to the transforaminal lumbar interbody fusion using a percutaneous biportal endoscopic approach. During the whole surgical procedure, we just need to make two incisions on both sides of the spinous process, including two 1.5-cm transverse oblique ones, and the other two 1.5-cm transverse incisions for inserting pedicle screws with the aid of fluoroscopy.[13,18] As a result, injuries to posterior musculo-ligamentous structures were minimized.[19] However, evidence for the surgical advantages of BE-TLIF is insufficiently reported currently.

Our retrospective case-control study compared open TLIF and BE-TLIF in terms of clinical outcomes and comprehensive inflammatory indicators including CRP, NLR, LMR, and PLR. CRP was named for its ability to precipitate C-polysaccharides from the somatic cells of Streptococcus pneumoniae, and was the first described acute phase protein.
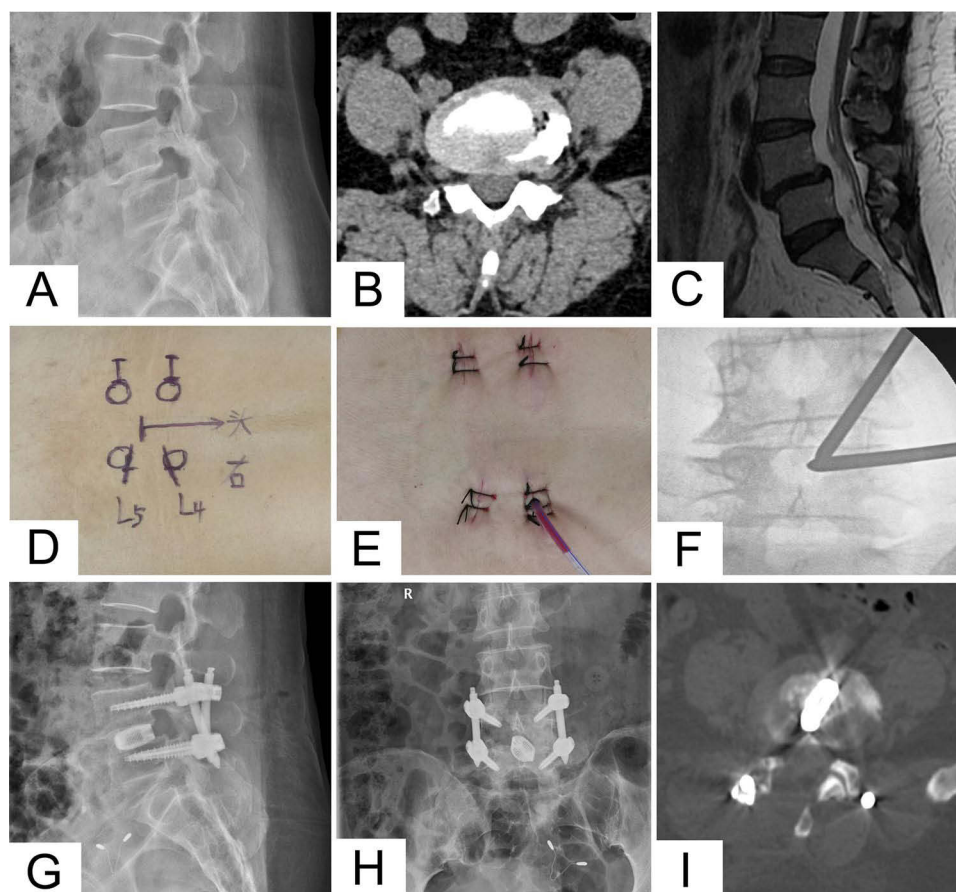
Figure 5 Perioperative imaging examinations, and intraoperative preparation in case 2. (**A**) Preoperative lateral DR showing the 4th lumbar developmental spondylolisthesis; (**B**) preoperative axial CT showing mild lumbar spinal stenosis; (**C**) preoperative sagittal MRI showing lumbar spondylolisthesis at L4-5 level; (**D**) photo image: the 4 circles on the skin represent the projection of the pedicle; the arrow points to the head end; the 2 short lines below the arrow are respectively the working portal and the endoscopic portal, and are also the entry points of pedicle screws; the 2 short lines above the arrow are the entry points of another two pedicle screws; (**E**) photo image: sutured skin incisions and 1 drainage catheter; (**F**) intraoperative fluoroscopy image showing 2 "pencil" guidance rods converged at the surgical target; (**G–I**) postoperative lateral and posteroanterior DR and sagittal CT after BE-TLIF.

CRP is a system marker extremely sensitive to inflammation and most forms of tissue damage.[20] NLR is a marker of extensive secondary damage to brain tissue caused by neutrophils and their products, and also an index of impaired cell-mediated immunity associated with systemic inflammation. Generally speaking, the higher the NLR, the worse the prognosis.[21,22] LMR represents the equilibrium between innate and acquired immunity, and can serve as a straightforward indicator of immune status and inflammation, and a prognostic biomarker. The lower LMR is associated with higher levels of systemic inflammation and vice versa.[23] PLR, like NLR and LMR, also becomes a useful and predictive marker for assessing changes in platelet and lymphocyte counts resulting from acute inflammation and prethrombotic conditions. A high PLR is indicative of a poor prognosis for the patient.[24] These four parameters can be quickly checked and cheaply obtained by routine blood tests in clinical practice.

Surgery is an invasive procedure for the human body, which can be reflected in changes in comprehensive inflammatory indicators.[8] We aimed to make a preliminary judgment about the degree of damage caused by open TLIF and BE-TLIF to the human body through perioperative systemic inflammatory markers. CRP, NLR, and PLR were significantly increased after operation in both groups ($p < 0.05$), while LMR was reduced considerably after surgery ($p < 0.05$). These results showed that both procedures could cause significant changes in comprehensive inflammatory indexes. Although the mean postoperative CRP, NLR and LMR values in the open TLIF group seemed higher than those in the BE-TLIF group, these differences were not statistically significant, which hints at a potential benefit in terms of comprehensive inflammatory response by adapting BE-TLIF.

Due to the space limitations of endoscopic procedures, surgeons need to take more time to deal with some details when performing BE-TLIF. Meanwhile, more radiological imaging assistance was required to place percutaneous screws and cages.[12] Therefore, it is understandable that BE-TLIF has a longer operative duration than open TLIF, which exposes patients to general anesthesia and a minimally invasive state for a long time, and is partially responsible for the increase of systemic inflammatory indexes postoperatively.[25] Although there was no significant difference between the two groups, the mean blood loss (374.1±172.1mL) in the BE-TLIF group seemed to be more than that in the open TLIF group (327.1±203.1mL). In our opinion, during the BE-TLIF procedure, a large amount of normal saline is needed to rinse continuously to maintain a clear endoscopic vision so that coagulation factors in the site of occult blood loss will be washed away before it works.

The mean drainage catheter stay was within 48 hours in both groups. Our standard for removing drainage catheters is that the drainage volume is less than 50 mL in 24 hours. The mean length of hospitalization in the two groups was 7.6 days, including waiting time for postoperative reexamination. According to published clinical articles, the mean duration of hospital stay for patients receiving BE-TLIF ranged from 5.36 to 14.53 days.[26] Enhanced recovery after surgery (ERAS) is a good idea to accomplish early recovery for patients who go through surgeries, so that can cut down the length of hospitalization. Kim et al[12] suggested that BE-TLIF had better clinical outcomes than MIS-TLIF during the early recovery period. Kang et al[11] reported that the one-year follow-up results after BE-TLIF were comparable to those of PLIF and MIS-TLIF procedures. The VAS and ODI scores were also substantially improved after both open TLIF and BE-TLIF. In our study, at the mean follow-ups (8.34 ± 3.78 months) in both groups, the BE-TLIF procedure has similar clinical outcomes with open TLIF surgery. Postoperative complications were not reported in both groups.

Several limitations merit consideration. First, a non-randomized retrospective case-control design was applied, which is a lower level of evidence in comparison with randomized controlled trials. Second, the study was conducted at a single center and only nineteen patients were included in each group. Third, our study started in July 2022, resulting in a relatively short follow-up period. Last but not least, the outcome indicators used in the study were limited. Only four of the most readily available inflammatory markers were compared between the two groups. Despite these limitations, the overall findings of our study hold certain significance for the application of BE-TLIF.

Conclusion

BE-TLIF can achieve direct neural decompression, interbody fusion and internal fixation similar to conventional open surgery. There was no significant difference found between BE-TLIF and open TLIF in terms of systemic inflammatory markers, and clinical outcomes. It is worth noting that BE-TLIF does have a longer operation time, indicating that there is still potential for further improvement in this technique. However, a larger number of patients should be studied with longer follow-up to ascertain the preliminary results obtained in this study.

Data Sharing Statement

Published data compiled for this study are available from the corresponding author at request.

Ethics Approval and Informed Consent

This study was approved by the Medical Ethics Committee of Shandong Provincial Hospital affiliated to Shandong First Medical University. Written informed consent was obtained from all participants to have the case details and any accompanying images published. The study was conducted in accordance with the Declaration of Helsinki Ethical Principles. All information about the participants will be kept strictly confidential.

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Disclosure

The authors declare that they have no competing interests in this work.

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