A personalised approach to spine surgery

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> Addition subchapters have results which are due to the combined efforts of my colleagues but not yet published. I have a statement of contribution stating the work from my self and my colleagues.
> In Chapter 4, this was a collaborative effort between myself and my supervisor A/Prof Ralph Mobbs. I contributed to study conception, data collection, radiographic and clinical follow-up, data analysis and writing the paper, which was 80% of the work in this paper. The paper is drafted but not yet submitted for publication.
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A personalised approach to spine surgery

Thesis Abstract

Background: Anterior lumbar interbody fusion (ALIF) remains one of the mainstay surgical approaches in treating painful degenerative disc disease with or without segmental instability in the lower spine. The risk factors and complication profile for ALIF differs significantly from other established fusion techniques.

Objectives: The goal of the first part of this thesis is to establish the factors associated with long-term clinical outcome (Chapter 2) and short-term perioperative outcomes (Chapter 3) following ALIF. Chapter 4 focuses on the long-term radiographic evidence for biomaterial alternatives for ALIF implants, namely titanium (Ti)-coated PEEK integrated cages.

Methods and Results: From a prospective cohort analysis of 147 patients undergoing ALIF, elderly age (≥64 years old) was associated with an increased rate of subsidence but does not affect clinical outcomes. Obesity was not associated with postoperative complications or follow-up patient-reported outcomes. Failed fusion was significantly higher for smokers, and they were significantly more likely than non-smokers to experience postoperative complications such as pseudoarthrosis. To assess risk factors for perioperative complications and readmissions after ALIF, the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database was analysed. ALIF was associated with prolonged length of stay and higher rate of return to operating theatre compared to posterior lumbar fusion. Obesity and alcohol intake increased the risk of 30-day readmissions. Discharge to non-home destination following ALIF was independently associated with wound complications and venous thromboembolism. Finally, a prospective follow-up study was performed to determine the long-term radiographic outcome following ALIF using Ti-coated PEEK cages with allograft and INFUSE. Effective fusion was achieved at up to 24-month follow-up for various indications including degenerative spine/disc disease, low grade lumbar isthmic spondylolisthesis, spondylotic radiculopathy and discogenic low back pain.

Conclusions: Collectively, this thesis highlights the importance of personalising the care of an ALIF surgery patient, through identification and optimization of individual risk factors for short-term and long-term outcomes, as well as through choice of implant biomaterial and design.

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This thesis and its contained research work could not have been done without the significant support and help from mentors, my family, and friends alike.

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Abstract

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the long-term radiographic outcome following ALIF using Ti-coated PEEK cages with allograft and INFUSE. Effective fusion was achieved at up to 24-month follow-up for various indications including degenerative spine/disc disease, low grade lumbar isthmic spondylolisthesis, spondylotic radiculopathy and discogenic low back pain.

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Chapter 1

Introduction

Acknowledgements

A/Prof Ralph Mobbs and Prof Bill Walsh have been instrumental to teaching me the basics, the complexities and the nuances of the theory of spinal surgery and biomechanics. The introduction comprises these teachings, my own readings and interpretation of current literature. Some descriptions and figures from the Introduction are adapted from a prior review paper (below) which I co-authored, and these have been referenced accordingly in-text.

Mobbs RM, Phan K, Malham G, Seex K, Rao PJ. Lumbar interbody fusion: techniques, indications and comparison of interbody fusion options including PLIF, TLIF, MI-TLIF, OLIF/ATP, LLIF and ALIF. J Spine Surg 2015;1(1):2-18.

Background

Lumbar degenerative spinal disease is a common and debilitating condition, causing significant pain and distress to patients and represents a significant burden on our healthcare system. The prevalence of low back pain due to lumbar spondylosis is 3.6% worldwide(1), and accounts for eighty-three million quality-adjusted life years affected by disability(2). With increasing population sizes and prolonged life expectancy, the proportion of patients with degenerative spinal disease is expected to rise. Correspondingly, it has been observed that the lumbar surgery rates and lumbar fusion procedures have increased(3). In Australia, the rate of lumbar fusion is 26 per 100 000 adults and is the fourth most costliest surgical operation at annual cost of $650 million(4, 5). Furthermore, the development of less invasive approaches and newer techniques and instrumentation have meant that fusion operations have become available in a more diverse patient population including more frail or less healthy patients with more comorbidities. The development of novel technologies and techniques should be matched with corresponding outcomes research, which will dictate and refine clinical practice to maximise patient outcomes. Here, we review the developments in techniques used in lumbar fusion, the historical evolution of ALIF implant designs, and current evidence for surgical outcomes and risk factors, which serves as the background to the objectives of this thesis.

The aims of this thesis are to determine how patient and surgical factors in the preoperative, surgical, and postoperative stages influence both short-term and long-term outcomes. Specific goals include:

- Determine effect of preoperative patient factors (age, obesity, smoking status) on long-term follow-up clinical outcomes in a homogenous ALIF cohort receiving integrated cages.
- Determine patient and operative factors contributing to 30-day readmission rates, discharge to non-home destination, and complications following anterior lumbar fusion.
- Investigate long-term radiographic outcome and complications in cohorts of patients undergoing ALIF surgery with titanium (Ti)-coated PEEK cages.

Approaches used in lumbar interbody fusion

Lumbar interbody fusion (LIF) is a well-established technique for several spinal conditions including degenerative disease, deformity, traumatic injuries, infective and neoplastic pathologies. Compared to traditional on-lay posterolateral fusion (PLF) approaches, LIF involves resection of the intervertebral disc and insertion of an implant or graft to assist fusion and hence stabilisation across the vertebral joint. The goal of a LIF procedure is to increase the fusion rate, which may indirectly alleviate neurological symptoms via stabilisation of spinal elements. Although the concept of spinal instability has existed for years since being described in ancient Indian and Egyptian texts(6-8), surgical intervention for this have only been reported since the late 19th century with the advent of anaesthesia and antisepsis techniques.

The history of PLF dates back to 1911 when Albee demonstrated the potential of this approach in a patient with destructive tuberculosis of the spine (Pott's disease)(9). Bone graft was harvested from the patient's tibia, which was then morselised into fragments then packed between adjacent decorticated spinous processes. Over time, the bone graft ossified and immobilised the symptomatic motion segment, thereby improving the patient symptoms. During these years, this technique was adopted and adapted by a number of surgeons, but notably used by Hibbs and Swift in 1929 for degenerative spine conditions(10). A paradigm-changing publication by Mixter and Barr in 1934(11) demonstrated that sciatica and back pain symptoms were not neoplastic in aetiology but rather due to disc herniation causing nerve root compression. They concluded that optimal treatment involved stabilisation across the diseased motion segment. This led to the era of fusion techniques in spinal surgery as a key technique.

Up to this point, the PLF technique was limited to posterior elements, including transverse processes, facets, and laminae but not between vertebrae, and thus only limited stabilisation was provided. It was later in 1994 that the concept of interbody fusion or LIF was pioneered by Briggs and Milligan(12). They described a patient where the bony fragments from the laminectomy was used to pack out the space between the vertebrae, which over time fused the adjacent vertebrae. This is known as one of the initial posterior lumbar interbody fusion (PLIF) procedures. This was further improved upon by Cloward in 1953(13), where a block of bone from the iliac crest was harvested and inserted in the intervertebral space.

Interbody fusion techniques were further enhanced at the end of the 20th century. In 1988, Bagby(14) used a stainless steel cylinder with grounded harvest packed inside and around an interbody device, which produced excellent restoration of disc height and indirect nerve root decompression. However, this approach was limited by subsidence likely due to significant differences in the modulus between natural bone and the stainless steel cage. Subsequently, Brantigan et al(15) proposed the use of synthetic interbody devices, which in this case was made of carbon fibre-reinforced PEEK which is radiolucent and has excellent biocompatibility. Carbon fibre-reinforced PEEK also has a modulus of elasticity (18 GPa) closer to that of bone (10-30 GPa) compared to alternative cage materials such as titanium (110 GPa)(16), which aimed to reduce subsidence rates(17). Since then, there has been an exponential increase in developments of synthetic cages in terms of design and materials used.

Traditional approaches for LIF

LIF involves placement of a cage, spacer or structural graft within the intervertebral space after disc removal and preparation of the vertebral endplates. Compared to the prior approach of posterolateral on-lay fusion, interbody fusion does not have the associated complications of donor site graft harvesting and has lower rates of failed fusion(18). Currently, the key approaches to LIF includes posterior lumbar interbody fusion (PLIF), transforaminal lumbar interbody fusion (TLIF or MI-TLIF), oblique lumbar interbody fusion/anterior to psoas (OLIF/ATP), anterior lumbar interbody fusion (ALIF) and lateral lumbar interbody fusion (LLIF)(Figure 1.1)(19). These typically can be performed using an open, mini-open or minimally invasive (MIS) access, although some select expertise and academic centres have reported using endoscopic access(20-23). Although there have been numerous attempts to compare radiological and clinical outcomes amongst these approaches, the literature is heterogeneous in terms of patient selection criteria, surgical technique and experience, and instrumentation used, and as such, published evidence for one centre is not necessarily directly translatable to other operators. As such, current evidence can only be interpreted to a limited extent and there are no clear major differences in follow-up outcomes. Rather the selection of surgical approach tends to be based on each surgeon's own training, technical expertise, and patient anatomy in the surgical corridor of access. However with rising healthcare costs and increasing expectations from patients and paradigm shift towards value-based care, there is an impetus to understand what factors contribute to not only long-term clinical outcome, but also short-term hospital stay, perioperative complications and rates of return to work. This has led to increasing innovation in surgical techniques which aims to reduce iatrogenic injury and postoperative morbidity. The following section outlines

the main surgical approaches available for lumbar fusion and their relative benefits and risks.

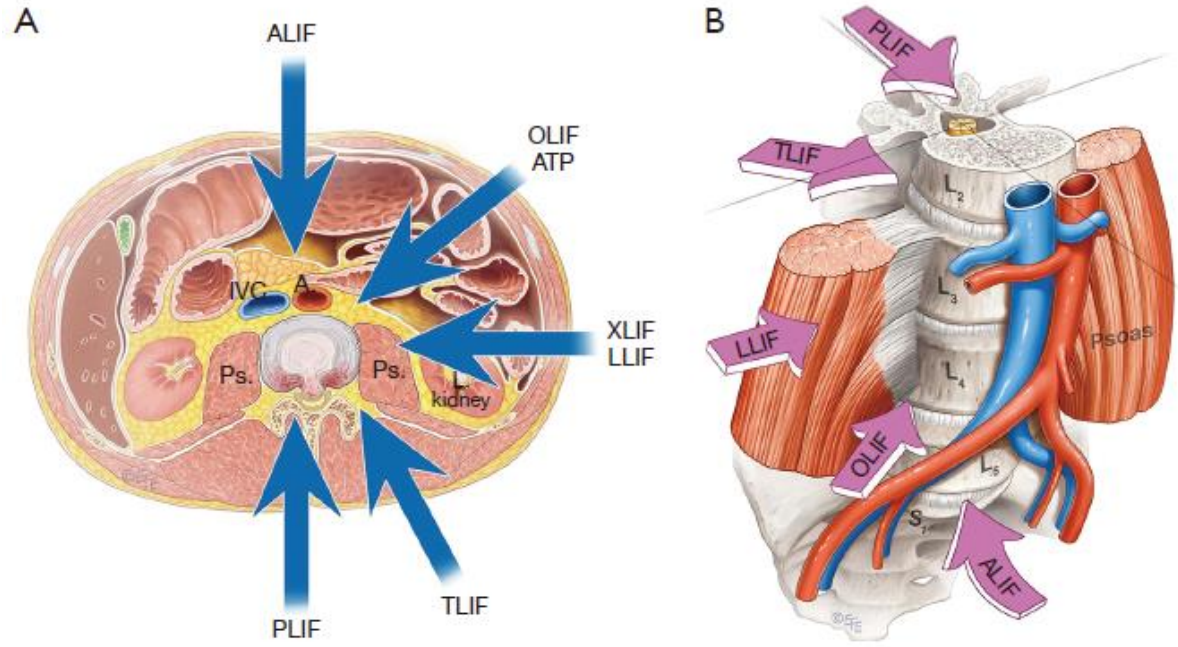

Figure 1.1. (A) Surgical approaches to the lumbar spine for interbody fusion techniques. The blue arrows demonstrate the key interbody fusion approaches, including anterior (ALIF), lateral or extreme lateral interbody fusion (LLIF or XLIF), oblique lumbar interbody fusion/anterior to psoas (OLIF/ATP), transforaminal (TLIF or MI-TLIF), and posterior (PLIF); (B) An oblique view of the spine, demonstrating the surgical approaches (purple arrows) to the lumbar spine for interbody fusion techniques. Figure reproduced from Mobbs et al (19).

Posterior lumbar interbody fusion

Briggs and Milligan in 1944(12) reported one of the earliest descriptions of PLIF. A posterior approach is used to gain access to the intervertebral disc and space (Figure 1.2). The patient is initially positioned in a prone position on an Andrews or Jackson table. For open-PLIF, a midline approach with bilateral muscle strip dissection is used, whereas for a mini- or minimally invasive PLIF, a paramedian Wiltse muscle splitting can be used to access the posterior spinal column. Once the levels of surgery (L1-S1) are identified, the surgeon should next identify the spinous process and laminae of the index level. A laminotomy is then performed medially to the facet, followed by retraction of the dura to exposure the surgical corridor to the disc space. The endplates and disc space is then prepared, to allow insertion of the interbody device, ideally flush to the vertebral endplates. PLIF can be further augmented with pedicle screw fixation to assist with disc space retraction or supplemental posterolateral bone grafting, both which may further add stability and improve fusion. In PLIF, the fusion is achieved at the intervertebral joint site (in contrast to PLF with posterolateral fusion), which allows for reconstruction of both anterior and posterior spinal columns biomechnically. This environment is more conducive to bone healing and fusion relative to PLF(24).

Suitable indications for PLIF includes: degenerative conditions requiring fusion, segmental instability (Figure 1.3), recurrent disc herniation, symptomatic spinal stenosis and pseudoarthrosis. Relative contraindications for PLIF typically include extensive epidural scarring, arachnoiditis, and active infection.

The advantages of PLIF include:

- Being a common and well-used approach by many surgeons, meaning that surgical trainees can easily gain training and expertise in this approach to lumbar fusion.
- Excellent visualization of the nerve roots without compromising blood supply to the graft(25).
- Effective restoration of intervertebral disc height, which promotes neural decompression whilst maintaining posterior spinal column support.
- Complete removal of facet joint is not necessary in this approach, which preserves stability at the intervertebral level(26).
- A 360-degree anterior and posterior fusion can be achieved through a single posterior incision, which minimises iatrogenic trauma to muscles.

The disadvantages of PLIF include:

- Paraspinal iatrogenic injury associated with prolonged muscle and thecal sac retraction(27)
- Less effective coronal and lordosis correction relative to anterolateral approaches.
- Endplate preparation may be more challenging compared to anterior fusion approaches.
- Retraction injury of nerve roots causing fibrosis and chronic radiculopathy(28, 29)

Figure 1.2. Posterior lumbar interbody fusion (PLIF). (A) Exposure of the interbody space, with retraction of the nerve root and dural sac. (B) Insertion of the PLIF interbody device. Bilateral insertion of cages shown and graft can be placed. (C) Pedicle screws with rods can be used to adjust lordosis as required and distract disc space. (D) The final instrumentation reinforces the joint until biologic fusion is achieved. Image and legend from Yashar et al.(30)

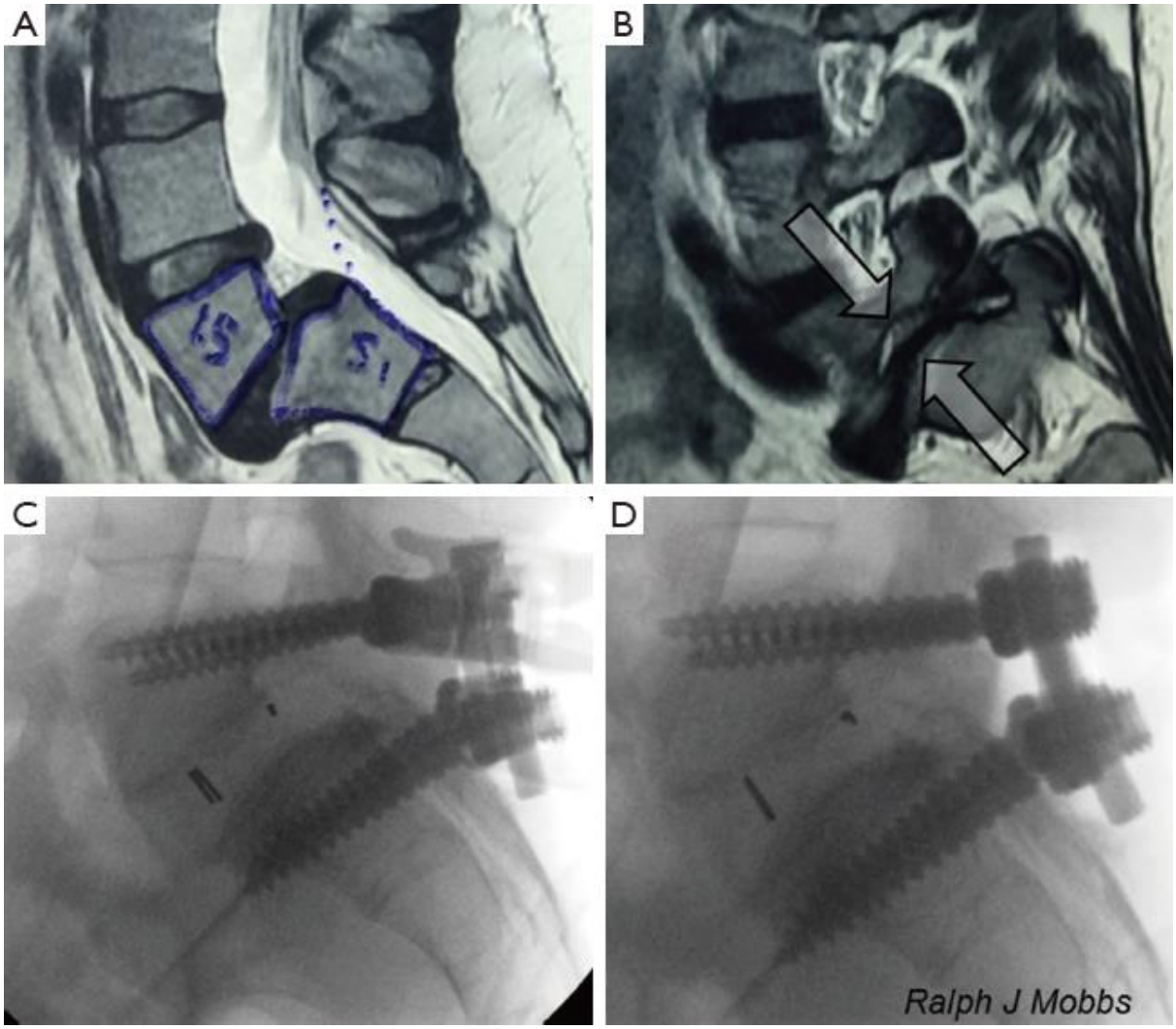

Figure 1.3. L5/S1 posterior lumbar interbody fusion (PLIF). An example case of high grade isthmic spondylolisthesis. The patient presented with bilateral L5 radiculopathy. (A) T2 weighted magnetic resonance imaging (MRI) demonstrated Grade II spondylolisthesis. (B) A different sagittal frame demonstrates severe foraminal stenosis with L5 nerve impingement. (C) Intraoperative imaging following bilateral pars and lamina resection, followed by initial insertion of the interbody cage (Vigor PLIF, A-Spine ASIA, Taiwan) and pedicle screw fixation (ES-2, Stryker, USA). Note that there is still considerable "overhang" of the L5 vertebrae on S1. (D) Reduction manoeuvre and final result. Figure and legend from Mobbs et al.(19)

Transforaminal lumbar interbody fusion

Surgeons were concerned with the considerable dural retraction required in the PLIF approach, which could result in dural tears, nerve root injury and epidural fibrosis(31, 32). This led to the development of an alternative approach with lesser requirement of neural retraction and thus nerve injury, which is now termed TLIF. A direct, unilateral access to the intervertebral foraminal space is used (Figure 1.4), whereas classic PLIF involves wide laminotomy with resection of ligamentum flavum. By opening the neural foramen on one side only, this reduces the risk of injury to important structures in this area such as nerve roots, dura and ligamentum flavum. A narrow one-sided approach also reduces dissection of paraspinal muscles required and maintains its structural integrity. Like other fusion procedures, TLIF can be performed via an open procedure or MIS "mini-open" technique with smaller incision sizes and use of microscopy. In some select centres, an endoscopic approach has also been described, however this is not routine.

For the TLIF approach, the patient is positioned prone after anaesthesia. A midline incision is performed for open-TLIF or paramedian incision can be used for mini-TLIF, to allow access to the disc space at levels L1-S1. The spinal canal is entered via a unilateral laminectomy and inferior facetectomy, discectomy is subsequently performed across to the opposite side. Like in PLIF, distractors and pedicle screws can be used to assist intervertebral space distraction. Single or double intervertebral body cages can be inserted.

Suitable indications for TLIF include degenerative pathologies, such as broad-based disc prolapses, degenerate disc disease, recurrent disc herniation, pseudoarthrosis, and symptomatic spondylosis. Relative contraindications are similar to PLIF and include

extensive epidural scaring, arachnoiditis, active infection, conjoined nerve roots and osteoporotic patients.

Advantages of TLIF include:

- Relatively easier access to posterior structures including the lamina, ligamentum flavum, facet joints.
- The pars are regularly removed, where by a "banana" shaped cage can be inserted. The same cage may be used in select PLIF cases but with more difficult since the pars is usually kept intact with the posterior approach.
- Preserves ligamentous structures and midline muscular structures via its unilateral approach, which may assist with biomechanical stability. In TLIF, a single unilateral incision is able to provide bilateral anterior column support(33-35)
- Opportunity to use a minimally invasion incision in combination with microscope magnification to further minimise associated muscle injury, bleeding risk and thus improved postoperative recovery.

Disadvantages of TLIF:

- May be associated with significant paraspinal iatrogenic injury with prolonged muscle retraction.
- May be more difficult to restore coronal imbalance and restore lordosis(28, 36, 37) compared to anterolateral approaches.
- More difficult endplate preparation relative to anterior approaches.

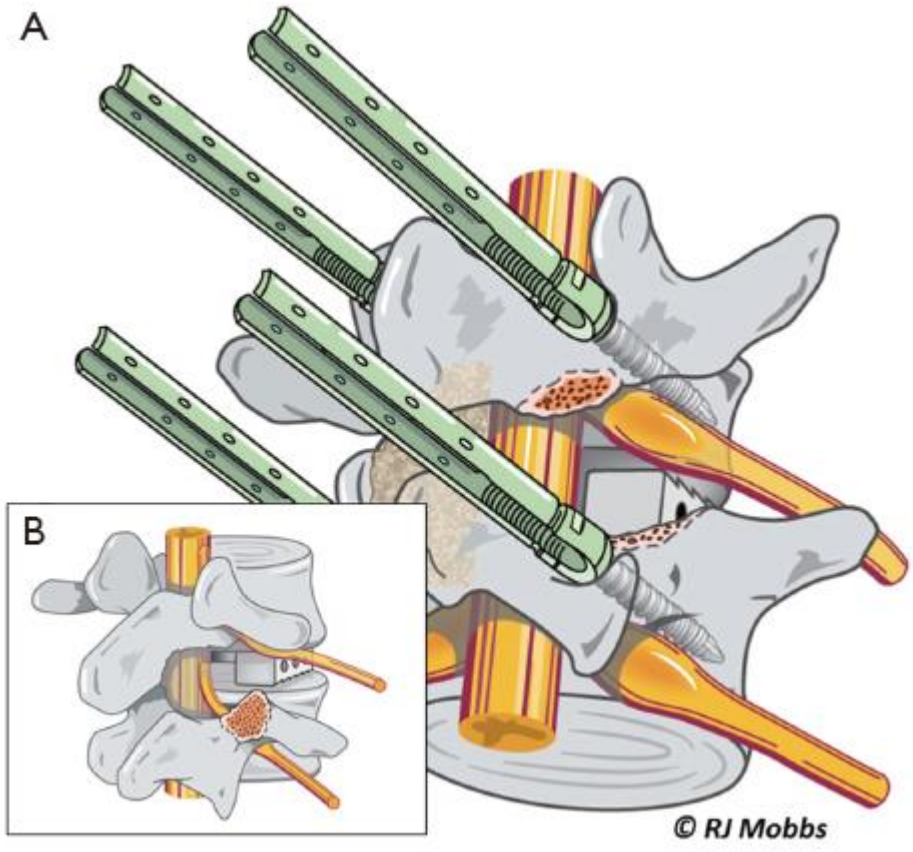

Figure 1.4. Transforaminal lumbar interbody fusion (TLIF). (A) TLIF with percutaneous screws offers a minimally invasive option for interbody fusion. Schematic also shows additional pedicle screw fixation using the ES-2 system (Stryker, USA). (B) Facetectomy followed by insertion of an interbody device can be performed via either a midline or paramedian approach. Figure reproduced from Mobbs et al.(19)

Lateral Lumbar interbody fusion

Ozgur et al in 2006 described the LLIF or extreme lateral interbody fusion (XLIF) technique(38). LLIF involves accessing the disc space via a lateral retroperitoneal, transpsoas corridor. LLIF is appropriate to access pathologies at levels T12/L1 to L4/L5. This approach is not suitable at level L5/S1, as the iliac crest obstructs the surgical corridor. Additionally, when the lumbar plexus courses anteriorly and the iliac vessels course more laterally, there is an increased risk of injury to these structures with a lateral approach.

To perform LLIF, the patient is positioned laterally, either left or right side up depending on surgeon's preference and ease of access (Figure 1.5). It is important to note that the laterally placed patient is inherent unstable, the patient should be secured for example with adhesive tape. The position and angulation of the intervertebral disc can be viewed on image intensification. This will help the surgeon guide the initial small lateral incision. Blunt dissection is performed through the external and internal oblique muscles and transversalis. Once the retroperitoneal space is accessed, the psoas muscle is blunt dissected which then allows access to the disc space. Neuromonitoring is essential for the transpsoas access to the disc space.

LLIF can be used in various degenerative disc disease pathologies, deformity correction of the sagittal and coronal planes, degenerative spondylolisthesis and adjacent segment disease. However, the LLIF approach may not be suitable for severe central canal stenosis, bony lateral recess stenosis and high-grade spondylolisthesis, where additional posterior decompression is required.

Advantages of LLIF:

- A minimally invasive muscle-splitting approach can be used to reduce surgical trauma and improve postoperative mobilisation.
- Aggressive deformity correction can be achieved with high fusion rates and comprehensive disc space clearance(18, 39).

Disadvantages of LLIF:

- Potential risks of lumbar plexus, psoas muscle and bowel injury, particularly at the L4/5 level. This may result in hip-flexion weakness, lumbosacral plexopathy and neurological injury(40-45).
- Vascular injury, if it occurs, may be difficult to control and represents another risk of the lateral transpsoas approach(46).

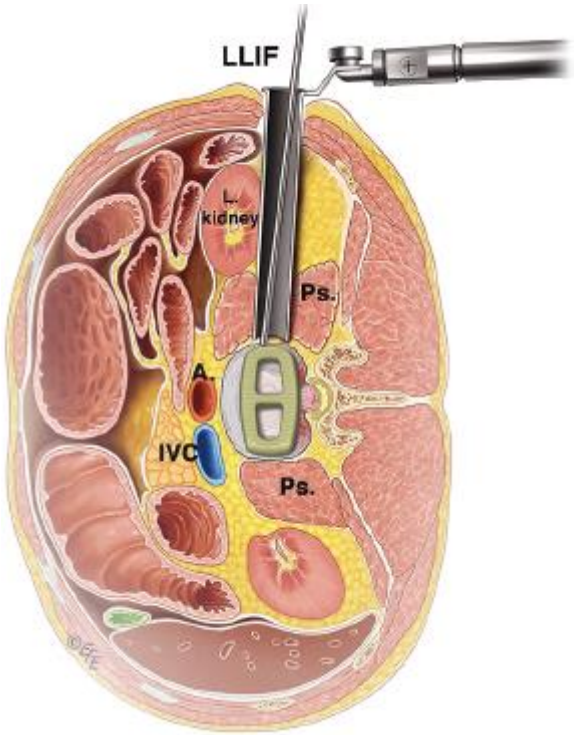

Figure 1.5. Lateral lumbar interbody fusion (LLIF). The transpsoas corridor is used to access the disc space via a retroperitoneal approach performed with the patient in the lateral position. Figure reproduced from Mobbs et al(19).

Oblique lumbar interbody fusion / anterior-to-psoas approach

The OLIF or anterior-to-psoas (ATP) approach was first described by Michael Mayer in 1977(47). The oblique approach takes advantage of the corridor between the peritoneum and psoas muscle. Similar to a lateral approach, the oblique approach avoids posterior surgery, laminectomy, facetectomy or stripping of spinal or paraspinal musculature. However, in contrast to the lateral approach, the OLIF technique does not dissect or traverse the psoas muscle(48, 49).

The patient is initially positioned laterally, similar to the LLIF approach. Image intensification is used to determine the position and angulation of the target disc space, which guides the surgeon's initial lateral and paramedian incision. The external oblique, internal oblique, and transversalis muscles are bluntly dissected to access the retroperitoneal space. With gravity assisting, the peritoneal sac is mobilised anteriorly, whilst the psoas muscle is retracted posteriorly but not dissected. This allows an oblique corridor to the disc space (Figure 1.6). Neuromonitoring is not necessary as the anatomical corridor anterior to the psoas muscle is used for access. The OLIF technique is suitable for levels L1-S1(50, 51).

Indications for OLIF include all degenerative indications. Similar to LLIF, OLIF is an effective choice for sagittal and coronal deformity correction, especially lumbar degenerative scoliosis with latero-listhesis. The stand-alone OLIF approach is contraindicated in patients requiring posterior decompression such as with severe central canal stenosis and high-grade spondylolisthesis.

Advantages of the OLIF approach:

- Facilitates minimally invasive surgery with rapid postoperative mobilization.

- Allows for aggressive deformity correction, high fusion rates with comprehensive disc space clearance (52, 53)
- Lumbar plexus and psoas injury are unlikely as dissection is performed anterior to the psoas.

Disadvantages of OLIF approach:

- Potential risks involved with OLIF surgery include sympathetic dysfunction and vascular injury(49, 54).

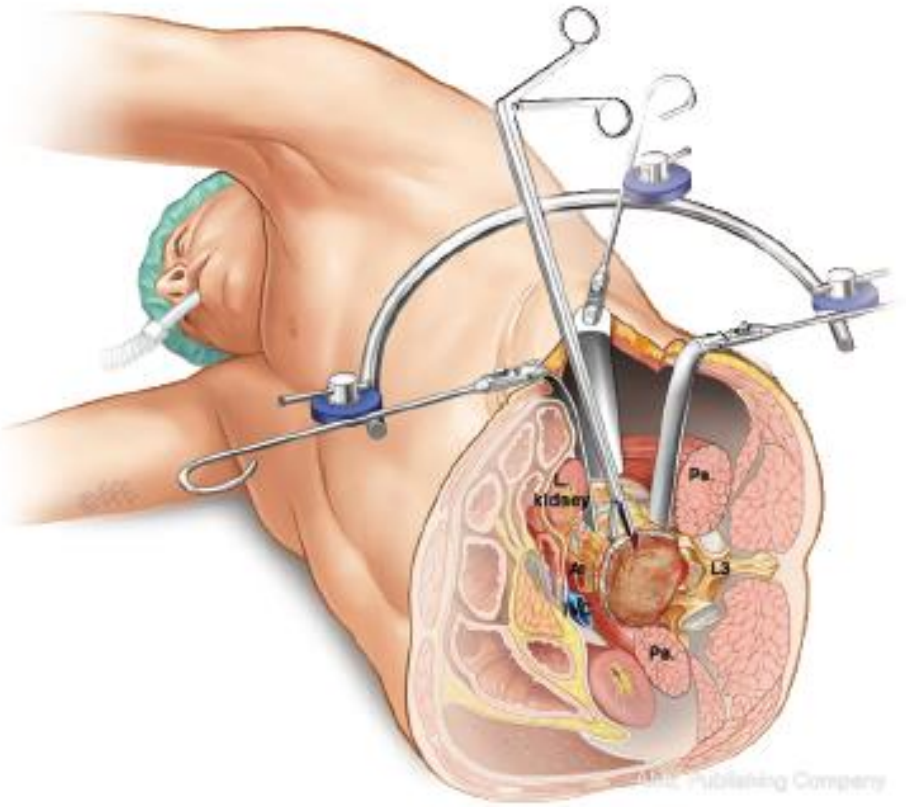

Figure 1.6. Oblique lumbar interbody fusion/anterior to psoas (OLIF/ATP). Lateral position for disc exposure anterior to the psoas. The exposure can be expanded via posterior retraction of the psoas to widen the corridor. Figure reproduced from Mobbs et al(19).

Anterior lumbar interbody fusion

In 1932, Capener first used an anterior approach to insert a bone graft spacer for 32 spondylolisthesis patients(55). Although met with some resistance first due to the risk of morbidity, this approach later gained more acceptance as a number of surgeons including Mercer(56), Friberg(57) and Merled'Aubigne(58) reported it to be effective for spondylolisthesis due to its biomechanical advantages. The retroperitoneal approach was suggested by Iwahara(59) and in 1948, Lane and Moore(60) were the first to utilize ALIF along with allogenic bone graft for lumbar degenerative disc disease and reported successful rates of 94% and fusion rates of 54%. Since then, the ALIF technique has evolved in terms of indications, technique, cage and instrumentation design and materials used.

One of the key unique features of the anterior approach is that it allows easier and greater access to the ventral surface of the disc space (Figure 1.7). This in turn facilitates more optimal discectomy and endplate preparation, as well as direct insertion of larger interbody devise.

The patient is prepared and positioned supine. It is recommended that access is performed by an experienced vascular surgeon. An abdominal midline, paramedian (all levels) or Mini-Pfannenstiel (L5/S1) incision with a retroperitoneal corridor is performed. The anterior vascular structures and peritoneum are mobilised laterally, which allows access anteriorly to the target disc space. The ALIF approach is suitable for levels L4/L5 and L5/S1. At levels L2/3 and L3/4, the risk of abdominal injury is significantly higher as extensive retraction of the peritoneum and kidney (L2/3) are required. Additionally there is also the potential for superior mesenteric artery thrombosis with mobilisation of the vascular structures at these higher levels, although the risk of this event is rare.

Indications for ALIF include: degenerative disc disease, discogenic disease and revision of failed posterior fusion. Contraindications of ALIF include significant prior abdominal surgery with adhesions or adverse vascular anatomy, severe peripheral vascular disease, solitary kidney on the side of exposure, spinal infection and high-grade (Grade 2+) degenerative spondylolisthesis in the absence of posterior fusion. Isthmic spondylolisthesis at L5/S1 is a relative contraindication and should include posterior fixation in combination with the ALIF technique.

Advantages of ALIF include:

- Allows direct midline view of the disc space and extensive lateral exposure of the vertebral bodies.
- This permits efficient disc space clearance with rapid endplate preparation.
- Anterior access allows maximization of the implant size and surface area, which facilitates aggressive correction of lordosis and foraminal height restoration(34).
- This may lead to high fusion rates with ample disc space preparation.
- ALIF also allows sparing of posterior spinal muscles and anterolateral psoas muscles, which may reduce postoperative pain and disability.

Disadvantages of ALIF include:

- Approach-related complications such as retrograde ejaculation, urinary incontinence, visceral and vascular injury(35, 61-63).
- Levels above L4–L5 are obscured by vascular anatomy, which may require extensive retraction of peritoneal and renal structures(26). Some(64) have reported being able to routinely approach the lumbar spine at levels L2-L3 to L5-S1 using Steinmann and Kirschner wires. These instruments are smaller relative to traditional ALIF retractors (Synframe, Condor, Thompson), have high

radial strength, and are low cost(64). This allows the surgeon to work with smaller incisions with adequate strength to maintain exposures for higher lumbar spinal levels(64).

- Additional posterior fixation may be required for 360^{o} support, such as for isthmic spondylolisthesis at L5-S1(65).

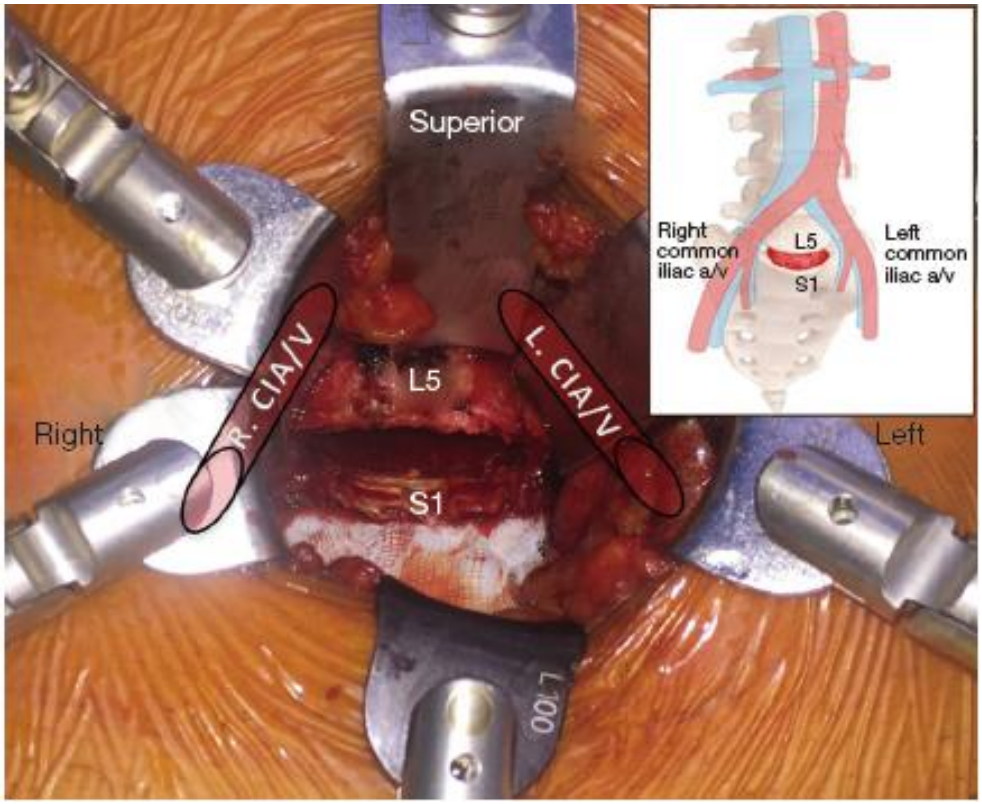

Figure 1.7. L5/S1 anterior lumbar interbody fusion (ALIF). Exposure achieved during the anterior approach, after the peritoneum is moved laterally. The working corridor at L5/S1 is shown, which is typically found between the iliac vessels below their bifurcation point. Excellent access to the intervertebral disc space is demonstrated at this level. At L4/L5 and higher levels, exposure is limited by the extent of mobilisation of the anterior vascular structures. Figure reproduced from Mobbs et al(19).

Selection of lumbar fusion approach based on technical and anatomical considerations

Based on the anatomy encountered by each surgical approach and the extent of resection, distraction and posterior fixation required, the following recommendations for selection of surgical approach are proposed.

T12/L1 and L1/L2

- ALIF is not recommended at this level due to significant vascular structures and peritoneum midline which are difficult or potentially unsafe to mobilise
- A posterior approach with PLIF/TLIF is possible in some cases. However, surgeons should be wary of the cord or conus in this area. This may impede efforts to retract dura, particularly with a midline approach.
- LLIF is a good option as it avoids the anatomical challenges of anterior vascular structure and cord posteriorly.
- These levels are also challenging due to the diaphragm insertions. The right crus of the diaphragm inserts into L3, and left crus into L2. Their tendinous insertions are usually taken down for exposure of L2-3.

L2/L3 and L3/L4

- ALIF is not routinely recommended here as the anterior vascular anatomy remains challenging to expose and retract (the level of vessel bifurcation occurs below). Some selected cases may be performed however the exposure by an experienced vascular surgeon is highly recommended.

- PLIF/TLIF/LLIF/OLIF are reasonable fusion options. For patients who require significant deformity correction, LLIF/OLIF may be preferred for extra antero-lateral support during reconstruction.

L4/L5

- PLIF/TLIF can be routinely performed at these levels
- For patients requiring more lordotic correction, ALIF may be a preferred option. It allows for greater access to the disc space, more endplate preparation, and insertion of larger interbody cages, thus achieving greater disc height restoration. The vascular anatomy at these levels can be mobilised more easily. Exposure with an experienced vascular surgeon is still recommended.
- OLIF/LLIF are also reasonable options. With the LLIF approach however, the surgeon should be wary about the increased risk of lumbar plexus and psoas injury. The psoas muscle belly here harbours constituents of the lumbosacral plexus and may be inadvertently injured during manipulation, resulting in thigh paraesthesia or hip flexion weakness. Neuromonitoring should be used for LLIF.

L5/S1

- ALIF is a reasonable option at this level. The anterior vascular vessels have already bifurcated at this level, and thus more easily and safely manipulated. The disc space can be cleared effectively. Larger sized cages can be placed for effective disc height restoration and lordotic correction. Surgeons should be aware of the potential for superior hypogastric sympathetic plexus injury.
- PLIF and TLIF are reasonable options too, particularly for pathologies with an element of canal stenosis or disc herniation which can be removed more easily posteriorly.

- OLIF appears to be a promising approach at this level. With an oblique approach, the peritoneum falls away from the oblique corridor due to gravity. This may result in less retraction stress for prolonged operative durations compared to a supine ALIF approach. A laterally placed access incision also avoids dissection of the midline rectus.
- LLIF is not appropriate at this level due to the iliac crest which inhibits access to the disc space laterally.

Multi-level

- Usually involves degenerative pathologies across multiple levels or considerable deformity correction across short or long segments.
- A combination of anterior and posterior reconstruction would be suitable. As such a combination of ALIF ± PLIF/TLIF/LLIF/OLIF would be reasonable. Alternatively, a single approach of ALIF/PLIF/TLIF/LLIF may be used in some cases but should be supported by posterior fixation.

Clinical outcomes: current evidence and shortcomings

Of note, the above proposed recommendations for each level of surgery are based on the theoretical advantages and disadvantages in terms of the anatomy of the surgical access and extent of disc space preparation and deformity correction. It does not consider the experience and expertise of each individual surgeon. Nor are the individual demographic factors and comorbidities of each patient considered. For example, obesity is significantly associated with symptomatic disc degeneration, but fusion surgery in this population has been considered problematic, fraught with major positioning and anaesthetic risk, as well as potential difficulty in mobilising viscera and major vessels anteriorly. Despite these potential risks, there are no clear guidelines when to recommend fusion surgery and if so which fusion surgical approach, should an obese patient present for surgery.

Furthermore, postoperative complications and follow-up outcomes are a significant contributor to the increasing cost of healthcare. According to a cost-analysis study, complications are the strongest indicator of full in-hospital costs per patient(66). As such there has been a shift in improving quality of patient healthcare by identification of short-term and long-term potential complications and readmissions and understanding the risk factors or comorbidities that contribute to this. A the time of writing, the Affordable Care Act in the United States sanctions penalties toward hospitals that fail to achieve standards for hospital readmissions(67).

There is limited high-quality clinical randomized trials available to guide and direct surgeons when comparing surgical approaches for lumbar fusion. The lack of data stems from the unique anatomical challenges and limitations of each technique, which means no single surgical approach can be used for all lumbar pathologies requiring fusion.

Indeed, there are no published studies available which directly compare ALIF, PLIF, TLIF, LLIF, OLIF in a head-to-head prospective and randomized manner. Furthermore, surgeons who have been trained in a specific technique may tend to favour that approach regardless of pathology and level of operation. Although there is consistent evidence supporting the superiority of interbody fusion approaches compared with on-lay posterior spinal fusion, the clinical differences between ALIF, PLIF, TLIF, LLIF and OLIF are not as well established. Given the lack of robust level I and level II evidence, we must turn towards prospective and retrospective observational cohort studies as the current evidence base to guide surgical practice.

When considering the literature for lumbar degenerative disc disease and published prospective comparative studies, up to Feb 2020 there are 7 prospective cohort studies and 7 randomized clinical trials which compare the safety profiles any combination of mini-TLIF/open-TLIF/mini-PLIF/open-PLIF/ALIF(68). The authors synthesis effect sizes across the studies using contrast-based network analysis, using open-TLIF as the reference group. When compared to open-TLIF, there was no difference in overall adverse events with ALIF, mini-TLIF and mini-PLIF, whereas open-PLIF had significantly higher risk of adverse events (RR 3.43). Neural events for open-TLIF were suggested to be lower compared to the other approaches although this did not reach statistical significance, which supports the intuitive recommendations above based on anatomy encountered. Interestingly pooled analysis did not demonstrate any significant differences in terms of vascular complications or wound infections. Similarly, literature searches up to July 2018(69) identified four randomized trials and four prospective cohort studies which evaluated pain scores and functioning improvement amongst open-TLIF, mini-TLIF, open-PLIF, mini-PLIF and ALIF. The authors found lower pain scores reported for mini-PLIF compared to open-PLIF and open-TLIF. Significantly

higher improvement in ODI scores for function were also reported for open-TLIF relative to other groups, albeit with longer operative duration.

Non-comparative single-arm cohorts (both retrospective and prospective) for ALIF have also been examined. In our systematic review(70) performed in mid-2017, 17 studies(65, 71-86) were identified which evaluated stand-alone ALIF outcomes. Although functional and radiographic outcomes were well-reported, there were few multi-centre and prospective studies which have examined in detail predictors of short-term postoperative complications as well as long-term follow-up complications following ALIF surgery. The indications for surgery included lumbar or lumbosacral degenerative disc disease (DDD), degenerative spondylolisthesis, iatrogenic spondylolisthesis, isthmic spondylolisthesis, revision of failed posterior fusion or decompression, foraminal stenosis, facet joint degeneration, and recurred herniated nucleus pulposus.

From the systemic review(70), clinical outcomes demonstrate clinically significant improvement by final follow up as measured by the Oswestry Disability Index (ODI), Visual Analogue Scale (VAS) for back pain and leg pain, and Short Form 36 physical component scores and mental component scores (SF-36 PCS and MCS). At least 75% of all measurements across the studies exceed the minimal clinically important differences, which have been reported with ranges of 4-16.3 ODI points(87-90), 10-19% VAS(88, 89) and 3-5.4 SF-36 points(87, 89, 90). In terms of opioid analgesic use, this declined as would be expected with absolute reduction of subjects continuously using opioids of 56.4% at 12 months compared with 77.8% at 6 months(79).

In terms of complication rates, relatively high rates of adverse events were reported as 31.1% after pooling results from all included studies except one case series(81) that only reported the lack of device-related complications and was excluded from analysis.

Adverse events can be divided into either approach related complications or specific implant- or pathology-related complications. These include any negative outcome including operative complications, secondary surgical interventions, ongoing pain, neurological deficit, cardiovascular damage, bone fractures, herniation, haematoma, retrograde ejaculation, and infection. Pooled secondary surgical intervention rates were low at 5.8% for supplementary fixations, 0.35% for device removals, 0.96% for other revisions and 2.4% for other reoperations. Of note however on our review(70), few of studies performed univariate analyses or identified predictive factors associated with specific complications.

These syntheses have several commendable aspects as well as limitations. Firstly, a homogenous population of lumbar degenerative disc disease was selected and pooled. Both PLIF and TLIF were separated into minimally invasive and open subgroups. Given the known risk of imprecise estimates from retrospective cohort studies, the authors selected and included only prospective studies, to minimize risk of selection bias. However as alluded to above, there are several shortcomings. Firstly, the set of outcomes reported by each study are not in common across the included pooled studies, and therefore complications were pooled into groups such as neural and vascular complications. This does not allow for comparison of procedure-specific complications such as aortic or iliac arterial injuries or hypogastric plexus injury with ALIF, lumbar plexus injury with LLIF, cord and dural retraction injuries with posterior approaches. The timing of complications is also not assessed. Complications which occur in the immediate postoperative period have a different profile compared to complications which are monitored for several years after the operation. The risk factors contributing to perioperative and long-term complications are also likely to differ. Secondly, surgeon experience varies from study to study, institution to institution. As such, the clinical

outcomes and complication rates following surgery will likely vary as well, and when combined across multiple studies will compound such heterogeneity. There are significant variations in the type of LIF interbody cages used and their biomaterials. Finally, these comparative studies do not account for factors inherent when selecting patients for surgery, such as age, comorbidities, body habitus, smoking status, bone quality, all which potentially adds to variability in the final reported clinical or radiographic outcome.

Therefore, in Chapter 2 and Chapter 3 of this thesis, we aim to contribute to addressing some of the above limitations in the current literature with regards to effect of preoperative factors. In Chapter 2, a single-surgeon prospective cohort of patients undergoing ALIF with integrated cages is evaluated, to minimise heterogeneity in surgical experience. Long-term patient reported clinical outcomes and radiographic outcomes are reported. Emphasis is placed on assessing the effect of preoperative demographic factors including age group, obese versus overweight body habitus and smoking status on follow-up outcomes, with multivariate adjustment to mitigate impact of confounding factors. In Chapter 3, we analyse nationwide database which collects perioperative outcome parameters not well collected and described in long-term follow-up studies. We aim to report multivariate adjusted risk factors for perioperative complications but also contributing factors to readmission to hospital and influence of discharge destination on outcomes. We evaluate the effect of risk factors for timing for postoperative complications (what factors contribute to an early vs delayed complications).

In addition to surgical approach and patient factors affecting clinical outcome following ALIF, the choice of biomaterial of interbody implant and cage design can also have a

considerable effect. In the following section we review the evolution in cage design and biomaterial choice in ALIF surgery.

Historical perspectives of anterior fusion surgery interbody cages

To help direct ongoing and future research efforts into anterior fusion cage design and development, it is important to appreciate its rich history. Adapting from the work of their predecessors as described in the ALIF section above, Hodgson and Stock(91) utilized the retroperitoneal technique and made a use of different graft materials for the management of Pott's disease. They removed the dead tissue, decompressed the spinal cord, and inserted corticocancellous blocks of autogenous bone. A comparable approach was also used by Ralph Cloward but with a cylindrical-shaped corticocancellous dowel(92). Although Cloward utilized a posterior approach, his idea of using dowels along with removing the disc and preparing the endplate was employed by other surgeons including Harmon(93) and Sacks(94), for anterior approach. Afterwards, O'Brien(95) suggested to use ALIF with trapezoid blocks to treat discogenic pain. Subsequently, a hybrid approach was constructed comprising of biologic fusion cage that includes femoral cortical allograft rings that are filled with autogenous cancellous bone graft.

Between 1970s and 1980s, stand-alone ALIF emerged and was increasingly used but with variable surgical techniques and fusion success rates that ranged between 1% up to 95% by each group(92, 93, 96). As a result, ALIF along with posterior fusion has become increasingly recognized and renowned. Till now, it is still unclear which of these two approaches is superior for degenerative lumbar spine diseases. It is also important to recognize the current continuous improvement in the instrumentation and access techniques including implant cages or devices for ALIF. A timeline of cage design evolution for ALIF is shown in Figure 1.8.

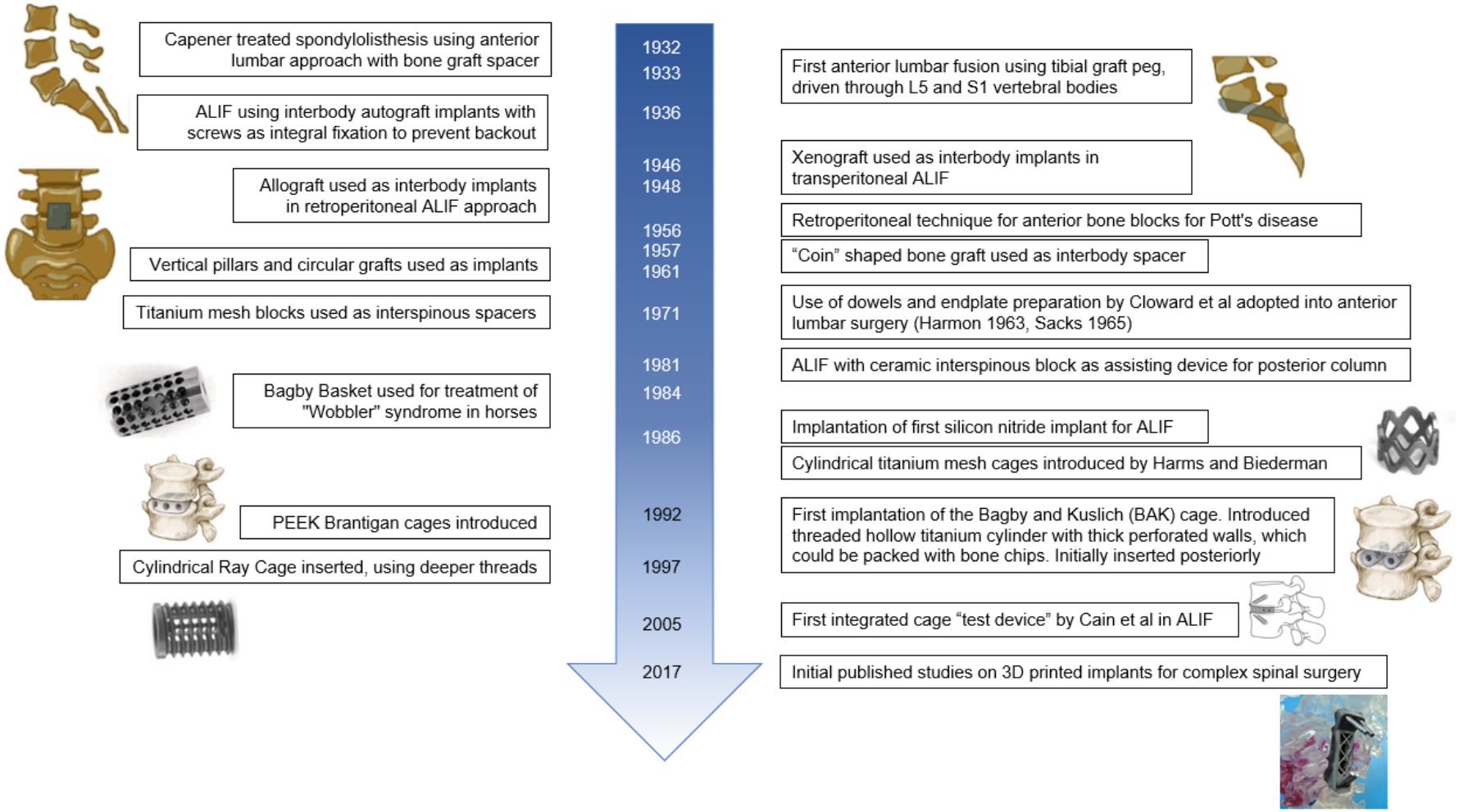

Figure 1.8. Timeline demonstrating development and modifications to cages and approach used for anterior lumbar fusion. Inset figures of Cylindrical Ray Cage and Mesh cages reproduced from Williams et al(97).

Evolution of anterior fusion implant materials

Silicon nitride interbody spacer

One of the earliest ALIF spacers manufactured synthetically and implanted in implanted in humans is the silicon nitride interbody spacer, which originated in Australia. During 1986 to 1988, reaction bonded silicon nitride interbody spacers for anterior lumbar surgery were designed, manufactured, and implanted in thirty patients in Australia(98). The design and manufacturer was performed by Sialon Ceramics Pty. Ltd. in Sydney, and subsequently surgery was performed by Dr Phillip Hardcastle in Perth, Australia. A simultaneous control study using standard iliac crest bone graft (ICBG) also was done as the comparator group, as this was the standard approach for fusion at the time. At the time of this series, only an interbody spacer was used. Synthetic interbody cages had been conceptualized at the time however was not routinely performed for clinical surgery. The surgeries were a technical success, however long-term radiographic outcomes of ALIF using silicon nitride are to be established in the literature.

Reaction bonded silicon nitride was considered and used for several reasons. Silicon nitride (Si3N4) is a non-oxide ceramic with distinct properties which make it useful for a variety of orthopaedic applications(99-103). It was a promising biomaterial initially because its low free energy makes it very stable and hence of low susceptibility to corrosion or reaction *in vivo*(104-106). Additionally, its processing is effectively net-shape(107) and the pore size can be controlled with a high degree of accuracy, neither of which can be achieved easily through conventional densification. Reaction bonded silicon nitride can be fabricated with relatively high purity, depending on the purities of the silicon metal and the nitriding gas. its low partial radiolucency establishes it as an

excellent radiographic material(108, 109). Further, it has been shown to exhibit decreased bacterial activity compared to polyether ether ketone (PEEK) and medical-grade titanium(110-112).

Titanium Implants

Titanium was the predominant material used in the early designs of ALIF interbody implants. This is due to several characteristic features of titanium of which is that it is biocompatible, has low density of around 4700 kg/m3, and forms TiO_2 which plays a significant role in resisting corrosion, as well as resistance to corrosion, low density, and capacity for osteointegration(113-115). Titanium cages were effective for achieving fusion. However, it has a propensity for subsidence(116-118), which was thought to be due to the difference in rigidity between titanium (as measured using Young's modulus of elasticity) and the bone of the vertebral body(119). From a practical point of view, titanium is not a translucent material due to its density, which may be an inconvenience during intraoperative imaging.

It is important to note that although traditional Ti and Ti alloy spacers and interbody cages work effectively in load bearing, without further processing or modification, their surfaces are inert and do not osseointegrate well with surrounding bone. The factors which influence the osseointegrative properties of Ti and its alloys are complex, including surface topography and surface chemistry. From a topographical perspective, it has been demonstrated that "rough" and porous titanium surfaces demonstrate improved osseointegration properties compared to smooth surfaces(120). The latter does bond and interlock well with adjacent bone, unprocessed surfaces are more susceptible to shearing forces(121). To further add to this complexity, material finishing

techniques (such as polishing versus grit-blasting) can affect nano-topographic features, which in turn can influence cell numbers, size, focal adhesion, and cytoskeletal and nucleoskeletal organization(122). Although the extent of influence of each factor is still subject to debate, it is agreed that all macro-scale, micro-scale and nano-scale morphology of Ti implant surfaces can influence osseointegration.

Osseointegration is also influenced by surface chemistry features, that is the chemical interactions between Ti/Ti alloy and surrounding bone. When considering only smooth surface implants, it has been suggested that Ti has higher adhesion (0.01 MPa) compared to PEEK, although both are very low in magnitude(123). In a study by Torstrick et al, as the surface topology changed from smooth to rough to porous, the differences in surface chemistry properties of Ti versus PEEK was attenuated(124). Although still subject to debate, the evolving evidence suggests that surface topography has a more dominant effect over surface chemistry in terms of osseointegration ability.

One way to address inertness is surface modification, which is designed to convert the inert surfaces of Ti/Ti alloys into bioactive surfaces to improve bony in-growth and on-growth. Treatment options to increase bioactivity of Ti or Ti alloy implants include: rough surface, modification of surface topography, heat treatment, alkali treatment, removal of Na ions, porous material conversion and hydroxyapatite (HA) coating(115). These modifications increase surface roughness and in effect increases friction between the implant surface and bone, which reduces micromovements, which in turns allow more initial fixation, thereby promoting subsequent adhesion and spread of cells and proteins(115, 122). It has been suggested that micromotions up to 50 μm promote osseointegration whereas movement in the range of 40–150 μm results in fibrous layer formation and lack of osseointegration(125, 126). Increased surface roughness of Ti in

cell culture resulted in increased protein and alkaline phosphatase, suggestive of osteogenic cell differentiation(127). Indeed, plasmapore-coated Ti implants have been used in the clinical setting without additional bone graft with fusion occurring at both cervical(128) and lumbar levels(129).

PEEK cage devices

A more common material used in synthetic interbody fusion cage is polyetheretherketone (PEEK) and carbon fibre. In the 1990s, AcroMed was the first to use PEEK fusion cages. Then, Carl McMillin developed this cage more and it was later known as Brantigan cage(130). The first anterior interbody PEEK cages were composed of hexagonal or round device and a central cavity for placement of bone graft. PEEK has been commonly used due its biocompatibility, imaging characteristics, high strength and fatigue resistance. It has considerable elasticity modulus similar to bones which boosts load sharing and provide better handling of stress, resulting in better fusion rates and a reduction in subsidence rates(131, 132). Besides that, reinforcement by carbon fibre would provide further equalization in the modulus of elasticity between the PEEK cages and bones. Most importantly, as compared to their titanium counterpart, PEEK implant materials offer better radiological assessment after fusion and its inert nature protects against microbial adhesion. The later resulted in a reduction in infection rates(133, 134). However this very property may also limit the extent of integration of PEEK into adjacent bone(135, 136).

Despite the high strength, biocompatibility, and imaging properties, PEEK implants are limited by its hydrophobic and chemically inert surface, which limits development of the implant-bone interface(137, 138). Conventional unmodified PEEK is inert and has

poor osseointegrative properties(17, 139). One contributing factor to this is that conventional PEEK has a “smooth” surface, which has limited osseointegrative ability compared to roughed and porous surfaces(140). Micromotion secondary to the lack of implant-bone interface can lead to fibrous layer formation and implant loosening. Several methods have been tested to determine whether PEEK osseointegration can be enhanced, including surface plasma or chemical etching(141, 142), bioactive coatings(143) (Ti or HA coatings), and PEEK composites(144) (including calcium silicate, bioglass and beta-TCP composites). Potential drawbacks however include delamination in physiological environments(145). Increasing the porosity of PEEK implants have also been tested, which promotes bony and vascular on-growth. Although increased osseointegration with increased bulk porosity has been demonstrated, it is limited by reduced implant strength(144, 146, 147). A compromise may be to introduce porosity only to the surface of the implant, which allows for bone and vascular in-growth whilst maintaining mechanical properties of the remainder of the implant(148). It remains unclear which aspects of porosity contributes the most to the biological properties of PEEK at the interface, whether it is pore size, porosity, or pore layer thickness.

From a clinical perspective, several researchers assessed the efficacy of utilizing PEEK cages along with anterior lumbar fusion. Amongst them, Schleicher et al. reported a relatively good flexion and extension loading for the tested PEEK cage. Hoff et al(149). conducted a prospective study, in 32 patients, with two years of follow-up and reported a significant enhancement in Oswestry Disability Index (ODI) and Visual Analog Scale (VAS) scores for those who had ALIF with PEEK cages.

Surface-coated PEEK cage devices

Even though PEEK material has several mechanical features that make it convenient to be used with ALIF, as outlined above it is regarded as chemically inert thus constraining its osseointegrative capacity to the bone environment. Hence, there have been several studies done to develop newer options and enhance the PEEK bioactivity. This included hydroxyapatite (HA)-PEEK composite cages and Ti-PEEK composite cages (Figure 1.9).

The rationale behind using HA is that it is one of the constituents of natural bone. Thus, it is thought that it would help it integrate and grow within the bone environment. Various attempts have been done to integrate HA with PEEK cages. In 1988, Bonfield attempted to integrate HA with PEEK cage to create an analogous material to natural bone substance(150). Wong et al.(151) has reused Bonfield's idea, but with innovation of a composite of strontium-containing HA-PEEK that has flexural modulus to bone and showed an improvement in the in vitro bioactivity. Khor's group utilized a 30% volume HA along with PEEK and reported a modulus of elasticity that is relatively similar to bones(152, 153). PEEK cages that are coated with nanocrystalline HA have been shown to have more osseointegration as compared to their uncoated counterparts(152, 153).

To improve the osteoconductivity of PEEK, some implants have been coated with titanium (Ti-PEEK). This can be done by coating the PEEK with "roughened" titanium, such as via plasma spraying. Wu et al. studied the difference in osseointegration between Ti-PEEK materials (PEEK cage plus TiO2 particles) and PEEK alone and found Ti-PEEK to be superior(154). Cell attachment and spreading were shown to be enhanced in Ti-PEEK as compared to PEEK alone. Moreover, it also had better bone regeneration in vivo. Similarly, Han et al. studied the difference between the two in

further and found Ti-PEEK to have improved bioactivity(143). Recent studies have suggested that titanium-coated PEEK implants may be susceptible to impaction-related wear debris(155), which have lead to localised inflammatory reactions in some animal and clinical studies(156-158). Walsh et al(159) demonstrated in an ovine model that plasma-sprayed Ti coating of PEEK implants improved shear strength at the bone-implant interface at follow-up. Further histomorphometric analysis demonstrated significant improvements in mean on-growth at 4-week and 12-week follow-up within cortical and cancellous sites compared to non-coated PEEK. Direct on-growth was demonstrated for Ti-coated PEEK whereas a fibrous tissue interface was seen for PEEK samples(159). There are some concerns associated with Ti-coated PEEK implants pertaining to the thinness of the coating. For this reason, the Ti-coating may wear or delaminate, and some studies have reported subsequently particle-induced osteolysis and aseptic loosening(155, 160).

From a clinical perspective, few studies have reported long-term radiographic outcomes in ALIF using Ti-coated PEEK implants and thus its long-term efficacy is still to be established. Schnake et al(161) conducted a randomized trial comparing PLIF using PEEK versus Ti-coated PEEK implants and followed up patients at 12-months. Cage migration was higher for PEEK compared with Ti-PEEK (2.8% vs 0%). Although bone growth through the pores was similar (94.4% vs 96.3%), bone growth outside the cage was significantly lower for PEEK compared with Ti-PEEK (58.3% vs 81.5%). No significant differences in ODI and VAS leg pain scores were found at 12 months. Rickert et al(162) randomized 40 patients to receive TLIF with a PEEK cage versus Ti-coated PEEK cage. At 12-month follow-up, pseudoarthrosis rates and fusion rates were equivalent. No differences were found in terms of ODI clinical outcome.

Other implants which are still ongoing research include silicon nitride and tantalum. Nitinol is a promising implant alloy of 50% nickel and 50% Ti that is superelastic and has a shape memory. Others that have been recently studied include Poly(L-lactide-co-D,L-lactide), which would help in developing promising bioabsorbable cages. Thus, it would gradually get absorbed and leave the spinal segments out of foreign material and with a radiologically enhanced assessment. This implant material still needs further studying as limited experience along with contradictory results are there.

Shortcomings in evidence

The current evidence base for Ti-coated PEEK implants in lumbar fusion surgery remains significantly limited. Neither randomized study by Schnake et al(161) or Rickert et al(162) evaluate clinical or radiographic follow-up in patients undergoing ALIF with a Ti-coated PEEK implant. Furthermore, both studies were limited to 12-month follow-up. It is unclear whether Ti-PEEK cages offer any superior clinical or radiographic advantages in the long-term follow-up at 24-months and beyond. Our experience with long-term radiographic follow-up of Ti-coated PEEK implants for ALIF is demonstrated in Chapter 4.

Although interest in silicon nitride as a biomaterial for spinal implants has re-emerged in the past decade, there remains limited long-term evidence. From a meta-analysis comparing 450 patients who received silicon nitride ALIF implants with 14 comparator cohorts of various lumbar interbody fusion procedures, no differences were found in terms of improvement in clinical outcomes and adverse events. Over 35,000 Si_3N_4 spinal fusion devices have been implanted, with <0.07% reportable adverse events (SINTX Technologies, Inc., 2019, unpublished data)(163).

Figure 1.9. (A) Ti/PEEK integral fixation ALIF implant. (B) Titanium endplates with PEEK forming the body of the implant. (C) X2 screw integral fixation. (Redmond Implant, A-Spine ASIA, Taiwan).

Development in cage designs for ALIF

Cylindrical BAK

An orthopaedic surgeon from Washington, Bagby constructed the first original cage implant and used it to treat horses with cervical instability and myelopathy due to Wobbler's syndrome in 1986(164). This cage implant was later named as “Bagby basket” and it had a stainless steel cylinder and horse autograft. Noteworthy, it resulted in successful fusion rates, and better stability and arthrodesis(14, 165).

In the late 1980’s, Stephen D. Kuslich came up with an idea of using “Bagby basket” for humans but with further modifications and improvements of the fusion and stability of the cage design(166). This included utilizing thick perforated walls and threaded hollow titanium cylinder which would help the neighboring vertebrae to be screwed by the cage. Moreover, there was no need to pack the hollow cage with autografts as it was replaced by cancellous bone chips which decreased the autografts’ morbidity and mortality. In 1992, this new cage came up to be known as Bagby and Kuslich (BAK) titanium cage (BAK, Spine-Tech, Minneapolis, USA)(166) and was first used in humans with successful rates, using a posterior approach. Later, this was also utilized for fusion with anterior approach and was approved in 1996 by the Food and Drug Administration (FDA).

Cylindrical Ray Cage

Ray introduced some slight changes to the BAK cage to help in improving the stability and providing “self-tapping”. This was done by adapting deeper threads. Remarkably,

imaging studies reported fewer artefacts as compared to the BAK cages. Additionally, it can be used along the posterior or anterior approach(167).

Cylindrical Mesh Cage

In 1986, Harms and Biederman were the first to introduce the titanium mesh cages. Although there is scarce evidence about the efficacy of using this mesh cage for anterior lumbar fusion, few reports have shown optimistic outcomes(168, 169). This mesh cage was designed in which titanium mesh would be rolled cylindrical and would be strengthened at their ends with rings. Packing this mesh cage with autograft from the iliac crest would result in high arthrodesis, but would also be associated with more complications with a rate that can go up to 25%(170, 171). Alternatives to that included coralline hydroxyapaptite and demineralized bone matrix, which were also shown to have good efficacy.

Lumbar-Tapered Cage

Unlike cylindrical implants with narrower area, using implants which are wider helps in resisting the substance and providing more axial strength. Lumbar-tapered cages or trapezoid cages, which have “wedge” like shape, emerged as promising cages with wider implants that may enhance segmental stability and provide better spinal alignments and angles(172-174). Moreover, it would enhance the lordosis of patients by symmetric reaming of endplates. In addition, bone morphogenic protein (rhBMP) or autograft can be used to fill or pack these cages.

Integral fixation implants

The construct stability of the ALIF implant is traditionally supported by additional posterior fixation, such as posterior pedicle screws or facet screws, to further stabilize the motion segment and prevent implant migration. However, these fixation methods often require additional posterior surgery and/or increased anterior exposure. The associated iatrogenic trauma, posterior paraspinal muscle dissection, and multiple incision sites may increase operative duration, postoperative pain and delayed recovery process, and may lead to poor clinical outcomes(175). To overcome this, stand-alone ALIF cages have been designed with integrated screws (Figure 1.10). This design allows for the insertion of the ALIF implant as well as multiple diverging interbody screws via a single anterior approach, which would still allow for stabilization of the motion segment and minimize cage migration. These integral fixation devices can be of two or up to four screws to help in the primary implant fixation.

Stand-alone cages without integral fixation have commonly been described in the literature, especially in earlier studies, and could consist of femoral ring allograft, titanium or poly-ether-ether-ketone (PEEK). Later studies included integral cage designs, such as the Synthes SynFix-LR PEEK cage with four diverging integral screws that anchor into stronger cortical bone anteriorly and peripherally(176). Most cages are open for bony ingrowth and roughened for bony on-growth, with ridges or teeth to grip endplates for initial stability(176).

In a biomechanical study of 14 cadaveric lumbar spines, Kuhns et al(177) compared flexion-extension, lateral bending, and axial rotation in interbody spacer alone versus ALIF with posterior fixation vs integrated cages (3 screw vs 4 screw designs). The

authors found that circumferential ALIF fusion with bilateral pedicle screws provided the greatest stability, but additional benefits were not significant when compared with both three-screw and four-screw integrated spacer designs(177). In another study by Kornblum et al, biomechanical testing showed that stand-alone cage with integrated screws provides more immediate stability than a cage alone and provides equivalent stability to ALIF constructs with supplemental fixation in lateral bending and axial rotation(178).

There are also other devices which utilize methods for fixation including implantable fin (ROI-A ® Oblique, LDR, Spine, France), rotatable teeth, and expanding screws (A-Spine ASIA, Taiwan) for fixation. However, there is limited published evidence on the clinical efficacy of integrated implants in ALIF surgery.

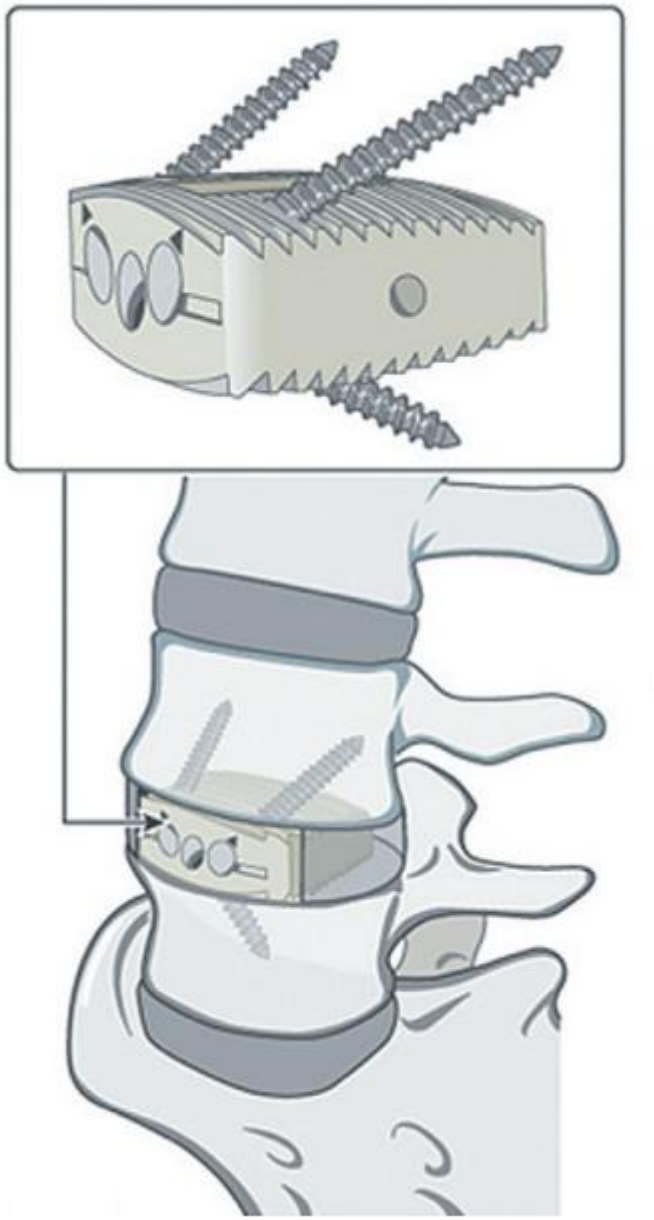

Figure 1.10. Schematic of an ALIF cage design with integrated fixation.

3D printed cages and patient-specific devices

Although not the focus of this thesis, it is important to overview some developments in 3D printing technology as this is currently topical within the field of spinal surgery. As emphasised in the above sections on the evolution in interbody cage materials and designs, achieving osseointegration at the bone-implant interface requires complex interplay of factors including not only surface material topology and chemistry, but also needs consideration of implant fixation and stabilisation. Nuances in surgical approach, anatomical complexity, endplate preparation, vertebral bone health, graft material choice also adds to the challenge of achieving optimal osseointegration and fusion.

Developments in additive manufacturing technology have allowed for complex geometries and shapes to be produced for implants in an affordable and feasible manner, which previously was technically challenging or financially prohibitive to produce. This technology aids in rapid layer-by-layer construction of objects with customized shapes from raw materials including polymers, metals, ceramics, bio-gels and living cells. Although there is a lack of evidence currently to support whether such custom-made implants have any significant improvement in long-term clinical outcomes in patients, the fact is this technology allows for significantly more complex and multifeatured implants to be made at a time- and cost-efficient manner, and thus garners exciting attention in the field of spinal surgery, particularly in cases with challenging anatomy.

The main process involves converting design drafts to STL (STereoLithography) file by using Computer Aided Design (CAD) programs(179). Subsequently, the STL file is utilized in further to construct platform and to sequence two-dimensional (2D) cross sections for the 3D printer to generate the geometry of the desired object. The

successful application of 3DP is also dependent on the usage of Computerised Tomography (CT) and Magnetic Resonance Imaging (MRI) which would help in the accurate production of 3D models of patient anatomy. Thus, when these high-resolution imaging studies and surgeon estimates are combined with 3DP, this would enable us to print objects such as medical prostheses with multiple varieties, and to develop patient-specific implants (PSIs). With 3DP, the surgeon can design the implant with features designed specific for the patient, such as strut size, orientation of surface additions, cage porosity, and improve their biomechanical properties.

Previously, the role of 3DP was only confined to surgical planning in spinal surgery and in accurate placement of pedicle screw in posterior fixation. Lately, its role expanded to include the production of off-the-shelf (OTS) implants and PSIs which are more accurate in design and have better customization to patients than the ones by conventional techniques. The 3DP has become increasingly used by manufacturers of spinal prosthetics to improve their properties. Moreover, providing better control of geometry and enhancement of parameters such as porosity. It is important to mention that these benefits were offered by both of OTS and PSIs but with the most noted benefits from the use of PSIs(179).

Patients may have different anatomical varieties due to congenital, traumatic or of pathological reasons (Figure 1.11). Hence, there may be no available OTS to be used for these patients without critical surgical remodelling when implanting it. Unlike OTS implants (by 3DP or traditionally manufactured), PSIs are created with more specificity to the patient's anatomy and needs. Thus, this preserves and limits the invasion and trauma of tissue when implanting it. Consequently, PSIs are associated with lesser

surgery time, dissection and blood loss, and better stabilization of anatomical structures(180).

On the other hand, PSIs necessitate more effort and planning before the production of the implant. Not to mention the need for expert personnel including biomedical engineers who are well acquainted with the use of CAD software, and high-end 3D printers which are not readily available. Thus, PSIs are limited by time, availability and costs(181). Evidence is still lacking about the long-term efficacy and safety of 3D PSIs and OTSs.

Several materials have been used in 3DP. However, one of the most widely used and considered to be suitable for 3DP is the biomedical grade titanium alloy (Ti¬6Al4V)(182). It resists corrosion, has outstanding biocompatibility and osseointegration potential(182, 183). Furthermore, there is evidence demonstrating radiological fusion for spinal implants, which affirms its applicability to be used in 3DP. However, it usage for spinal implants are limited by the high modulus of elasticity (110 GPa) and its stiffness as compared to cortical (3-30 GPa) and cancellous bone (0.02-2 GPa)(184, 185), which is associated with an increased rate of subsidence. Additionally, the titanium component means it is radiodense, which may impede accurate assessment of in CT and planar x-ray imaging, as well as producing artefact/flaring in MRIs(186).

A study by McGilvray et al(187) compared 3D printed porous titanium cages with PEEK and titanium-coated PEEK cages in a sheep model of lumbar interbody fusion. It was demonstrated that the 3D printed implants reduced range of motion in flexion–extension testing and increased stiffness, whilst having greater bone volume than the PEEK and titanium-coated PEEK cages. This biomechanical animal model study

demonstrated the feasibility of bony growth onto the 3D architecture of the implant, with superior kinematic properties compared to standard off-the-shelf style implants. Their histological data also supported improved ingrowth with titanium compared to PEEK and titanium-coated PEEK implants. Furthermore the risk of delamination and wear debris as reported in some titanium-coated PEEK implants is theoretically reduced in 3D printed cages due to a lack of interface between materials of two materials of different moduli(187).

Silicon nitride is another promising material for spinal implants. It has good bacteriostatic potential (relative to PEEK and titanium implants) and bone growth and fusion. There is scarce data discussing the outcomes of silicon nitride usage in spinal implants. The use of ceramics in 3DP has led to an advancement in building cellular structure, which can be as potential surface for bone in-growth.

As 3DP technology is advancing in the future, it is expected that a new implant from a combination of materials can be formed with better osseointegration, lower subsidence potential, and more sterility. The 3DP technology is still in its infancy with lesser availability, expertise input required, and higher costs. Therefore, large-scale randomized trials are currently not feasible. As such, there is significantly limited evidence assessing the potential role of 3D-printed PSIs in spinal surgery and which indications it may be suitable for. The short and long-term outcome of using PSIs and OTSs are not well studied, and so future well-designed studies are warranted.

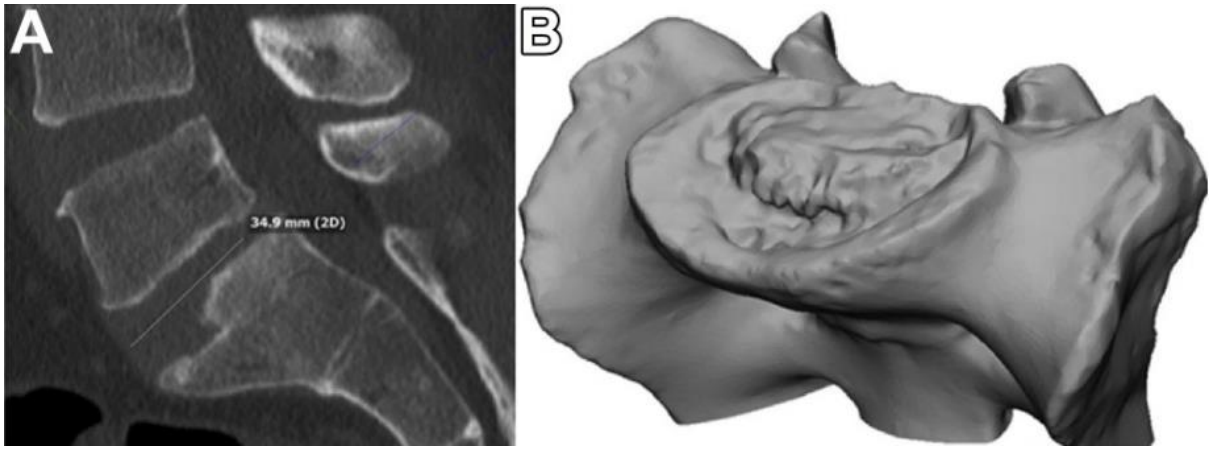

Figure 1.11. L5/S1 degenerative disc disease with unusual end plate anatomy not suitable for an off-the-shelf implant. (A) Unique S1 end plate anatomy. (B) Three-dimensional modelling of end plate shows a complex anatomic geometry. Reproduced from Mobbs et al(179).

Rationale and research objectives

As highlighted in the shortcoming sections above, current clinical evidence for ALIF is outcomes-focused, with a lesser emphasised placed on impact of patient demographic and comorbidities as potential confounders. Pooled synthesised evidence is highly heterogeneous in terms of surgical technique used, surgeon experience, variations in instrumentation and implant materials, as well as various patient-reported outcomes used. High quality robust comparative evidence amongst surgical approaches is sparse, and limited due to anatomical challenges unique to each approach. Reports of detailed short-term perioperative outcomes following ALIF and predictive factors of hospital stay and hospital readmissions are lacking, despite an increasing emphasis on value-based care by hospitals, providers, and government stakeholders. Although the clinical outcomes of Ti-coated PEEK implants for ALIF have been reported, there is limited long-term radiographic outcomes published in the literature.

This thesis aims to highlight that a patient-centric approach in spinal decision making would best serve our patients. Selection of surgical fusion approach should account for potential complications associated with each patient's unique demographic and comorbidity profile. Perioperative factors such as hospital stay duration and discharge destination may be novel markers of important value-based outcomes such as readmission rates to hospital and 30-day complication rates. Choice of ALIF implant material should be tailored to each patient's unique anatomical profile to maximise long-term radiographic osseointegration.

Therefore, the objectives of this thesis are:

1. Using a prospectively collected data of ALIF patients which is homogenous, I aim to determine specific which patient factors contribute to longer-term follow-up surgical complications, efficacy, clinical outcome, fusion rates of ALIF.
2. Using a nationwide prospective database of 30-day perioperative complications, I aim to determine the complication profile of ALIF, risk factors contributing to early readmission, the influence of discharge destination on outcomes, and predictors of wound complications and venous thromboembolism.
3. To investigate long-term radiographic follow-up outcomes of Ti-coated PEEK integrated cages for ALIF surgery.

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Chapter 2

Effect of patient demographics on follow-up clinical outcomes after anterior lumbar interbody fusion

Preface and objectives

The initial reports of anterior lumbar fusion in the literature were reported for treatment of spinal tuberculosis or Pott's disease. Since the development of anterior lumbar interbody fusion (ALIF) surgery in the 1930s until the 1980s, there was limited changes in the surgical technique and technology involved. During this period, posterior lumbar interbody fusion (PLIF) and transforaminal lumbar interbody fusion (TLIF) approaches became common. More recently with the development of improved retraction technologies, bone grafting substitutes and implant instrumentation, there has been a resurgence in ALIF for the management of several spinal pathologies.

The ALIF procedure is varied amongst surgeons, with large number of options in terms of implant types and graft materials, as well as the decision to implement additional posterior stabilisation, such as via posterior pedicle screws. Therefore, many publications in the literature report combined or pooled outcomes which have heterogeneity due to variations in technique or surgical outcome. More recently, the development of cage designs for ALIF has led to a new generation of implants called "integrated cages" or "stand-alone implants". Such design allows for fixation screws to be placed through the truss of the implant into adjacent vertebral bodies anteriorly, which removes the need for supplemental fixation.

Furthermore, indications for ALIF surgery are variable and is dependent on surgeon preference and their comfort with the approach. Traditional indications for ALIF include degenerative and isthmic spondylolisthesis, degenerative disc disease, degenerative lumbar scoliosis, and adjacent segment disease where there is degeneration of a vertebral disc above or below a fused joint due to altered biomechanics. There is

lesser published evidence for pseudoarthrosis where there has been previously failed union across vertebrae, and recurrent disc herniations due to prior failed discectomy procedures.

The objectives of this chapter are to assess whether patient factors including age, obesity, smoking status, influences follow-up clinical and radiographic outcomes following ALIF surgery

Acknowledgement of co-authors and co-investigators

The data, results and methods within this chapter have been incorporated in a number of publications as follows. However, the data has been further analysed, combined, and synthesised for the purpose of this dissertation chapter. The author contributions statement is appended.

Phan K, Ramachandran V, Tran T, et al. Impact of elderly age on complications and clinical outcomes following anterior lumbar interbody fusion surgery. World Neurosurgery. 2017 Sep 1;105:503-9.

Phan K, Rogers P, Rao PJ, et al. Influence of obesity on complications, clinical outcome, and subsidence after anterior lumbar interbody fusion (ALIF): prospective observational study. World neurosurgery. 2017 Nov 1;107:334-41.

Phan K, Fadhil M, Chang N, et al. Effect of smoking status on successful arthrodesis, clinical outcome, and complications after anterior lumbar interbody fusion (ALIF). World neurosurgery. 2018 Feb 1;110:e998-1003.

Background

In Chapter 1, we reviewed a range of surgical options available for fusion of the lumbar spine. It was highlighted that each approach has its own merits and disadvantages. In particular ALIF, the anterior approach allows better visualization of the disc space, it is easier to adequately prepare the endplates and to insert the implant, and also facilitates greater lordosis correction to the spine. With the anterior approach, this circumnavigates the issue of need to manipulate nerve structures that are present posteriorly(1). However, the ALIF approach does have its own risks. It involves significant mobilisation of abdominal structures including the peritoneal sac and major vessels. This increases the potential risk for vascular injury(2). Other associated risks include retrograde ejaculation, postoperative ileus, and abdominal wall complications(3-5). If one is not well experienced with the management of such complications, when they occur, the potential consequences may be disastrous. However, having enough anterior access experience or operating with an access or vascular surgeon, may mitigate these risks considerably.

There is limited evidence to conclusively recommend one technique over the other for lumbar fusion. Comparative studies to date are limited by significant heterogeneity in pathologies studied, as well as selection bias which limits comparability. For instance, a patient may be selected to undergo a posterior surgical approach rather than anterior approach due to difficult vascular anatomy anteriorly. Another example would be an anterior approach offered in a patient who has had prior posterior surgery and is now has considerable fibrotic and scarred tissue here, which would make meticulous dissection challenging. These cases have their own operative nuances and would not be

routinely compared directly. Rather, each case should be considered based on their individual patient circumstances.

With the above context, it is suggested that what would be of more significant value to the clinician is understanding how patient risk factors contribute to clinical and functional outcomes if a specific fusion approach is selected. This information alongside with assessment of each patient's individual anatomy can assist the surgeon in determining the preferred procedure and better optimise perioperative care for high-risk patients.

Age group is one characteristic which has been studied in spinal surgery. For patients undergoing adult spinal deformity surgery such as for scoliosis, higher age is associated with increased length of stay as well as 30-day follow-up rates of urinary tract infections, requirement for blood transfusions, readmission to hospital, and renal complications(6). Likewise, Murphy et al. showed that in patients undergoing lumbar decompression surgery, higher age was associated with increased length of stay and number of complications(7). However, the effect of age group on ALIF surgery outcomes has not been well explored. It may be possible that with increasing age, the major vessel vasculature becomes more calcified or more fragile, being more difficult to mobilize, which could be associated with higher complication rate.

Obesity is another factor which has been linked to perioperative morbidity in lumbar spinal surgery(8-13). Obesity is a challenge for management of spinal surgery patients, in the preoperative, intraoperative, and postoperative stages. Preoperatively rehabilitation and physiotherapy may be less effective in patients with high weight. From an anaesthesia point of view, there is higher risk of intubation, anaesthetic

complications, and resuscitation. Intraoperatively, a large body habitus means it is more challenging for the surgeon to navigate around vital structures to access the disc space, which leads to longer operative time, increased blood loss, higher infection risk, and nerve injuries. Larger and deeper incisions are required, often through fat and muscle, which further makes the postoperative recovery process even more difficult to patients. The influence of obesity on anterior lumbar interbody fusion (ALIF) is not well established. The evidence for the influence of obesity on outcomes following ALIF surgery is limited to retrospective, single-centre studies with conflicting results: some studies report increased complication rates, whilst others have observed similar complication rates between patients with a normal versus overweight and obese BMI groups(2, 8, 13, 14).

Smoking status is a preoperative factor which remains a leading preventable cause of morbidity and mortality globally (15). Poor surgical outcomes have been associated with both tobacco smoke and nicotine, with patients having increased rates of wound infections, sepsis, and delayed healing. In the lumbar spine, smokers tend to have more brittle and lower density bone, susceptible to fractures and leading to poor healing and chronic low back pain (16-18), for both active smokers and those chronically exposed to second-hand smoke exposure(19-21). Despite this, the clinical evidence investigating outcomes in smokers undergoing lumbar spine surgery have not been consistent (22-26). There have been few prior studies specifically in ALIF. One previous study has analysed the effect of smoking on surgical outcomes of ALIF, and found no significant association(27).

Despite the increasing literature in ALIF surgery, there has been limited studies to date specifically assessing the influence of the above factors in follow-up clinical and

radiographic outcomes after ALIF surgery. With a prospectively observational study, there is the opportunity to assess the impact of age group, weight group and smoking status on the effectiveness fusion, complication rates and disc height restoration following ALIF surgery.

Therefore, we aimed to assess whether patient factors including age, obesity and smoking status, are associated with follow-up clinical and radiographic outcomes following ALIF surgery.

Methods

Study design and ethical approval

This study was designed as a prospective observational study. Ethical approval was granted through the Human Research Ethics Committee of New South Wales Health (reference No. 11/183 and 13/090). Patients underwent ALIF surgery by the same senior neurosurgeon (A/Prof Ralph Mobbs) across two hospitals in Sydney, Australia. Follow-up was performed with review of clinical and radiographic outcomes.

Recruitment and consent

Allowed indications for surgery included: degenerative disc disease without radiculopathy, degenerative disc disease with radiculopathy, spondylolisthesis, failed posterior fusion, adjacent segment disease, and recurrent disc herniation.

Exclusion criteria of this study included patients with concurrent local or systemic infection, neoplasia, significant cardiac disease, fever (>38.5°C), or metal allergy; as well as patients who were pregnant or breast-feeding, who were mentally incompetent, who had a history of alcohol or drug abuse, and who were at increased risk of vascular or bowel complications related to the anterior approach.

Patients presenting at each site's preadmission clinic, typically within six weeks of surgery, were identified and screened via chart review. All patients underwent ALIF surgery as part of their routine management of their presenting pathology. All included patients provided written consent for their data to be analysed and be included as part of this research study.

No Randomization and blinding

There was no randomization or allocation concealment as part of this prospective study. All patients underwent planned ALIF surgery as appropriate for their presenting pathology as assessed by the senior neurosurgeon.

Interventions

Patients underwent ALIF surgery under a single senior neurosurgeon as part of this study. A standard retroperitoneal approach was performed via a midline or transverse incision and subsequent left sided corridor. A transverse incision is preferred for L5-S1 pathology (Figure 2.1). For all cases, an assisting vascular surgeon was involved in mobilisation of the peritoneum and vascular structures to exposure the anterior spine at

the level of surgery. The anterior longitudinal ligament is dissected, which exposes the 2 vertebrae and intervertebral disc. An example of such an exposure is shown in Figure 2.1(D), demonstrating exposure of L5 and S1, which allows for discectomy for the L5-S1 intervertebral disc and preparation of the endplates.

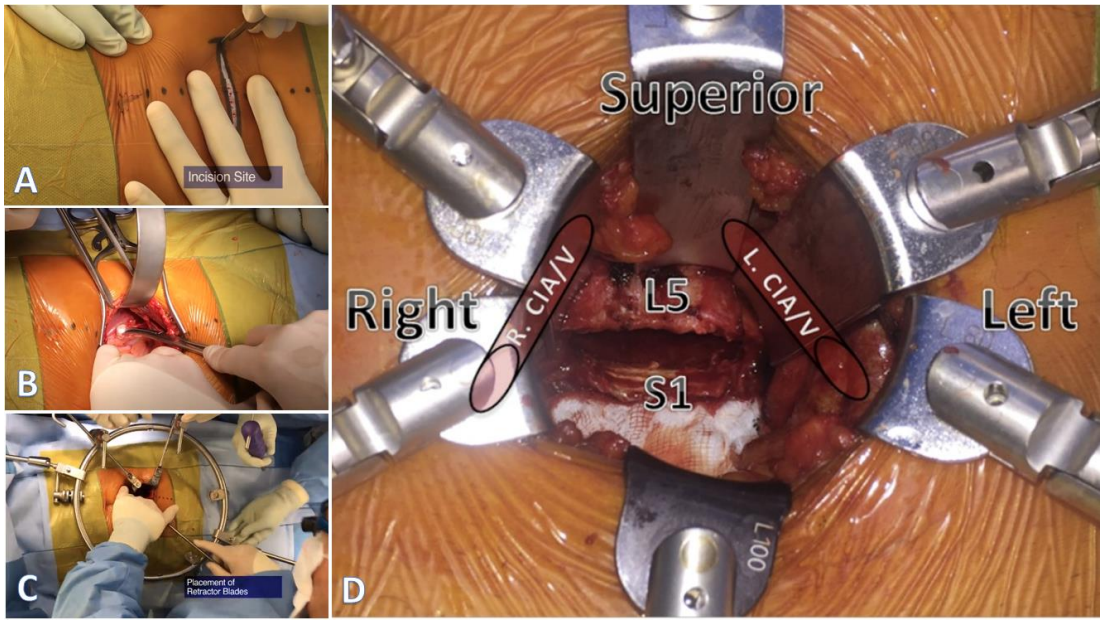


Figure 2.1. Example workflow involved in the exposure for anterior lumbar interbody fusion (ALIF) surgery. (A) For L5-S1 exposure, a transverse incision is preferred. Dissection through skin and soft tissue is performed through diathermy. The Linea Alba is dissected and rectus muscle is retracted. (B) Blunt dissection is used for exposure of the retroperitoneal plane. Inferior epigastric vessels are visualized, preserved and retracted anteriorly. Care is taken not to damage the psoas muscle and genitofemoral nerve. (C) A low-profile narrow blade retractor system is used for exposure. (D) Top view demonstrating the position of the iliac vessel in relation to the disc space. This view demonstrates the excellent exposure that an anterior approach offers, which allows excellent access for disc space clearance and implant placement. R CIA/V, right common iliac artery and vein; L CIA/V, left common iliac artery and vein. Images reproduced from Mobbs et al.(28)

Patients all received stand-alone integral cage devices with Polyetheretherketone (PEEK) as base material. From the cage designs used, 89.1% underwent ALIF with the SynFix-LR PEEK integral cage device (DePuy Synthes, West Chester, PA, USA) with four diverging intrinsic screws and anterior locking plate. In our study, additional anterior plating or posterior instrumentation was not routinely used. Cage designs are summarized in Table 2.1.

Once the intervertebral disc space is prepared, the cage is inserted such as in Figure 2.1(D). Multiple trials are used to determine the best fitting device, to ensure approach height and lordotic angle correction. The implant sizing ranged from 12-19 mm height with either 8° or 12° lordotic angle to ensure sufficient distraction.

To facilitate fusion, bone graft substitute i-FACTOR (Cerapedics, Westminster, CO, USA) was used for 136 patients. This synthetic age is composed of anorganic bone matrix bound to anorganic P-15 small peptide, which promotes attachment of osteogenic cells. For the other 11 patients, recombinant human bone morphogenetic protein 2 (rhBMP2) (Medtronic Sofamor Danek, Memphis, TN, USA) was used. In 7 (4.8%) patients there had been a previous fusion performed and no patients required additional posterior pedicle screw fixation to augment ALIF.

Integral screws are then passed through the device into the vertebrae above and below the cage to fix the device in place. The peritoneal sac is then released, and the wound closed with nylon to the fascial layer and vicryl to the subcutaneous layers and skin. Postoperatively patients underwent rehabilitation after an initial 3-5 day hospital stay, typically involving physiotherapy and hydrotherapy regimes as indicated. Throughout

clinical follow up, patients were assessed for progress and managed for any complications that arose.

Table 2.1. Cage designs commonly used for anterior lumbar interbody fusion

Name	Model	Number Screw	Base material	Origin
SynFix	SynFix-LR	4	PEEK*	DePuy Synthes, West Chester, PA, USA
Centinel	STALIF Midline	3	PEEK*	Centinel Spine, West Chester, PA, USA
A-SPINE	Redmond ALIF	2	Ti-PEEK†	A-SPINE Asia, Taipei, Taiwan
Stryker	AVS Anchor-L	3	PEEK*	Stryker Spine, Allendale, NJ, USA
Evolution	Evolution ALIF	3	PEEK*	Evolution Surgical, NSW, Australia
Signature	ALIF Cage	3	PEEK*	Signature Orthopaedics Europe, Dublin 2, Ireland
K2M	CHESAPEAKE	3	PEEK*	K2M Group, Leesburg, VA, USA

Key: N Screw: number of integrated screws | *polyether-ether ketone | †titanium-PEEK composite

Clinical outcomes assessment

Clinical outcome was measured preoperatively and postoperatively using the Oswestry Disability Index (ODI) and the Patient Satisfaction Index (PSI). Questionnaire data from the Short Form 12 Item survey (SF-12) were compiled in a custom-designed database. The data was compiled and cleaned. For comparison of factors across three or more groups, analysis of variance (ANOVA) and repeated-measures general linear models were performed.

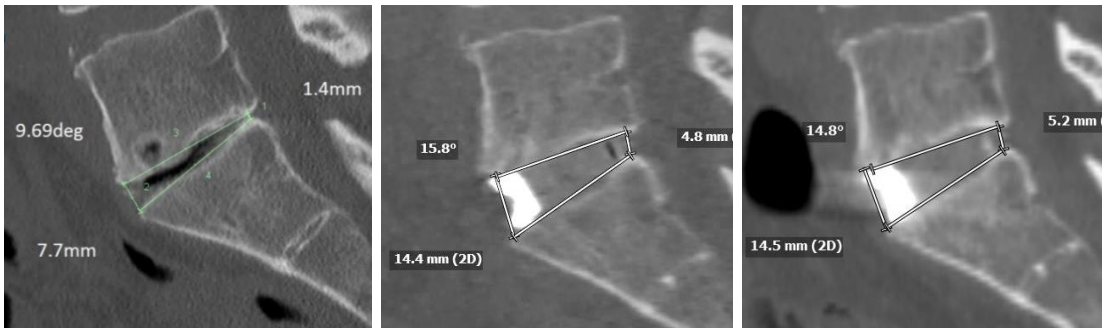
Radiological outcomes assessment

Lateral radiological scans of the lumbosacral spine were obtained preoperatively and at multiple time points postoperatively by searching medical records and databases of six major radiology providers (Southern Radiology, South East Radiology, Spectrum, Vision XRAY, PRP Diagnostic Imaging and Castlereagh Imaging; all based in Sydney, Australia) for each patient.

All patients received an MRI preoperatively, with a CT scan day 1 postoperatively (0 – 0.5 months) and follow up scans at 3 months and 6 - 12 months. Plain radiographs (X-rays) were performed at 1.5 months to check implant position. Radiological measures were performed for each available scan and assessed by myself, a senior neurosurgeon (RJM), and clinical radiologist for the patient.

Radiographs, including X-rays and CT scans, were analysed using Visage 7.1 (Pro Medicus Limited, Richmond, VIC) or InteleViewer (Intelerad Medical Systems Incorporated, Montreal, QC) software.

Anterior and posterior disc heights were measured using the anterior and posterior margins respectively of the inferior endplate of the upper vertebrae and superior endplate of the lower vertebrae, whilst segmental lordosis was measured between these two endplates. Endplate levels were taken as a straight-line average of the endplate as seen on the most central image in all planes, using the most anterior and posterior points excluding osteophytes. Osteophytes were identified as superficial extrusions of bone anteriorly or posteriorly beyond the main vertebral body. This allows for reliable disc height estimation without being confounded by central disc erosion. However, we acknowledge it can be difficult to accurately measure in images where there is significant abnormalities including anterolisthesis, retrolithesis, or osteophyte formation. Example measurements are shown in Figure 2.2.



Preoperative Postoperative 0 Postoperative 3

Figure 2.2. Radiological scans (CTs) measured for one patient at three different time points before and after L5-S1 anterior lumbar interbody fusion (ALIF) surgery. Anterior and posterior disc heights were measured using the anterior and posterior margins respectively of the inferior endplate of the upper vertebrae and superior endplate of the lower vertebrae, whilst segmental lordosis was measured between these two endplates. Endplate levels were taken as a straight-line average of the endplate as seen on the most central image in all planes, using the most anterior and posterior points excluding osteophytes.

Subsidence was defined as greater than or equal to 2 mm loss of height. Subsidence occur before 6-week follow-up was defined as early subsidence whereas if it occurred after 6-week follow-up this was defined as late subsidence. As per Malham et al.'s study(29), inferior endplate subsidence was classed as type 2 and superior endplate subsidence was considered type 1 subsidence.

Reconstructed axial and coronal fine-cut CT imaging was used to assess fusion. Criteria for established fusion were bridging trabecular formation across the intervertebral disc space with the absence of radiolucency spanning more than half of the implant. Consensus of fusion outcome was determined by the principal surgeon (RJM), myself and the CT radiologist.

The local disc angle (LDA) was determined by the angle formed by the intersection of the inferior endplate line and the superior endplate line of the index disc level.

Lumbar lordosis (LL) was measured between the superior endplate of L-1 to the superior endplate of S-1 using the Cobb method.

Statistical analysis

Analyses were based on 2-sided tests with values of $p < 0.05$ considered significant. Descriptive and comparative statistics of demographics, comorbidities, operative parameters, and postoperative complications were analysed for all patients. For univariate analysis, categorical variables were assessed using Pearson's chi-square or Fisher's exact test where appropriate. Continuous variables were examined using 1-way analysis of variance (ANOVA) test. Multivariate analysis was performed by adjustment for confounders, determined by significant differences discovered on univariate analysis. This was presented as odds ratio (OR) and 95% confidence interval (CI). Analyses were based on 2-sided tests with values of $p<0.05$ considered significant. Data analysis and statistical evaluation was conducted using IBM SPSS Statistics 24 (IBM Corporation, Armonk, NY, USA).

Results

Baseline characteristics of overall cohort

A total of 147 patients were included, with mean age of 57.3 ± 13.6 years. Sixty-five patients (44.2%) were female. Patient factors, comorbidities, and indications are summarized in Table 2.2.

Radiological outcomes of overall cohort

91.2% (n=114/125) of patients with appropriate radiological follow-up demonstrated fusion by latest follow-up. Appropriate CT scans at 6 months were not available for 22 patients.

15 patients (10.2%) demonstrated subsidence of mean 4.7mm (range 2.4 – 7.8). All of these cases were classified as delayed cage subsidence (DCS).The mean age of the patients with subsidence was 67 years old.

The preoperative anterior disc height was 8.6mm, which improved to 16.9mm postoperatively immediately, 15mm at 6-week follow-up, and 15.1mm at latest follow-up. For posterior disc height, preoperative (4.7mm) improved to 9.1mm (immediately postoperatively), 9.4mm (6-week follow-up) and 8.7mm (latest follow-up).

The mean LL angle was 42.5° and the mean LDA was 6.7°. The mean cage height, length and width was 13.4mm, 37.8mm and 30.0mm respectively. The mean cage lordosis was 9.0°.

Patient-reported functional outcome of overall cohort

There was significant reduction in VAS and ODI scores and increase in SF-12 scores. VAS pain scores improved from 7.1 (preoperatively) to 2.7 (postoperatively) with significant difference ($P<0.0001$). ODI scores were improved significantly from 57.8 (preoperatively) to 28.8 (postoperatively), with significant difference noted ($P<0.0001$) (Figure 2.3). Preoperative SF-12 physical component summary (PCS) was 33.2, which was increased to 41.7 post-operatively ($P<0.0001$). Preoperative SF-12 mental component summary (MCS) score increased from 38.0 to 48.9 post-operatively ($P<0.0001$).

Table 2.2. Patient demographics and indications for surgery

Demographic	Mean ± Standard Deviation; or Proportion (%) (n=147)
Age (years)	57.3 ± 13.6
Females	44.2
Males	55.8
Smokers	15.6
Diabetes	4.8
Obese	6.8
Overweight	28.6
Worker's compensation	16.3
L4/L5 level	50.3
L5/S1 level	64.6
Multilevel	19.7
Common Indications	
DDD without radiculopathy	14.8
DDD with radiculopathy	54.8
DDD with radiculopathy and stenosis	0.7
DDD with radiculopathy & spondylolisthesis	1.5
Spondylolisthesis	28.2

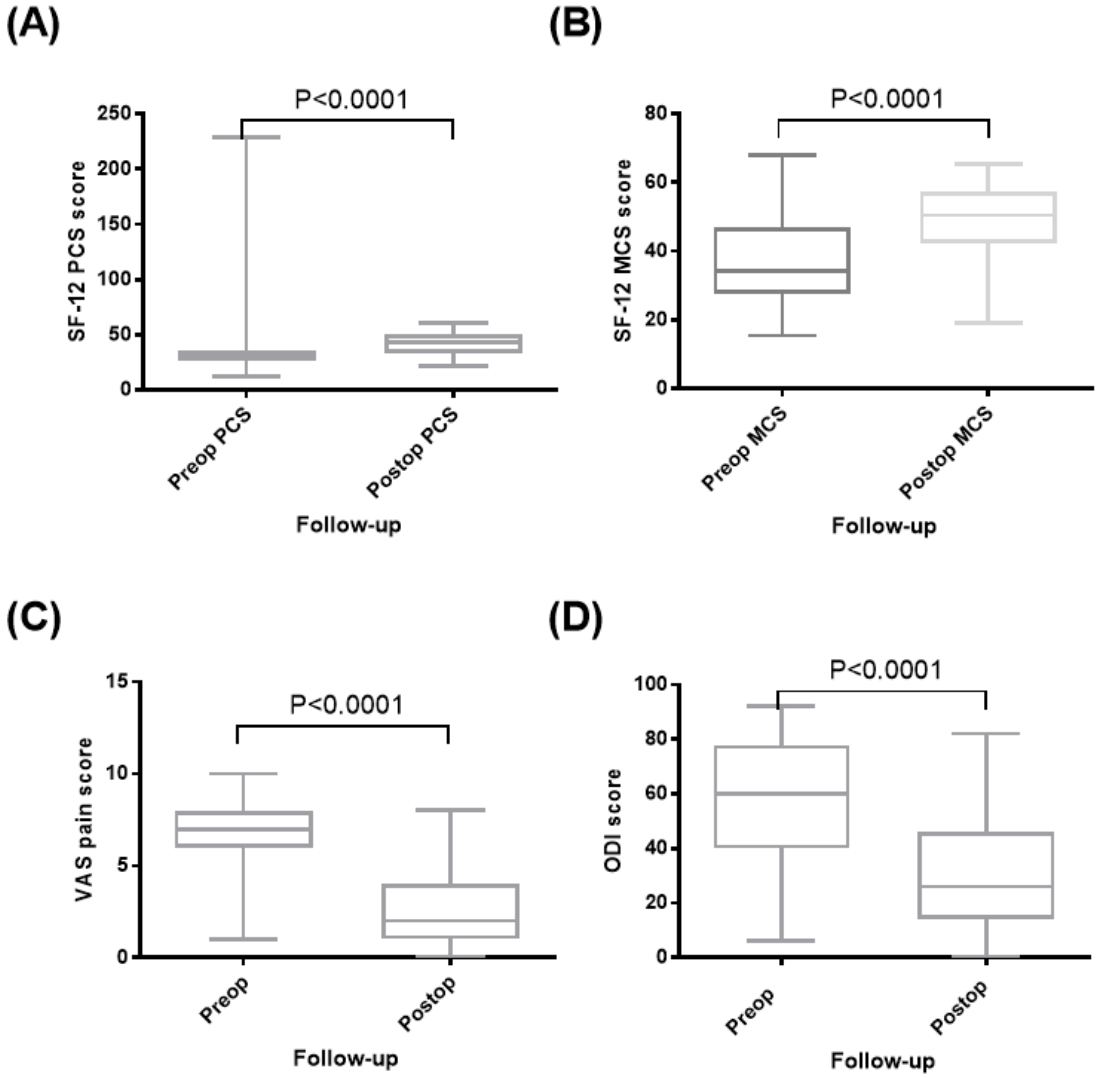


Figure 2.3. Clinical outcomes of overall cohort at follow-up following anterior lumbar interbody fusion surgery. Boxplot preoperative and postoperative scores are shown for (A) SF-12 physical component scores (B) SF-12 mental component scores, (C) VAS pain scores, (D) ODI scores. VAS, visual analogue scale; ODI, Oswestry disability index; PCS, physical component score; MCS, mental component score. Box plot and whiskers correspond to minimum, first quartile, median, third quartile and maximum.

Influence of age group on complications and outcomes

Our cohort of patients were divided into 3 equal groups based on age: Group 1(≤49 years old), Group 2 (50-63 years old), and Group 3 (≥64 years old). Of the original cohort, complete data was available for 137 patients for this analysis. In terms of baseline characteristics across the three age tertiles, there was no significant differences in terms of sex, body mass index, history of diabetes mellitus, respiratory comorbidities, cardiac history, or depression. It was noted that smoking had the highest prevalence in the age group ≤49 years old (26%), whereas hypertension was highest in the group of patients aged ≥50 years old.

In terms of postoperative complications, operation duration, blood loss, and hospital stay did not differ significantly based on age groups. The total number of complications did not differ significantly among the three groups (p=0.258). Patients ≥64 years old had the highest rates of postoperative hematoma (6.5%, p=0.048) and delayed subsidence (21.7%, p=0.007). Postoperative complications such as wound infection, DVT, postoperative ileus, vessel injury, pneumonia, wound dehiscence, pseudoarthrosis, and death were similar amongst the three age groups (Table 2.3).

With radiographic follow-up, all groups had significant improvements in anterior and posterior disc heights immediately postoperatively. This improvement magnitude lessened with longer follow-up, with slight decreases at 6-week follow-up and 12-week follow-up compared to immediately postoperatively. This was similar across all three age groups (Table 2.4). Lordosis angle (˚), lumbar lordosis (˚), cage height (mm), and cage lordosis (˚) measurements did not differ significantly at latest follow-up.

In terms of clinical patient-reported outcomes, there was no significant difference in terms of VAS, SF-12 MCS or PCS scores, or ODI (all P>0.05)(Table 2.5).

A more thorough multivariable analysis was performed to determine if age is a risk factor for delayed cage subsidence following ALIF surgery. This analysis demonstrated that relative to the youngest age group, the old age group ≥64 years was independently associated with greater prevalence of delayed cage subsidence (OR 9.174, 95% CI 1.248-66.67, P=0.029).

Table 2.3. Effect of age group on surgical parameters and complications following anterior lumbar interbody fusion. Asterisk* represents significant differences with $P<0.05$.

	Age ≤49 years (n=45)	**Age 50-63 years (n=46)**	**Age ≥64 years (n=46)**	**P-value**
Hospital stay (days)	4.32±1.76	4.25±1.59	5.30±3.21	0.130
Blood loss (mL)	104.55±120.83	68.84±43.48	116.79±137.68	0.261
Operation duration (mins)	103.18±35.6	96.81±35.94	106.67±35.36	0.771
Total Complications, n (%)	6	2	7	0.258
Wound infection	1	0	2	0.394
DVT	1	0	0	0.386
Postoperative ileus	1	0	1	0.599
Postoperative hematoma	0 (0%)	0 (0%)	3 (6.5%)	0.048*
Vessel injury	0	0	1	0.369
Pneumonia	1	0	0	0.357
Wound dehiscence	1	0	0	0.357
Death	1	0	0	0.357
Pseudoarthrosis	2 (4.4%)	2 (4.3%)	3 (6.5%)	0.675
Delayed subsidence	2 (4.4%)	2 (4.3%)	10 (21.7%)	0.007*

Table 2.4. Effect of age group on fusion and radiographic changes following anterior lumbar interbody fusion. Asterisk* represents significant differences with P<0.05.

	Age ≤49 years (n=45)	**Age 50-63 years (n=46)**	**Age ≥64 years (n=46)**	**P-value**
Fused successfully, n (%)	36	38	39	0.972
Preoperative data:				
Anterior disk height (mm)	8.9±3.3	8.7±3.3	8.3±3.1	0.756
Posterior disk height (mm)	5.5±1.9	4.8±2.1	4.4±1.9	0.122
Average height (mm)	7.2±2.2	6.8±2.4	6.3±2.3	0.382
Directly postop:				
Anterior disk height (mm)	17.8±5.2	16.4±4.3	16.2±4.4	0.290
Posterior disk height (mm)	9.4±2.8	8.6±2.9	9.1±2.5	0.477
Average height (mm)	13.6±3.7	12.5±3.2	12.6±3.1	0.329
6 weeks postop:				
Anterior disk height (mm)	16.9±3.7	15.5±3.3	13.3±3.6	0.006*
Posterior disk height (mm)	10.1±3.2	10.3±3.5	7.7±3.1	0.020*
Average height (mm)	13.5±2.9	13.8±4.7	10.5±2.6	0.006*
At final follow-up:				
Anterior disk height (mm)	15.6±3.7	16.5±3.2	13.7±2.8	0.042*
Posterior disk height (mm)	9.5±3.0	9.4±2.8	7.4±2.3	0.045*
Average height (mm)	12.6±2.8	13.0±2.8	10.0±3.2	0.013*
Lordosis angle (degrees)	6.5±4.0	6.9±3.6	6.7±4.4	0.958
Lumbar lordosis (degrees)	37.8±9.9	42.2±10.5	44.7±10.6	0.056
Cage height (mm)	13.3±1.2	13.4±1.4	13.5±1.1	0.782
Cage lordosis (degrees)	9.2±1.8	9.0±1.6	8.8±1.4	0.456

Table 2.5. Effect of age group on patient-reported outcomes following anterior lumbar interbody fusion. PCS, physical component score; MCS, mental component score; SF-12, short-form 12; ODI, Oswestry disability index

	Age ≤49 years (n=45)	**Age 50-63 years (n=46)**	**Age ≥64 years (n=46)**	**P-value**
Preoperative SF-12 PCS	32.4±6.6	31.4±6.8	36.3±32.4	0.506
Postoperative SF-12 PCS	40.8±11.8	41.0±9.1	41.6±11.0	0.951
Change in SF-12 PCS	9.9±12.0	12.5±11.0	6.3±34.0	0.515
Preoperative SF-12 MCS	35.9±11.2	39.7±13.1	39.0±14.0	0.380
Postoperative SF-12 MCS	48.7±9.1	47.9±9.5	50.7±10.4	0.423
Change in SF-12 MCS	15.0±12.9	11.2±13.0	13.2±17.5	0.574
Preoperative ODI	59.3±20.0	57.9±20.2	57.0±26.7	0.900
Postoperative ODI	29.3±20.8	31.8±17.9	25.4±19.4	0.379
Change in ODI	29.5±23.8	29.8±21.3	36.1±27.4	0.453
Patient satisfaction index	1.7±0.7	1.9±0.8	1.5±0.7	0.134

Influence of obese and overweight weight groups on complications and outcomes

From our cohort, patients were divided into 3 groups based on BMI being normal (n=85, 62%), overweight (n=42, 30.7%), and obese patients (n=10, 7.3%). Normal BMI was defined as <25, overweight BMI as from 25 up to 30, and obese BMI as ≥30. There was no significant different in baseline demographics among these groups. It is noted that fewer obese patients underwent ALIF surgery at the L3/L4 level compared to normal/overweight groups. However, the rate of worker's compensation cases was also significantly lower in the normal weight group versus overweight/obese groups.

There were no statistical differences between groups in length of hospital stay, loss of blood, duration of operation, or total complications (Table 2.6). Pseudoarthrosis was more common following ALIF in obese patients, with 30% of obese patients experiencing failed fusion. This is significantly higher compared to ALIF patients with normal weight (2.4%) and overweight groups (6.3%)(P=0.003). This was the only statistically significant surgical complication showing a difference between normal, overweight, and obese groups.

In terms of radiographic characteristics, preoperative anterior disc collapse was greatest in the obese group. In all groups, disc heights improved significantly after ALIF surgery and this was maintained higher than baseline at 6-weeks follow-up. (Table 2.7). It was noted that fusion rates significant differed amongst the groups, with rates of 88.2% in the normal BMI group compared with overweight BMI (76%) and obese BMI (60%) (P=0.014).

Functional scores in terms of PSI, ODI, and SF-12 outcomes were not significantly different amongst the BMI groups (Table 2.8).

Multivariate analysis of obesity as a risk factor for failed fusion was conducted. After adjustment for age, sex and confounding baseline characteristics, the analysis showed no statistical difference between overweight and normal groups ($p=0.230$) and between obese and normal groups ($p=0.147$) in terms of rates of pseudoarthrosis.

Table 2.6. Effect of weight group on surgical parameters and complications following anterior lumbar interbody fusion. Asterisk* represents significant differences with $P<0.05$.

	Normal	**Overweight**	**Obese**	**P-value**
Hospital stay (days)	4.25±2.40	5.31±2.22	5.75±0.50	0.083
Blood loss (mL)	82.69±65.98	125.36±167.51	100.00±88.31	0.263
Operation duration (mins)	100.59±36.61	105.67±33.69	125.00±7.07	0.605
Surgical Complications				
Total Complications, n (%)	6 (7.1)	4 (9.5)	4 (40)	0.377
Wound infection	2 (2.4)	0 (0)	1 (10)	0.197
DVT	0 (0)	1 (3.1)	0 (0)	0.332
Postoperative ileus	2 (2.4)	0 (0)	0 (0)	0.537
Postoperative hematoma	2 (2.4)	1 (3.1)	0 (0)	0.886
Vessel injury	0 (0)	0 (0)	0 (0)	0.320
Pneumonia	0 (0)	0 (0)	0 (0)	0.320
Wound dehiscence	0 (0)	0 (0)	0 (0)	0.320
Death	0 (0)	0 (0)	0 (0)	0.320
Complications of bone fusion				
Pseudoarthrosis	2 (2.4)	2 (6.3)	3 (30)	0.003*
Delayed subsidence	9 (10.6)	5 (15.6)	0 (0)	0.527

Table 2.7. Influence of weight group on radiographic outcomes. Data given for preoperative, immediate postoperative, 6-week, and final follow-up disc height. n, number of patients. Significant differences P<0.05 are indicated by an asterisk (*).

	Normal	**Overweight**	**Obese**	**p-value**
Fused successfully, n (%)	75 (88.2)	32 (76)	6 (60)	0.014*
Preoperative data				
Anterior disc height	8.31±3.26	9.74±2.69	6.43±3.63	0.040*
Posterior disc height	4.69±1.90	5.31±2.15	4.14±1.74	0.288
Average height	6.50±2.27	7.53±2.15	5.28±2.38	0.049*
Immediate postoperative				
Anterior disc height	16.24±4.20	17.81±5.25	17.41±5.93	0.246
Posterior disc height	8.93±2.68	9.37±2.96	8.25±2.66	0.576
Average height	12.56±3.14	13.64±3.69	12.83±4.10	0.303
6 weeks postoperative				
Anterior disc height	15.39±3.57	15.58±4.09	11.60±0.42	0.219
Posterior disc height	9.05±3.03	10.12±3.96	6.64±0.84	0.181
Average height	12.17±2.91	13.70±4.68	9.12±0.30	0.074
At final follow-up				
Anterior disc height	14.44±2.44	17.05±3.93	11.33±2.07	0.004*
Posterior disc height	8.23±2.87	9.69±2.80	7.20±1.25	0.165
Average height	10.97±3.10	13.37±2.91	9.27±1.65	0.017*
Lordosis angle (degrees)	6.58±4.13	6.90±3.99	6.83±3.49	0.954
Lumbar lordosis (degrees)	42.88±9.15	41.95±13.53	32.50±7.12	0.077
Cage height (mm)	13.29±1.06	13.53±1.62	13.64±1.14	0.513
Cage lordosis (degrees)	8.91±1.61	8.99±1.59	9.62±1.70	0.448

Table 2.8. Effect of weight group on clinical outcomes measured by short form-12 quality of life questionnaire (SF-12) mental component score (MCS) and physical component score (PCS), Oswestry-disability index (ODI), and patient satisfaction index (PSI). Significant differences P<0.05 are indicated by an asterisk (*).

	Normal	**Overweight**	**Obese**	**P-value**
Short form-12 (SF-12)				
Preoperative SF-12	70.12±14.14	67.94±12.20	76.87±19.98	0.295
Postoperative SF-12	91.70±15.82	88.83±17.46	85.20±13.82	0.465
Change in SF-12	25.46±19.29	25.07±17.34	14.58±14.96	0.526
Physical Component Score of SF-12 (PCS)				
Preoperative PCS	34.68±23.85	30.45±5.85	34.7±10.75	0.559
Postoperative PCS	38.88±10.27	39.91±11.14	34.55±9.83	0.468
Change in PCS	8.28±25.77	13.51±10.98	0.25±4.91	0.373
Mental Component Score of SF-12 (MCS)				
Preoperative MCS	38.10±13.20	37.57±10.83	42.17±18.28	0.686
Postoperative MCS	45.83±11.77	45.94±10.01	50.64±7.34	0.543
Change in MCS	13.90±15.31	11.24±12.36	14.83±19.79	0.693
Owestry-Disability Index				
Preoperative ODI	56.43±22.31	60.59±20.84	62.23±29.95	0.582
Postoperative ODI	25.84±18.01	33.14±20.05	46.73±27.17	0.036*
Change in ODI	33.10±26.40	28.72±18.89	34.17±27.54	0.705
Patient Satisfaction Index				
PSI	1.61±0.78	1.81±0.74	2.0±0.1	0.333

Influence of smoking status on complications and outcomes

Our cohort was divided into current smokers (n=23, 16.8%) and non-smokers (n=114, 83.2%). Ex-smokers >12 months were considered current non-smokers due to limited statistical power of our cohort size. There were no significant difference in baseline characteristics.

Surgical parameters, including hospital stay, blood loss and operation duration, did not differ significantly between the two groups (Table 2.9). A greater number of smokers experienced complications compared to non-smokers (30.4% vs. 7%, P=0.004), particularly rates of pseudoarthrosis (21.7% vs. 1.8%, P≤0.001).

The percentage of patients with successful fusion differed significantly between smokers and non-smokers (69.6% vs. 85.1%, P=0.006) (Table 2.10). At latest follow-up, the correction in posterior disc heights for smokers was reduced compared to non-smokers. However improvements in anterior disc height and average height were not impacted. No significant difference between the groups was demonstrated for lordosis angle, lumbar lordosis, cage height, and cage lordosis at the final follow-up.

Preoperative and postoperative clinical assessment showed no significant differences in clinical outcomes between smokers and non-smokers, in terms of SF-12 MCS/PCS, ODI and PSI (Table 2.11).

Multivariate analysis with adjustment for confounders showed that smokers undergoing ALIF was independently associated with higher rates of total postoperative complications (OR, 7.74; 95% CI, 2.22-26.97; P=0.001), and of failed fusion (OR, 37.19; 95% CI, 3.79-365.20; P=0.002) than non-smokers.

Table 2.9. Effect of smoking status on surgical parameters and complications following anterior lumbar interbody fusion. Asterisk* represents significant differences with $P<0.05$.

	Non-smoker	**Smoker**	**P Value**
Hospital stay (days)	4.70±2.50	4.40±1.67	0.617
Blood loss (mL)	90.56±113.47	132.67±93.91	0.183
Operation duration (mins)	100.00±33.49	111.92±39.35	0.294
Total Complications, n (%)	8 (7.0%)	7 (30.4%)	0.004*
Wound infection	3 (2.6%)	0 (0%)	0.062
DVT	1 (0.9%)	0 (0%)	0.075
Postoperative ileus	1 (0.9%)	1 (4.3%)	0.309
Postoperative hematoma	2 (1.8%)	1 (4.3%)	0.426
Vessel injury	1 (0.9%)	0 (0%)	0.832
Pneumonia	0 (0%)	1 (4.3%)	0.168
Wound dehiscence	0 (0%)	1 (4.3%)	0.168
Death	0 (0%)	1 (4.3%)	0.168
Pseudoarthrosis	2 (1.8%)	5 (21.7%)	<0.001*
Delayed subsidence	12 (10.5%)	2 (8.7%)	0.572

Table 2.10. Influence of smoking status on radiographic outcomes. Data given for preoperative, immediate postoperative, 6-week, and final follow-up disc height. n, number of patients. Significant differences P<0.05 are indicated by an asterisk(*).

	Non-smoker	**Smoker**	**P Value**
Fused successfully, n (%)	97 (85.1%)	16 (69.6%)	0.006*
Preoperative data:			
Anterior disk height	8.84±3.32	7.52±2.45	0.152
Posterior disk height	4.92±2.03	4.44±1.72	0.390
Average height	6.88±2.38	5.98±1.78	0.170
Directly postop:			
Anterior disk height	16.68±4.78	17.34±4.06	0.578
Posterior disk height	9.09±2.89	8.71±2.06	0.587
Average height	12.89±3.51	13.03±2.68	0.870
6 weeks postop:			
Anterior disk height	15.37±3.87	14.90±3.30	0.708
Posterior disk height	9.56±3.46	8.31±3.15	0.271
Average height	12.81±3.88	11.61±2.88	0.334
At final follow-up:			
Anterior disk height	15.55±3.42	13.41±2.85	0.106
Posterior disk height	9.07±2.63	6.82±3.31	0.040*
Average height	12.06±3.26	10.12±2.41	0.120
Lordosis angle (degrees)	6.52±3.93	7.31±4.31	0.485
Lumbar lordosis (degrees)	42.91±10.63	37.69±9.83	0.081
Cage height (mm)	13.44±1.28	13.13±1.12	0.325
Cage lordosis (degrees)	8.97±1.60	9.05±1.68	0.846

Table 2.11. Effect of smoking status on clinical outcomes measured by short form-12 quality of life questionnaire (SF-12) mental component score (MCS) and physical component score (PCS), Oswestry-disability index (ODI), and patient satisfaction index (PSI). Significant differences P<0.05 are indicated by an asterisk(*).

	Non-smoker	**Smoker**	**P Value**
Preoperative PCS	33.74±21.29	31.71±6.02	0.667
Postoperative PCS	39.23±10.67	37.56±9.78	0.511
Change in PCS	9.73±24.06	8.61±11.46	0.837
Preoperative MCS	38.79±12.59	35.37±13.61	0.269
Postoperative MCS	46.18±11.60	45.97±8.19	0.938
Change in MCS	13.22±14.84	12.90±13.88	0.928
Preoperative SF-12	70.46±13.97	67.08±14.07	0.318
Postoperative SF-12	90.84±16.54	88.67±14.78	0.579
Change in SF-12	25.79±19.02	21.59±16.67	0.358
Preoperative ODI	56.38±22.57	65.50±19.64	0.090
Postoperative ODI	27.87±18.76	32.57±21.88	0.324
Change in ODI	31.54±25.04	32.93±21.67	0.817
Patient satisfaction index	1.63±0.76	1.90±0.69	0.124

Examples of complications following anterior lumbar interbody fusion

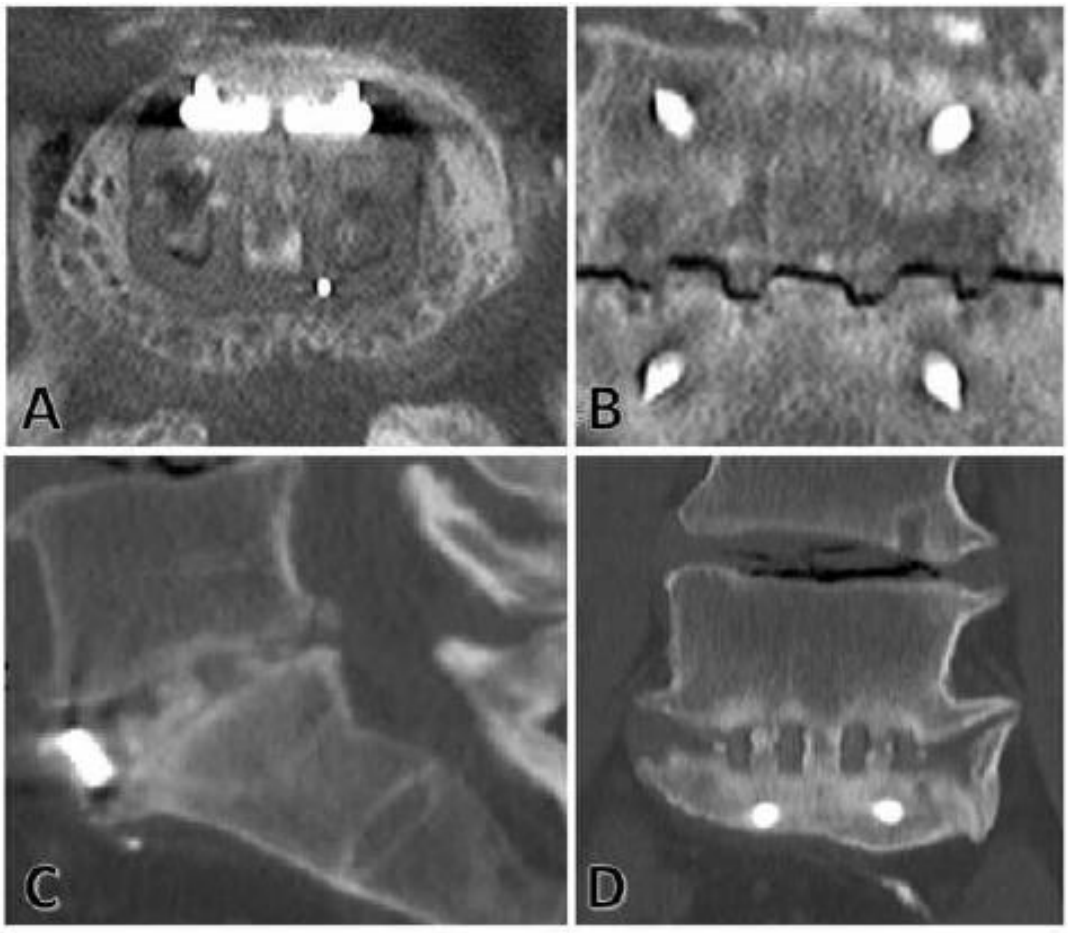


Figure 2.4. Case demonstrating failed fusion follow-up ALIF surgery at follow-up. A 73-year old male was diagnosed with degenerative disc disease without radiculopathy, and underwent L4/L5ALIF surgery. (A-B) Coronal and axial computed tomography (CT) views 10 months postoperatively demonstrating non-union at L4/L5 (C-D) Another case demonstrating failed fusion. A 63-year old presented with degenerative disc disease without radiculopathy and underwent ALIF surgery. Sagittal and coronal images demonstrate non-union at L5/S1. Sagittal and coronal CT images show with non-union at L5/S1 at 12-month follow-up.

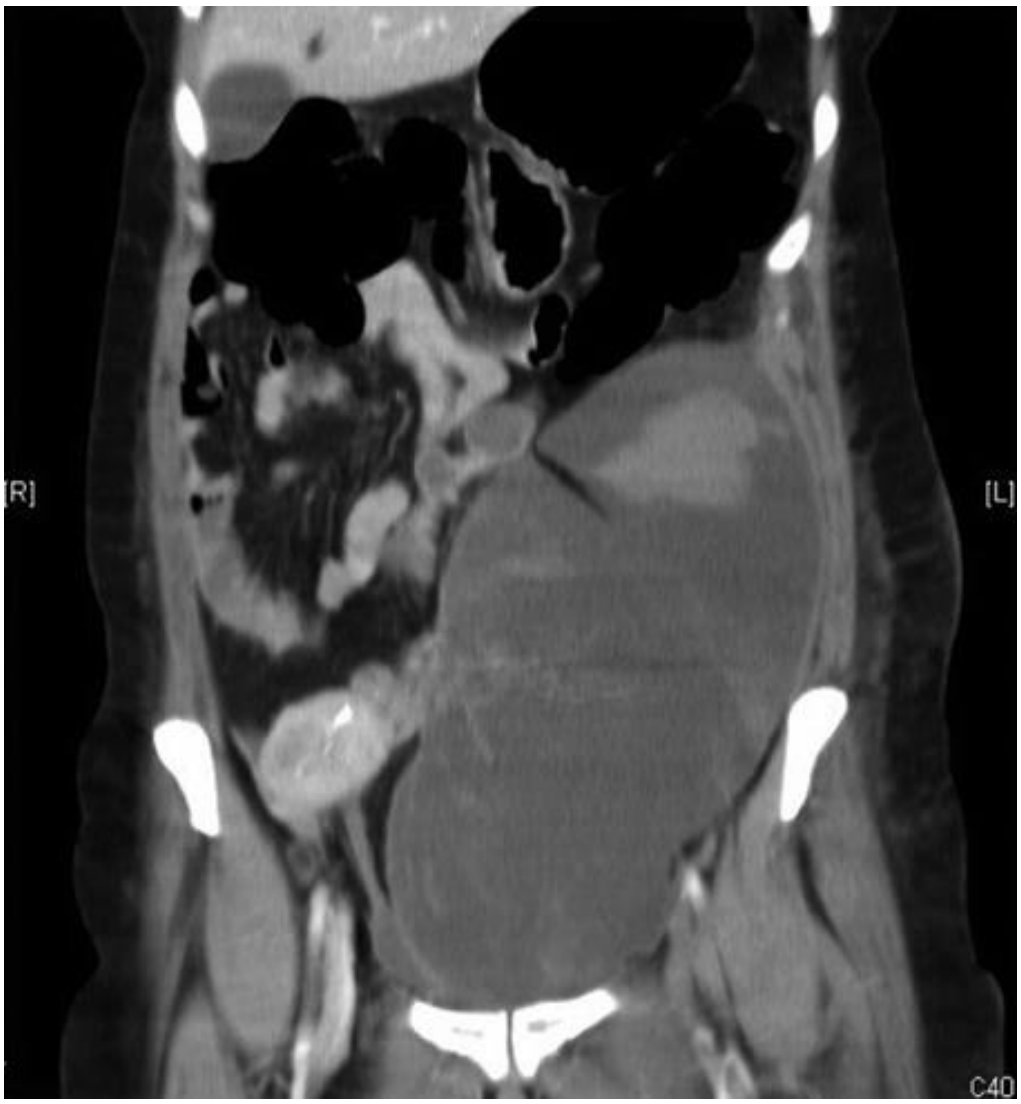


Figure 2.5. Large retroperitoneal hematoma following anterior lumbar interbody fusion, requiring drainage and exploration. Source: A/Prof Ralph Mobbs, also published in Mobbs et al.(30)

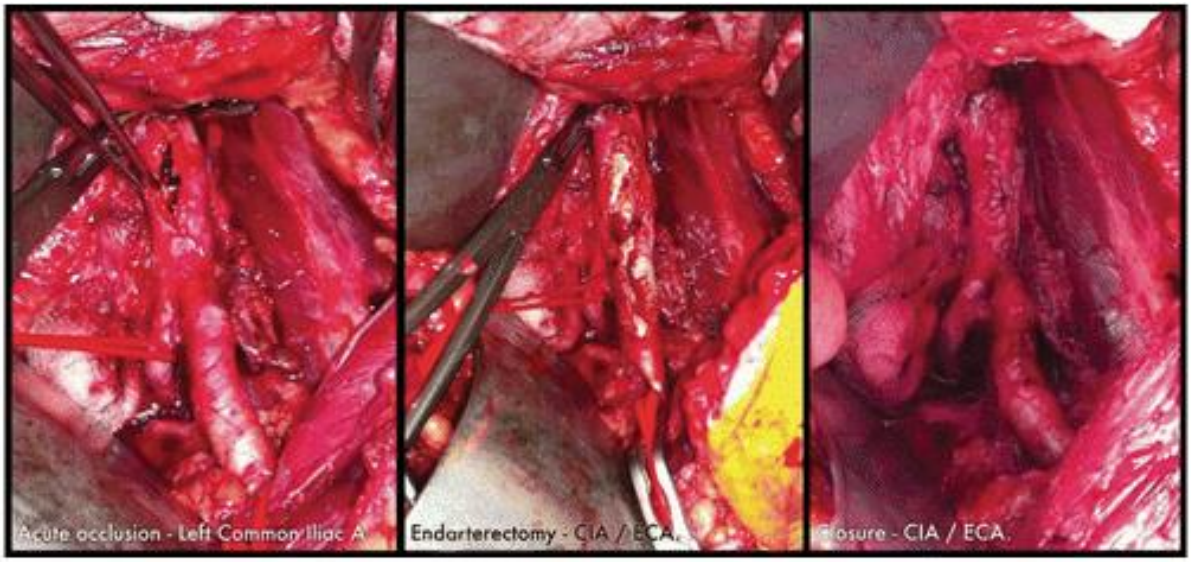


Figure 2.6. Left common iliac artery: acute occlusion and thrombectomy following anterior lumbar interbody fusion. Abbreviations: CIA, common iliac artery; ECA, external carotid artery. Source: A/Prof Ralph Mobbs, also published in Mobbs et al.(30)

Discussion

The decision to choose a specific surgical approach for lumbar fusion is one that should be individualised to the patient. Aside from clear anatomical limitations of each surgical approach, it remains to be clearly established which risk factors are associated with complications and poor fusion rates specific to ALIF compared to other posterior approaches such as PLIF or TLIF.

Three key demographic characteristics of patients who often present for lumbar fusion for various pathologies were investigated: age group, weight group and smoking status. These three factors were chosen as in our personal practice, they often form part of a clinician's "gestalt" when deciding whether an ALIF operation is high risk for a patient or not. However, there is limited risk scores which quantify the extent of risk associated with these factors. Furthermore, the investigation of spine surgery outcomes in relation to age, obesity, and smoking status have produced mixed data depending on population studied and the exact nature of the ALIF procedure performed.

For example, many nationwide database studies pool data for ALIF but do not specify the type of cage (cage alone or with integrated screws) and whether supplemental fixation was used or not. We have previously evaluated four different stand-alone ALIF cages with 2, 3 or 4 screw designs (Synfix-LR, Redmond Lumbar Cage, Midline STALIF, PILLAR SA PEEK spacer) in terms of their stability under axial and torsional loading(31). We demonstrated that for each cage type, the addition of integrated screws to the cage construct decreased subsidence relative to testing of the same cage without screws inserted (Figure 2.7). Subsidence rates also differed based on the number of integral screws each integral ALIF implant had.

Furthermore, load stress and fusion rates after an ALIF performed using an integrated cage may potentially differ from ALIF performed with a routine cage and supplemental posterior fixation. The biomechanics and load distribution of these two constructs, especially under movement or stress, are not precisely the same(32). Choi et al(33) compared the stress distribution amongst 3 cages: SynCage-LR (anterior cage alone), SynFix-LR (anterior cage with integrated screws), and SynCage-LR with added posterior pedicle screws. The authors demonstrated that the load distribution of the integrated anterior cage is most similar to the intact spine, whereas anterior cage with posterior fixation had higher posterior loads which can theoretically result in posterior migration(33).

As such, given the significant differences in terms of load distribution and stress tolerance between cage designs and whether posterior fixation is used or not, it is important to study ALIF outcomes in a population that has had similar cage designs placed. Therefore for the present prospective study, we sought to collect follow-up radiological and clinical outcomes from patients operated on by a single senior neurosurgeon, all receiving the same type of integrated ALIF cage without additional posterior fixation. Furthermore, in all cases, a senior vascular surgeon assisted with access to the anterior spine.

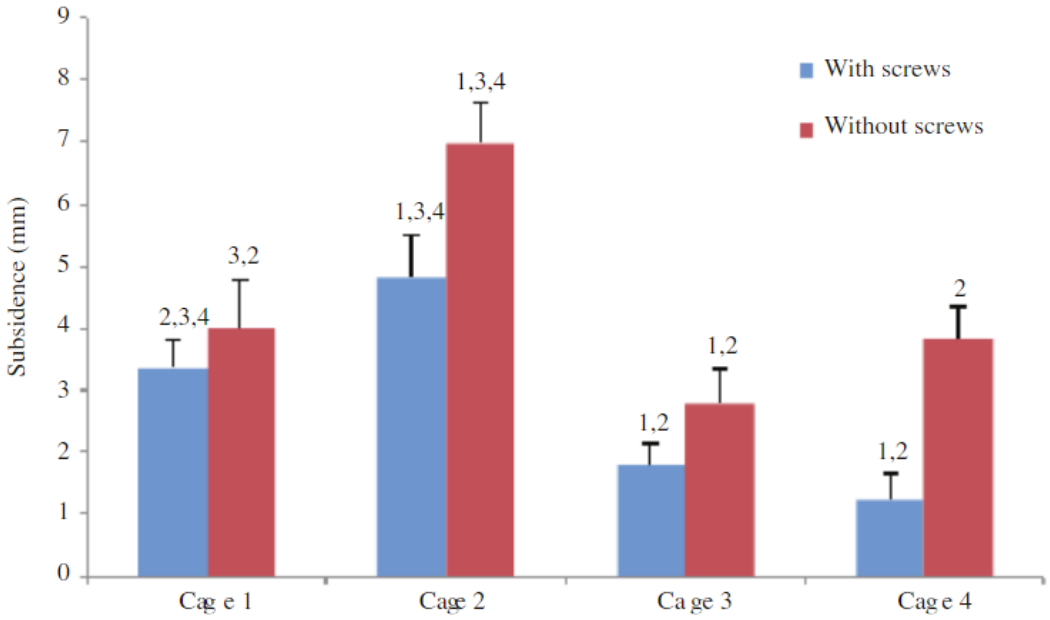


Figure 2.7. We have previously evaluated four different stand-alone ALIF cages with 2, 3 or 4 screw designs (Synfix-LR, Redmond Lumbar Cage, Midline STALIF, PILLAR SA PEEK spacer) in terms of their stability under axial and torsional loading. 400N loading force was applied and the rates of subsidence were measured. Cages with and without screws were compared. Mean and standard deviation illustrated with SD bars. Numbers above each bar represent the corresponding inter-cage tests that differed significantly ($P<0.05$). Significant ($P<0.05$) intra-cage differences with and without screws were indicated by in cage 2, 3, and 4. It is demonstrated that for each cage type, the addition of integrated screws to the cage construct decreased subsidence relative to testing of the same cage without screws inserted. Subsidence rates also differed based on the number of integral screws each integral ALIF implant had. Figure reproduced from Assem et al.(31)

Age group alone should not influence decision to undergo anterior lumbar interbody fusion

With advances in surgical techniques and anaesthesia, there has been an increasing demand for operations in higher risk candidates. This has also been the case with elderly patients with spinal disorders. However, the guidance on what age limit, if at all, constitutes high risk of complications and morbidity for spinal fusion remains conflicted. Some studies have demonstrated increased morbidity in spinal operations performed in the elderly(34, 35) whereas others support operating in the elderly population without significantly added risk(36, 37). There is also variability in the literature with what age is regarded as "elderly".

A significant portion of the literature to date has used 65 years as the threshold, but with an increasing number of surgeons pushing the bounds of what is possible, there are some reports of successful operations performed in patients greater than 80 years of age. The Japan Association of Spine Surgeons with Ambition (JASA) performed a multicentre study was performed in patients aged 80 years or older who underwent 262 spinal surgeries at 35 facilities(38). Their analysis demonstrated that age ≥80 years was not significantly associated with major complications. There was an increased risk, albeit a small different in absolute terms, of perioperative complications (Hazard ratio 1.007, 95% CI 1.001-1.009). However, the population studied was highly heterogeneous with both degenerative and traumatic indications as well as operations done at cervical, thoracic and lumbar levels with various forms of cages and instrumentation. The impact of age on laminectomy or microdecompression surgery for lumbar spinal stenosis was investigated by Giannadakis et al(39) via analysis of the Norwegian Registry for Spine Surgery. From an analysis of 1503 patients, patient-

reported clinical outcomes as well as complication rates did not significantly differ in patients aged 80 years and older versus younger patients(39). Although this population studied is more homogenous compared to the JASA study described above, the procedures studied are considered more minor and less traumatic compared to other extensive more complex spinal surgeries. For comparison, in a study of spinal surgery for traumatic indications, Winkler et al(40) analysed the National Sample Program of the National Trauma Data Bank and compared outcomes of middle-aged (55-69 years) and elderly (≥70 years) patients who had traumatic fracture of the lumbar spine. The authors found that elderly age was associated with higher morbidity, including periprocedural complications, prolonged hospitalization, and lowered likelihood for discharge to home. Comparison of the above studies suggest that the nature of the surgery (limited/minor versus extensive/prolonged/traumatic) appears to play a greater role in dictating potential complications rather than age group alone.

Our study provides evidence that for ALIF specifically, elderly age (≥64 years old) results in increased rate of subsidence but does not affect clinical outcomes. Our results suggest that age alone should not be a contraindication to ALIF. We do agree with the conclusions of the Japan Association of Spine Surgeons with Ambition (JASA)(38) that elderly patients with considerable comorbidities are at higher risk for complications. Further to this, comorbidities and reduced physiologic reserve are documented predictors of adverse surgical outcomes in elderly populations. Frailty, a lack of physiologic reserve across multiple organ systems, is more common in older patients(41). In this study, the eldest tertile was not necessarily frailer nor did they have more comorbidities, which would explain a lack of difference in clinical outcomes between the groups. Therefore age alone should not be a contraindication to ALIF

surgery, however elderly age along with comorbidities or markers of frailty is more likely to result in greater complications.

Our study demonstrated that the elderly tertile was independently associated with higher risk of delayed subsidence following ALIF surgery. A possible explanation for the delayed subsidence observed in the most elderly tertile in our study is osteoporosis. The incidence of osteoporosis progressively increases with age, increasing from 5.1% in individuals between 50-59 to 26.2% in those 80 and above(42). Additionally, a statistically significant older patient population with osteoporosis was shown to have an increased rate of subsidence, but did not have greater surgical revision or complications compared to the younger, non-osteoporotic group(43). Therefore, subclinical or undiagnosed osteoporotic patients may have an increased incidence of subsidence.

We suggest that while increasing age may raise concern for the possibility of comorbidities, elderly age alone should not serve as a contraindication for ALIF surgery. Thus, the surgeon should engage the elderly patient in a discussion of the benefits and risks of ALIF surgery, taking into account individual patient factors including comorbidities. In conjunction, elderly patients with a history of osteoporosis or fractures should be made aware of the increased risk of implant subsidence during the decision-making process with ALIF surgery.

Obesity alone should not influence decision to undergo anterior lumbar interbody fusion

Obesity has been linked to operative outcomes and surgical complications in studies. However, it is not clear whether obesity itself is the driving factor, or whether obesity is

a surrogate for other factors and comorbidities which are then associated with outcomes. With regards to lumbar spinal surgery, obesity has been associated with access-related problems, poor wound healing, and increased frequency of comorbidities and risk factors such as diabetes mellitus(8-13). Operative complications include surgical site infection, deep vein thrombosis, and pulmonary embolism. Jackson and Devine performed a systematic review examining the effects of obesity on outcomes and complications of spinal surgery, and found increased rates of postoperative complications in the obese cohort, particularly related to infection and venous thromboembolism(44).

Increased blood loss, recovery times, and operative times have been observed in surgical procedures for the obese, due to the increased technical challenges of the surgery, and comorbidities. For some cases, the surgical exposure in obese patients may be more time-consuming and challenging, particularly with the deep soft tissues obscuring a clear trajectory to the disc space. Thus there have been reports of increased complication rates (8-12). Owens and colleagues analysed 82 propensity-matched patients that were stratified into normal, overweight, and obese categories based on their BMI. They found that estimated blood loss and operative times were statistically significantly greater in the overweight and obese cohorts than in the normal cohort, but that lengths of hospital stay and perioperative complication rates were similar in all groups(45).

In our experience, we did not find that obesity was associated with clinical outcome. Although we acknowledge that our findings are limited by the small sample size in the obese category, our presents series suggests that being overweight or obese should not be the sole contraindication for performing ALIF in this population. The technical

difficulty of access and exposure in our study was in part mitigated by enlisting the experience of a senior vascular surgeon who has significant expertise in such exposures, as well as the use of a retractor system which comprises a ring placed around the surgical site. It is fixed to both sides of the operating table with arms. Using retractor blades, the ring allows 360 degree access to the surgical exposure from any side.

It was noted that the obese group had lower fusion rates compared to the normal weight group. Only 60% of obese patients achieved successful bone fusion, compared with 76% of overweight patients, and 88.2% of normal-weight patients. This is not the first time such an observation has been noted. Behrbalk et al. prospectively investigated ALIF procedures in 25 patients. Their analysis showed higher rates of subsidence in patients with a higher BMI(46). The investigators postulated that these obesity-related postural changes due to increased lumbar disc degeneration may lead to lumbar olisthesis, cage subsidence, and more instability in the obese cohort. Another explanation offered by Djurasovic and colleagues as to why fusion rates may be lower in obese patients is that their "pain generating" source may not be clearly or accurately identified. Due to their truncal body mass, it is difficult to elucidate to what extent a patient's mechanical back pain is due to segmental instability versus paraspinal muscle fatigue. For this reason, the presumed effectiveness of a fusion procedure may be overestimated in the obese population(47).

Obesity is increasingly recognised as a state of increased systemic inflammation, characterized by abnormal cytokine production, acute phase reactants, and activated inflammatory signalling pathways(48). Cytokines such as tumour necrosis factor (TNF), interleukin 6 (IL-6) and adipokines such as adiponectin, leptin, and resistin, are associated with obesity and may correlate with cartilage inflammation and disc

degeneration(49-51). Such cytokines may interact with pathways involved in bony fusion and have an inhibitory effect, however such hypothesis requires further exploration and validation.

Another possible link between obesity and poorer fusion noted is due to higher associated atherosclerotic-related vascular ischemia(44). The vertebral body blood supply comprises nutrient and metaphyseal arteries, which have centrifugal branches that terminate at the end plates(52). The disc space has no direct blood supply, and instead relies on diffusion of bloods supply from the adjacent vertebral bodies(53). In obese patients, this blood supply may be compromised, which leads to poor fusion outcome.

We recommend that obesity alone should not be considered a contraindication to surgery in patients with appropriate indication to undergo ALIF. Patients should be aware however that obesity is associated with lower fusion rates radiographically, although this may not necessarily translate into any difference in clinical outcome or complications at follow-up.

Smoking is associated with higher rates of total complications and failed fusion following anterior lumbar interbody fusion

Although smoking rates are declining worldwide, it remains one of the leading preventable causes of morbidity and mortality(15). There is large body of literature exploring the effects of smoking and tobacco consumption on surgical outcomes, particularly on respiratory and cardiac function. Smokers are at higher risk of post-surgical complications, including wound infections, sepsis and delayed healing(54).

Regarding the lumbar spine, an association has been documented between smoking and poor bone quality, lumbar spine fractures and lower back pain(16-18), for both active smokers and those chronically exposed to second-hand smoke(19-21). Smoking increases cortisol levels which subsequently results in oestrogen imbalance, inhibits periosteal cell proliferation, downregulates collagen synthesis, impedes calcitonin, and decreases oxygen supply and calcium absorption(19, 55, 56). Overall this results in an osteoporotic effect, increasing vertebral and endplate porosity and decreased trabecular thickness(57), resulting in degenerative spinal conditions which require arthrodesis or lumbar interbody fixation. Further contributing factors likely involve accelerated bone demineralization, altered vasculature and changes in gene expression(58).

In additional to changes in vertebral bone, smoking also affects the process of bone healing in spinal fusion. Vertebral bone fusion in spine arthrodesis is similar to the healing process of long bones, occurring in three key stages: the early inflammatory stage, the repair stage, and the late remodelling stage(59). The inflammatory phase involves formation of a hematoma with infiltration of fibroblasts and inflammatory cells such as macrophages, monocytes, lymphocytes, and polymorphonuclear cells, which results in granulation tissue and migration of mesenchymal cells. The repair stage involves vascular ingrowth facilitated by fibroblasts. The next stages involves development of a collagen matrix, formation of soft callus and subsequent callus ossification to form bridge of woven bone. Over time, the remodelling is further fine-tuned by mechanical stresses. To further facilitate bony healing and fusion, it is common in spinal arthrodesis to use of bone graft or graft substitute for structural support and scaffolding. Options typically include autograft bone, allograft bone, synthetic bone graft substitutes or extenders, and bone promoting molecules or

cells(60). The use of graft may facilitate osteogenesis, osteoinduction, and osteoconduction.

Each of the above processes can be negatively affected by smoking, particularly via inhibition of vasculature, inhibition of molecular pathways which promote fusion and healing, as well as mechanical stability. There is increasing emphasis on specific molecular pathways and cytokines which are affected by nicotine and smoking. Particularly, Bone Morphogenic proteins (BMPs) 2, 4, and 6, basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), and type I and II collagen have been implicated in the neo-vascularisation within the fusion mass (in addition to general nutrient supply to the vertebral bone). Nicotine, by reducing expression of VEGF and bFGF, inhibit the pathways involved in neo-vascularisation in the fusion mass. BMPs 2, 4, 6 are involved in osteogenesis, osteoblast differentiation and formation of new bone mass. By inhibition of BMPs, nicotine inhibits formation of new bone(61).

Clinical studies examining the influence on outcomes of lumbar spine surgery have demonstrated variable results(22-26). Brown et al. reported a rate of pseudoarthrosis of 40% for smokers, compared to 8% for non-smokers(24). Glassman et al. reported a 26.5% rate of failed fusion in smokers, significantly higher than the 14.2% in non-smokers(62). In a retrospective case series of 426 patients, Andersen et al. described a pseudoarthrosis rate of 18.2% in patients who smoked more than 10 cigarettes per day, compared with 9.8% in those smoking fewer than 10 cigarettes per day and 8.9% in non-smokers. Smoking was shown to significantly increase the likelihood of non-fusion, with an odds ratio of 2.01(63). Mooney et al. investigated the effects of smoking on spinal fusion over 4 years, and concluded that smoking significantly reduced long-

term fusion maintenance(25). However, in a recent study by Kalb et al(27) assessing outcomes for ALIF specifically, no association was reported between smoking and pseudoarthrosis. Likewise, Bydon et al. found an association between smoking and pseudoarthrosis rates only for 2-level posterolateral fusion; for the single-level procedure, smokers did not have significantly higher levels of pseudoarthrosis(22).

Whilst ALIF is a common used interbody fusion approach for a number of spinal conditions, the impact of smoking on ALIF spine surgery has not, to date, been extensively researched. The majority of the evidence of smoking on lumbar spinal fusion outcomes has been focused on posterior surgical approaches, however it is reasonable to hypothesise that smoking has a similar impact on fusion rates and complications in ALIF. In our series, we showed that smokers have significantly lower rates of successful fusion than non-smokers. Of the significantly higher proportion of postoperative complications reported for smokers, pseudoarthrosis rates in particular were shown to differ significantly. In our multivariate analysis, the rate of failed fusion and pseudoarthrosis. These findings are consistent with several previous studies on the outcomes of lumbar fusion.

In our study, results for other postoperative complications did not differ significantly between the groups. This finding must be evaluated against the conflicting evidence in the literature on lumbar fusion. It has been reported that smoking increases the risk of surgical site infection and delayed wound healing in spinal procedures(64). Bydon et al. investigated the development of postoperative complications in 281 cases of posterolateral fusion, and found that smokers did not have significantly higher rates of complications than non-smokers(22). However, Dean et al. had earlier reported increased blood loss and transfusion requirements for smokers after lumbar fusion(26).

In contrast, Appaduray & Lo concluded from a multivariate analysis of data on 902 patients that a positive smoking history was not a significant risk factor for postoperative complications following lumbar spine surgery(65). In a retrospective review of 14,500 patients who had undergone elective spine surgery, Seicean et al. reported similar rates of minor and major complications for both smokers and non-smokers after 30 days(66).

We did not find any significant difference in preoperative and postoperative patient-reported outcomes between smokers versus non-smokers. Although this could be due to limited statistical power, our results are consistent and aligns with data from Andersen et al., which reported no significant influence of smoking on postoperative function after lumbar fusion, as assessed by the Dallas Pain Questionnaire, and no significant association between smoking and patient satisfaction on multivariate analysis(63). In contrast, Glassman et al. reported significantly lower return-to-work rates and worse patient satisfaction scores for smokers compared to non-smokers, following a lumbar fusion procedure(62). Similarly, Eubanks et al. demonstrated that smokers were 5 times more likely to have a considerable limitation of physical activity after posterior cervical fusion, controlling for age, gender and diagnosis(67).

Based on the above, we recommend that all patients undergoing ALIF surgery should fully cease smoking if possible, or at least within a timeframe prior to operation. In a collaborative systematic review study by the World Health Organization (WHO), the University of Newcastle, Australia and the World Federation of Societies of Anaesthesiologists (WFSA)(68), every tobacco-free week after 4 weeks improves health outcomes by 19%, due to improved blood flow throughout the body to essential organs. As such, pre-operative smoking cessation at least 4-weeks prior to operation is

recommended to optimize patient health and improve potential surgical outcomes as much as possible. Postoperative smoking cessation will help improve vascularization and improve long-term fusion. In the real world, smoking cessation or compliance is not always possible in every patient. In these instances, nicotine replacement therapy to help smokers quit perioperatively and use of osteoinductive bone protein with autogenous bone has been suggested, however their effectiveness and value is currently still under ongoing research(60, 69).

Limitations

It is important to recognize the limitations of this study. Firstly, there was significant heterogeneity in the study due to usage of different graft materials along with innate variations in the included patient population. Bone mineral density was also not measured but has been shown to potentially play a role in the disc subsidence. Smoking status could only be analysed as a binary variable, rather than by more specific measures of smoking such as pack-years, which could have allowed for greater insight into the dose effects of smoking on surgical outcomes. We were not able to assess bone quality in our patients used methods such as DEXA scans. One alternative in the absence of bone density analysis would be to use CT Hounsfield units to analyse the rate of subsidence and fusion. Patients with Hounsfield CT values <110 may be considered osteoporotic and values >160 are considered normal(70, 71). Although this was not performed for the current study, it is an avenue for future investigation for ALIF. Secondly, confounding variables may have contributed to the reported differences between patients with a normal BMI and those with a raised BMI, including

differences in baseline comorbidities and characteristics. Another limitation of the present study was that cage dimensions were not included in the analysis. Cage dimensions, particularly width and length, may be correlated with subsidence(72). Cages that are contained inside the outer ring of the endplate are more prone to subside compared to those that extend more laterally(73). Given that the present study is a single centre study encompassing patients from a similar geographic area, the results of the study would benefit from replication at other institutes from different geographic areas to be more widely applicable. Functional outcomes were measured using subjective patient-reported questionnaires, such as the SF-12 and the ODI questionnaires. Whilst useful for gauging patient satisfaction and perception of improvement, more robust measures of functional outcome must be considered for future study to permit more objective comparison.

Nevertheless, our study is a large prospective study investigating the disc subsidence in ALIF to date. The strengths of our study include its prospective design, multivariate adjustment of potential confounders, use of several domains of outcome measures, and follow-up outcomes. The measurement of disc subsidence was done using fine cut CT scans and the technique was standardized across all patients.

Conclusions

Increased age was not associated with adverse perioperative outcomes and complications of ALIF. There was an increased incidence of delayed subsidence in patients with age ≥64 years old. While increasing age may raise concern for the possibility of comorbidities, our data is suggestive that elderly age alone should not

preclude patients from undergoing ALIF surgery. ALIF surgery can be safely and effectively performed in obese patients, and that BMI should not be considered as the sole contraindication to surgery. The rate of successful fusion after ALIF surgery was found to be significantly lower for smokers compared to non-smokers. No significant association was found between smoking status and other perioperative complications or adverse clinical outcomes. It is acknowledged that the current dataset has limitations in terms of statistical power and potential confounding factors such as bone density and cage characteristics.

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Chapter 3

Risk factors for perioperative complications and hospital readmissions following anterior lumbar interbody fusion

Preface and objectives

In the previous chapter, we demonstrated evidence based on our experience that ALIF is an effective and safe surgical option for patients requiring lumbar interbody fusion for a number of indications. This improvement in clinical functional and radiographic outcome was maintained over the follow-up period.

Of equal importance is understanding the rates of complications in the perioperative period and potential contributing risk factors. This is not only with regards to the clinical wellbeing of patients, but also from a healthcare provider perspective. With increasing surgical volume and lack of resources, some hospitals may consider minimising costs by streamlining discharges and reducing length of stay, which in turn may be related to patient comorbidities, intraoperative and perioperative complications.

By identifying predictive factors for perioperative complications and readmissions after ALIF, this may allow clinicians to anticipate potential complications and discharge needs postoperatively, and potentially mitigate associated discharge and length of stay costs.

Therefore, the objectives of this chapter are to:

(1) Determine 30-day morbidity and mortality rates following ALIF using a nationwide database and to compare this to the traditional posterior lumbar fusion.
(2) Analyse risk factors for perioperative readmissions and discharge destination following ALIF.

(3) Determine incidence and risk factors for wound complications and venous thromboembolism (VTE) following ALIF during the perioperative period, and whether this differs if the complication is before or after discharge.

Acknowledgement of co-authors and co-investigators

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I also acknowledge that Associate Professor Cho and the American College of Surgeons (ACS) for access to the National Surgical Quality Improvement Program (NSQIP) database, from which perioperative data on ALIF analysed. The ACS-NSQIP database stores data related to risk-adjusted 30-day postoperative morbidity and mortality outcomes of many surgeries. Clinicians from over 500 hospitals in the United States of varying size, location, and academic affiliation collect more than 150 demographic, preoperative, intraoperative, and 30-day postoperative variables which is collated in this central database. The data collection is standardised with clear definitions of co-morbidities, preoperative investigations, operations, pathology and complications, and onsite auditing to ensure reliability and consistency of data. I acknowledge the assistance of colleagues Drs Jun Kim, Nathan Lee, Parth Kothari, John Di Capua, Vignesh Ramachandran, Tommy Tran, and other lab members in assistance with statistics, interpretation and editing.

The author contributions are appended. The data, results and methods regarding risk factors for readmissions section have been incorporated in the following publication. However the data has been further analysed, combined, and synthesised for the purpose of this dissertation chapter.

Phan K, Lee N, Kothari P, et al. Risk Factors for Readmissions Following Anterior Lumbar Interbody Fusion. Spine (Phila Pa 1976). 2018 1;43(5):364-369.

The results and discussion from the following subchapters are being drafted and prepared for submission to international peer-reviewed journals.

Phan K, Lee N, Mobbs RJ, et al. ALIF versus PLIF: comparison of perioperative outcomes (being prepared for submission).

Phan K, Di Capua J, Mobbs RJ, et al. Discharge destination associated with ALIF perioperative outcomes (being prepared for submission).

Phan K, Di Capua J, Mobbs et al, et al. Factors associated with timing of wound and venous thromboembolism after ALIF surgery (being prepared for submission).

Background

In recent years, there has been an increasing focus on measuring economic cost in health care. National quality assurance schemes and rating systems such as the Centers for Medicare and Medicare Services and National Quality Forum have focused on perioperative outcomes, complications, and readmission rates as a yardstick for economic cost(1). This is particularly the case for surgeries for spinal pathologies. With the ageing population and increasing prevalence of degenerative spinal pathologies, the rates of lumbar spinal surgery have increased from 0.3 to 1.1 per 1000 enrolees over the age of 65 years based on the United States Medicare data(2, 3). Over 500,000 procedures are performed in the United States alone annually(3, 4). The financial burden of spinal and orthopaedic procedures is set to outpace many other sectors of the healthcare(5).

Fusion surgery remains an effective treatment for carefully selected patients to relieve pain and neurological symptoms, particularly in the setting of degenerative lumbar disc disease(6). Over time, several different surgical approaches for lumbar interbody fusion have been developed and used, with the aim to achieve arthrodesis with optimal improvement in biomechanics of the lumbar spine. Approaches have included posterior lumbar interbody fusion (PLIF)(7, 8), transforaminal lumbar interbody fusion (TLIF)(9, 10), anterior lumbar interbody fusion (ALIF), lateral lumbar interbody fusion (LLIF)(11, 12), and most recently the oblique lumbar interbody fusion (OLIF)(13, 14). Despite technological advances and the continually expanding surgical armamentarium, these developments have not been matched with rigorous comparative clinical evidence(15). A large amount of evidence to date on interbody fusions are retrospective

in design and lack comparison to alternative approaches. There are limited studies which have directly compared the surgical and functional outcomes of anterior versus posterior fusion (16-19). From the limited available literature, conclusions and recommendations have not been consistent, with conflicting data regarding relative complication rates, length of stay, and reoperation rates between approaches(20).

The significance of readmission rates on the economic cost of surgery is increasingly being recognised. From the Medicare claims data, Jencks et al(1) reported 19.6% of Medicare beneficiaries who were discharged and rehospitalised within 30 days, and 34.0% of those rehospitalised within 90 days, accounted for approximately $17.4 billion healthcare expenditure in 2004 in the United States. However, the readmission rates following specific lumbar fusion approaches is not well reported in the literature. Furthermore, there may be differences between types of surgical fusion approaches, such as anterior versus posterior techniques. Wang et al(21) reported significantly lower readmission rates for a posterior approach compared to anterior approach (odds ratio 0.67, P=0.001), based on an analysis of the US Medicare beneficiaries database. However, a retrospective analysis of 227 ALIF cases by Mobbs et al(22) revealed only one case of readmission due to an acute arterial thrombosis.

Hospital stay and discharge destination are other factors linked to economic cost of a patient's surgical journey. The mean hospital stay is approximately 3-6.7 days following ALF surgery(23, 24). Factors such as additional cost, patient well-being, and increased risk of nosocomial complications from prolonged stay often influence clinicians to discharge patients earlier whenever possible(23, 25). Discharge destination – whether to home, a skilled nursing facility (SNF), or rehabilitation – following elective ALIF surgery is another major consideration for post-operative care. However, there is little

literature investigating the impact this decision has on outcomes. Understanding risk factors for patient discharge following surgery is an essential step to help improve patient recovery, physician workflow and reduce financial burden on the healthcare system. Early recognition of patient discharge can allow caring health professionals to plan and optimize preparations for the patient, make appropriate and timely decisions, which in turn can reduce hospital length of stay and associated costs.

Understanding demographic and other risk factors for postoperative outcomes following ALIF surgery may assist the healthcare team in providing optimal monitoring and management following surgery. Wound complications and venous thromboembolism (VTE) are two such key complications. Importantly, few studies have investigated whether risk factors differ according to timing of the complication, whether it occurs prior to or after discharge. Insight into predictive factors may be used to be used to optimize patient care planning to reduce postoperative wound complications – a feat which may not only facilitate quicker discharge times but also increase satisfaction among healthcare professionals and patients as well as reduce healthcare costs.

To address these limitations, we sought data from the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP)(26), a large nationwide, multi-institutional database. The objectives of this chapter are:

(1) To perform a propensity score-adjusted analysis in order to compare perioperative outcomes of anterior versus posterior approaches for interbody fusion of the lumbar spine.
(2) To analyse risk factors for readmissions following anterior lumbar interbody fusion using prospectively collected data from the ACS-NSQIP.

(3) To determine any associations between discharge destination and adverse short-term 30-day perioperative complications following elective ALIF.

(4) Determine demographic and comorbidity factors associated with timing of postoperative complications including wound complication and VTE.

Methods

Data source and patient selection

The source of data used for this chapter is from the ACS-NSQIP. This is a large nationwide, multi-institutional database which provides surgical outcomes data for participating institutions. Detailed information on patient demographics, preoperative comorbidities, laboratory values, operative variables, as well as postoperative 30-day outcomes are recorded by surgical clinician reviewers. As the database is publically available on request and no identifiable data was used, the need for ethics approval was waived by the ethics board committee.

Inclusion criteria

ALIF versus PLIF comparison of perioperative outcome

Patient data was attained from NSQIP database from 2005-2012. Inclusion criteria for surgical cases were identified based on the Current Procedural Terminology (CPT) codes for anterior/lateral lumbar interbody fusion (CPT 22558) or posterior/transforaminal lumbar interbody fusion (CPT 22630).

Readmission to hospital following ALIF surgery

Patient data was attained from NSQIP database from 2005-2012. Inclusion criteria for surgical cases of patients aged ≥ 18 years who were identified based on the Current Procedural Terminology (CPT) codes as undergoing anterior or lateral lumbar interbody fusion (22558).

Discharge destination as factor associated with ALIF perioperative outcome

Adult patients (≥18 years) who underwent elective anterior lumbar fusion surgery between 2010 and 2014 were identified based on Current Procedural Terminology (CPT) code 22558. Discharge destination data was only available in the NSQIP database during this time period.

Factors associated with timing of wound complications and venous thromboembolism after ALIF surgery

Adult patients (≥18 years) who underwent elective anterior lumbar fusion surgery between 2010 and 2014 were identified based on Current Procedural Terminology (CPT) code 22558. Outcomes were separated into pre-discharge and post-discharge.

Exclusion criteria

Exclusion criteria of the present study included the following:

- aged <18 years
- those who underwent spinal deformity surgery (CPT 22800, 22802, 22804, 22808, 22810) and combined anterior-posterior fusions
- non-elective surgery
- being pregnant
- ventilator dependent
- underweight (BMI < 18.5 kg/m^2)
- preoperative systemic sepsis
- emergency operations

- length of stay (LOS) > 365 days
- central nervous system tumour
- disseminated cancer
- chemotherapy for malignancy within 30 days before operation
- radiotherapy for malignancy within 90 days before operation
- acute renal failure

Explanatory and control variables

Recorded patient characteristics were classified into the following groups: baseline demographics, preoperative medical comorbidities, preoperative laboratory values, and operative variables. Patient demographics included:

- age
- sex
- race (white, black, hispanic, other, unknown)
- body mass index (BMI) class
- American Society of Anaesthesiologists (ASA) score
- Diabetes
- Smoker
- alcohol user
- dyspnea
- functional dependence prior to surgery

Comorbidity variables included:

- pulmonary comorbidity

- cardiac morbidity
- peripheral vascular disease
- neuromuscular injury
- stroke
- steroid use
- recent weight loss
- bleeding disorder

Operative variables included operative time >4 hours and total relative value units (RVU).

A cardiac comorbidity was defined as a history of congestive heart failure (within 30 days before admission), myocardial infarction (within six months before admission), percutaneous coronary intervention, cardiac surgery, angina (within one month before admission) or use of hypertensive medication.

A pulmonary comorbidity was defined as history of severe chronic obstructive pulmonary disease, or current pneumonia. Peripheral vascular disease was defined as a history of revascularization or amputation for peripheral vascular conditions, and rest pain. Smoking history (current smoker within one year) and chronic steroid use (regular use within 30 days before admission) were also assessed.

For non-home discharge destinations after ALIF surgery, this included skilled and non-skilled care facilities, nursing homes, assisted living, and rehabilitation centres.

Outcomes

The study endpoint variable included any 30-day follow-up postoperative complication. This included:

- mortality
- pulmonary complications (pneumonia, intubation, or ventilator requirement)
- renal complications (progressive renal insufficiency or acute renal failure)
- central nervous system (CNS) complications (stroke or coma)
- cardiac complications (cardiac arrest or myocardial infarction)
- pulmonary embolism (PE)
- deep vein thrombosis (DVT)
- sepsis or septic shock
- peripheral nerve injury
- urinary tract infection (UTI)
- wound complications (superficial wound infection, deep incisional surgical site infection, organ space surgical site infection, or wound dehiscence)
- graft or flap failure
- intraoperative or postoperative blood transfusions

Other outcomes included return to operating room (OR), unplanned readmissions (2011-2012), unplanned reoperations (2011-2012), and prolonged length of stay (LOS > 5 days).

Propensity score matching

Propensity score matching allowed for reduction of the risk of selection bias within this population. Propensity scores were assigned to patients in each cohort based on all preoperative factors including patient demographics and comorbidities. The process of matching was performed by selecting one patient from the anterior fusion cohort and matching with a patient in the posterior fusion cohort with the closest propensity score. This technique helped to correct for differences in case mix between patients. Propensity score matching has been well-described in the literature (18, 19). Matching was performed using R Software (Vienna, Austria, http://www.R-project.org/) package "MatchIt "(27).

Statistical analysis

Descriptive and comparative statistics of demographics, comorbidities, operative details, and postoperative complications were analysed for all patients. In the univariate analysis, categorical variables were assessed using Pearson's chi-square or Fisher's exact test where appropriate. Continuous variables were examined using 1-way ANOVA test. Variables with a P-value < 0.2 in the univariate analysis were carried forward into the multivariate analysis. Multivariate logistic regression analysis was used to determine independent risk factors for each postoperative complication that showed a significant difference between cohorts in the univariate analysis. A p-value < 0.05 was considered significant. SAS software (Version 9.3, SAS Institute Inc., North Carolina) was used for statistical analyses.

Results

ALIF versus PLIF and predictors of perioperative outcomes

For the period 2005-2012, a total of 2,320,920 surgical cases were performed and recorded in the NSQIP dataset. Of these surgeries, 7594 cases made up the ALIF and PLIF approaches. After exclusion of deformity cases, there was 7479 ALIF and PLIF cases. Following application of other exclusion criteria, 2390 patients remained for analysis. This included 1,463 posterior fusion (61.2%) and 927 anterior fusion (38.86%) cases.

As seen in Table 3.1, unadjusted comparisons demonstrated that the posterior fusion group had more patients aged ≥65 years (32.7% vs 23.2%, P<0.0001), morbidly obese with BMI≥40 (7.5% vs 5.2%, P=0.006), have ASA score ≥3 (42.8% vs 31.8%, P<0.0001), and dyspnoeic at rest or moderate exertion (8.4% vs 5.2%, P=0.014) compared to patients undergoing ALIF. In terms of baseline comorbidities, the posterior fusion cohort had a higher proportion of cardiac comorbidity (52.8% vs 41.0%, P<0.0001), neuromuscular injury (7.4% vs 5.1%, P=0.025), and diabetes (15.8% vs 11.5%, P=0.004) (Table 3.2).

Following propensity-score adjustment, no significant differences were found between matched posterior and anterior fusion cohorts in terms of age distribution, sex, race, BMI class, ASA score, smoker status, alcohol use, dyspnoea and functional status prior to surgery. No significant differences were also found in terms of baseline comorbidities, including cardiac comorbidity and neuromuscular injury.

30-day complications were compared between anterior versus posterior fusion cohorts after propensity score adjustment. Return to OR was significantly higher in the anterior fusion versus posterior fusion groups (7.4% vs 3.0%, P<0.0001), whilst no significant differences were detected in terms of any complication, deaths, wound complication, pulmonary complication, renal complication, CNS complication, VTE, sepsis, cardiac complication, intraoperative or postoperative blood transfusions, or unplanned readmissions. Total length of stay >5 days were also significantly higher in the anterior versus posterior fusion group (23.8% vs 17.7%, P<0.0001) (Table 3.3).

In a multivariable logistic regression model, with propensity score included, it was shown that an anterior versus posterior approach for lumbar interbody fusion was significantly associated with return to OR within 30 days of surgery, with an adjusted OR of 2.8 (95% Confidence Interval (CI): 1.7-4.4, P<0.001). The other significant predictors of return to operating room were being totally dependent prior to surgery compared to independent (OR 7.8; 95% CI 1.2-49.1, P=0.035), neuromuscular injury (OR 3.6; 95% CI 1.9-6.7, P<0.0001), steroid use (OR 3.5; 95% CI, 1.4-8.8, P=0.0097), and operative time >4 hours (OR 1.92; 95% CI 1.2-3.0, P=0.003) (Table 3.4).

Multivariable logistic regression model was also used to determine independent predictors of prolonged LOS > 5 days. The anterior approach, compared to posterior approach, had a significantly higher odds of prolonged LOS (OR 1.9, 95% CI 1.5-2.5, P<0.0001). Other independent predictors of a prolonged LOS>5 days were ASA scores ≥3 (OR 1.9, 95% CI 1.4-2.5, P<0.0001) and having operative time >4 hours (OR 4.6, 95% CI 3.5-5.9, P<0.0001) (Table 3.5).

Table 3.1. Demographics and clinical characteristics of anterior versus posterior fusion approaches

	PLIF/TLIF				Anterior/lateral lumbar interbody fusion		P value	
	Unadjusted		Matched					
	1463		927		927		Unadjusted	Matched
Demographics	N	%	N	%	N	%		
Age, mean								
18 to 64	985	67.33%	705	76.05%	712	76.81%	**<0.0001**	0.9288
65 to 79	415	28.37%	197	21.25%	191	20.60%		
>= 80	63	4.31%	25	2.70%	24	2.59%		
Sex		0.00%		0.00%		0.00%		
Female	778	53.18%	511	55.12%	498	53.72%	0.795	0.544
Male	685	46.82%	416	44.88%	429	46.28%		
Race								
White	1088	74.37%	754	81.34%	759	81.88%	**<0.0001**	0.984
Black	97	6.63%	52	5.61%	48	5.18%		
Hispanic	108	7.38%	67	7.23%	66	7.12%		
Other	21	1.44%	14	1.51%	12	1.29%		
Unknown	149	10.18%	40	4.31%	42	4.53%		
Inpatient vs. Outpatient								
Inpatient	1405	96.04%	914	98.60%	916	98.81%	**<0.0001**	0.681
Outpatient	58	3.96%	13	1.40%	11	1.19%		
BMI Class								
NonObese (18.5-29.9)	777	53.11%	546	58.90%	554	59.76%	**0.006**	0.464
Obese I (30-34.9)	386	26.38%	236	25.46%	212	22.87%		
Obese II (35 - 39.9)	190	12.99%	97	10.46%	113	12.19%		
Obese III (≥40)	110	7.52%	48	5.18%	48	5.18%		
ASA								
1 or 2	837	57.21%	639	68.93%	632	68.18%	**<0.0001**	0.726
3 or 4	626	42.79%	288	31.07%	295	31.82%		
Smoke	408	27.89%	272	29.34%	256	27.62%	0.885	0.410
Alcohol	46	3.14%	32	3.45%	33	3.56%	0.580	0.900
Dyspnea								
At Rest	8	0.55%	2	0.22%	2	0.22%	**0.014**	0.917
Moderate Exertion	115	7.86%	51	5.50%	47	5.07%		
No Dyspnea	1340	91.59%	874	94.28%	878	94.71%		
Functional Status Prior to Surgery								
Independent	1420	97.06%	895	96.55%	896	96.66%	0.782	0.991
Partially Dependent	40	2.73%	29	3.13%	28	3.02%		
Totally Dependent	3	0.21%	3	0.32%	3	0.32%		

Table 3.2. Comorbidities and Operative Features of anterior versus posterior fusion approaches								
	PLIF/TLIF				**Anterior/lateral lumbar interbody fusion**		**P value**	
	Unadjusted		**Matched**					
	1463		**927**		**927**		**Unadjusted**	**Matched**
Comorbidities	**N**	**%**	**N**	**%**	**N**	**%**		
Pulmonary Comorbidity	27	1.85%	33	3.56%	30	3.24%	0.105	0.701
Cardiac Comorbidity	773	52.84%	403	43.47%	380	40.99%	**<0.0001**	0.280
Peripheral Vascular Disease	15	1.03%	5	0.54%	4	0.43%	0.111	0.738
Neuromuscular Injury	108	7.38%	56	6.04%	47	5.07%	**0.025**	0.362
Diabetes	231	15.79%	117	12.62%	107	11.54%	**0.004**	0.476
Stroke	30	2.05%	19	2.05%	13	1.40%	0.245	0.285
Steroid Use	37	2.53%	20	2.16%	20	2.16%	0.562	1.000
Recent Weight Loss	6	0.41%	5	0.54%	6	0.65%	0.424	0.762
Bleeding Disorder	18	1.23%	8	0.86%	11	1.19%	0.924	0.489
Operative Variables								
Operative Time > 4 hours	466	31.85%	266	28.69%	280	30.20%	0.397	0.476
Total RVU, mean (SD)	40.80 (20.61)		41.99 (21.80)		43.90 (23.83)		**0.001**	0.072

Table 3.3. 30 Day Postoperative Complications

	PLIF/TLIF				Anterior/lateral lumbar interbody fusion		P value	
	Unadjusted		Matched					
	1463		927		927		Unadjusted	Matched
Complication	**N**	**%**	**N**	**%**	**N**	**%**		
Any Complicaton	193	13.19%	116	12.51%	122	13.16%	0.982	0.677
Death	3	0.21%	2	0.22%	1	0.11%	0.571	0.563
Wound Complication	27	1.85%	13	1.40%	20	2.16%	0.593	0.219
Pulmonary Complication	13	0.89%	7	0.76%	16	1.73%	0.069	0.059
Renal Complication	3	0.21%	2	0.22%	3	0.32%	0.573	0.654
CNS Complication	3	0.21%	2	0.22%	0	0.00%	0.168	0.157
VTE	16	1.09%	10	1.08%	14	1.51%	0.373	0.411
Sepsis	9	0.62%	6	0.65%	8	0.86%	0.483	0.592
Peripheral Vascular Disease	3	0.21%	3	0.32%	3	0.32%	0.573	1.000
Cardiac Complication	6	0.41%	2	0.22%	4	0.43%	0.937	0.414
Intra/postoperative Blood Transfusion	137	9.36%	80	8.63%	94	10.14%	0.532	0.265
UTI	32	2.19%	19	2.05%	16	1.73%	0.434	0.609
Graft Failure	0	0.00%	0	0.00%	2	0.22%	0.076	0.157
Return to OR	44	3.01%	27	2.91%	69	7.44%	**<0.0001**	**<0.0001**
Unplanned Reoperation (2011-2012)	9	1.60%	5	0.54%	3	0.86%	0.347	0.474
Unplanned Readmission (2011-2012)	28	4.96%	17	1.83%	11	3.17%	0.194	0.244
Total Length of Stay > 5 days	259	17.70%	138	14.89%	221	23.84%	**0.0003**	**<0.0001**

Table 3.4. Multivariate Logistic Regression to Assess Anterior/lateral lumbar interbody fusion vs. PLIF/TLIF as Independent Risk Factor for Return to OR w/in 30 Days of Surgery

Risk Factor	Adjusted Odds Ratio	95% Confidence Limits		P Value
Anterior/lateral lumbar interbody fusion vs. PLIF/TLIF	2.763	1.738	4.391	**<.0001**
Female vs. Male	1.527	0.986	2.365	0.0579
Alcohol	1.899	0.722	4.994	0.1936
Functional Health Status Prior to Surgery: Partially Dependent vs. Independent	1.024	0.336	3.115	0.1655
Functional Health Status Prior to Surgery: Totally Dependent vs. Independent	7.806	1.239	49.161	**0.0354**
Neuromuscular Injury	3.593	1.919	6.728	**<.0001**
Steroid Use	3.455	1.35	8.844	**0.0097**
Recent Weight Loss	3.795	0.757	19.025	0.1049
Bleeding Disorder	3.438	0.942	12.548	0.0616
Operative Time > 4 Hours	1.92	1.248	2.955	**0.003**

Table 3.5. Multivariate Logistic Regression to Assess Anterior/lateral lumbar interbody fusion vs. PLIF/TLIF as Independent Risk Factor for Prolonged LOS (>5 Days)

Effect	Adjusted Odds Ratio	95% Confidence Limits		P Value
Anterior/lateral lumbar interbody fusion vs. PLIF/TLIF	1.9	1.474	2.448	**<0.0001**
Age: 65 to 79 vs. 18 to 64	1.512	1.127	2.029	0.9008
Age: ≥80 vs. Age 18 to 64	2.169	1.107	4.25	0.0951
BMI: Obese I vs. Nonobese	0.594	0.432	0.818	0.1316
BMI: Obese II vs. Nonobese	0.812	0.541	1.22	0.5173
BMI: Obese III vs. Nonobese	0.592	0.325	1.077	0.3506
ASA 3/4/5 vs. ASA 1/2	1.87	1.423	2.457	**<0.0001**
Functional Health Status Prior to Surgery: Partially Dependent vs. Independent	2.229	1.198	4.146	0.0915
Functional Health Status Prior to Surgery: Totally Dependent vs. Independent	42.269	4.777	374.041	**0.0028**
Operative Time > 4 Hours	4.563	3.545	5.874	**<0.0001**

Factors associated with readmission to hospital following ALIF surgery

From the data available, 347 ALIF cases were identified, including 336 patients (96.8%) who did not undergo readmission versus 11 cases (3.2%) who underwent readmission.

There was no significant difference between the 2 groups in terms of age group, females, race, smoking status, dyspnoea, and functional health prior to surgery. A significantly higher proportion of morbidly obese patients was noted in the readmissions group versus those without admissions (27.3% vs 4.5%, P=0.008), as well as a higher proportion of insulin-dependence (18.2% vs 1.8%, P=0.008), and ethanol consumption >2 drinks/day (18.2% vs 2.4%, P=0.002) (Table 3.6).

In terms of baseline demographics, there was no significant differences in terms of pulmonary comorbidity, cardiac comorbidity, neuromuscular injury, peripheral vascular disease, strokes, steroid use, recent weight loss or ASA score ≥3. In terms of operation parameters, no difference was found in the proportion of patients who had operative time >4 hours between the two groups (Table 3.7).

Postoperative outcomes were stratified by readmission status. The readmissions group was significantly associated with higher proportion of any complications (54.6% vs 15.8%), wound complications (27.3% vs 0.6%), pulmonary complications (9.1% vs 0.9%), UTIs (9.1% vs 1.2%), septic shock (18.2% vs 0%), graft failure (9.1% vs 0%), return to OR (27.3% vs 1.2%) and unplanned reoperations (9.1% vs 0%). There were no deaths or CNS complications in either group, and no significant differences in terms of cardiac complications, venous thromboembolism, intra/postoperative blood transfusion, or length of stay >5 days (Table 3.8).

Following multivariate adjustment for confounding factors, morbid obesity independently predicted unplanned 30-day readmission (OR 15.6, P=0.002). Alcohol use was also a significant and independent predictor of readmission for ALIF (OR 16.9, P=0.004). Sex, pulmonary comorbidity, cardiac comorbidity and steroid use were not found to be significant independent predictors of unplanned 30-day readmission in anterior lumbar interbody fusion (Table 3.9).

Table 3.6. Univariate Analysis of Demographics and Comorbidities for those with and without Readmission, N = 347

	Readmission				
Feature	**No (n=336)**	**Yes (n=11)**	**Total**	**% Readmit**	**P value**
Overall				3.2%	
Age					
18 to 64	242	10	252	3.97%	0.3778
65 to 79	85	1	86	1.16%	
≥ 80	9	0	9	0.00%	
Sex					
Female	184	9	193	4.66%	0.0755
Male	152	2	154	1.30%	
Race					
Caucasian	280	9	289	3.11%	0.740
African American	14	1	15	6.67%	
Other	5	0	5	0.00%	
Unknown	15	1	16	6.25%	
BMI, kg/m²					
Non-Obese (<30)	200	6	206	2.91%	**0.008**
Obese I (30-34.9)	78	1	79	1.27%	
Obese II (35-39.9)	43	1	44	2.27%	
Obese III (>=40)	15	3	18	16.67%	
Comorbidities					
Diabetes					
Insulin	6	2	8	25.00%	**0.001**
Non-Insulin	28	0	28	0.00%	
None	302	9	311	2.89%	
Current Smoker	87	5	92	5.43%	0.148
EtOH > 2 drinks/day in 2 weeks before admission	8	2	10	20.00%	**0.002**
Dyspnoea					
At Rest	1	0	1	0.00%	0.916
Moderate Exertion	21	1	22	4.55%	
No	314	10	324	3.09%	
Functional Health Status Prior to Surgery					
Dependent	7	0	7	0.00%	0.629
Independent	329	11	340	3.24%	

Table 3.7. Univariate Analysis of Demographics and Comorbidities for those with and without Readmission, N = 347

	Readmission				
Feature	**No**	**Yes**	**Total**	**% Readmit**	**P value**
Pulmonary Comorbidity	8	1	9	11.11%	0.168
Cardiac Comorbidity	149	3	152	1.97%	0.261
Neuromuscular Injury	5	0	5	0.00%	0.684
Peripheral Vascular Disease	2	0	2	0.00%	0.798
Stroke	5	0	5	0.00%	0.684
Steroid Use Within 30 Days	10	1	11	9.09%	0.255
Recent Weight Loss	4	0	4	0.00%	0.716
Bleeding Disorder	0	0	0		
ASA >= 3	114	3	117	2.56%	0.646
Operative Variables					
Operative Time > 4 hours	97	3	100	3.00%	0.9084
Outpatient	5	1	6	16.67%	0.057
Total RVU (mean)	52.55 (21.96)	47.85 (24.86)	52.40 (22.04)		0.488

Table 3.8. Postoperative Outcomes Stratified by Readmission Status					
	Not Readmitted (N = 336)		**Readmitted (N = 11)**		
	N	**%**	**N**	**%**	**P**
Any Complication (≥1)	53	15.77%	6	54.55%	**0.0008**
Death	0	0.00%	0	0.00%	
Wound Complication (≥1)	2	0.60%	3	27.27%	**<0.0001**
Pulmonary Complication	3	0.89%	1	9.09%	**0.0122**
Cardiac Complication	1	0.30%	0	0.00%	0.856
CNS complication	0	0.00%	0	0.00%	
Renal Complication	0	0.00%	1	9.09%	**<0.0001**
VTE	5	1.49%	1	9.09%	0.057
UTI	4	1.19%	1	9.09%	**0.031**
Intra/postoperative Blood Transfusion	48	14.29%	2	18.18%	0.717
Sepsis/Septic Shock	0	0.00%	2	18.18%	**<0.0001**
Graft Failure	0	0.00%	1	9.09%	**<0.0001**
LOS > 5 days	71	21.13%	3	27.27%	0.625
Return to OR	4	1.19%	3	27.27%	**<0.0001**
Unplanned Reoperation (2011-2012)	2	0.60%	1	9.09%	**0.0027**

Table 3.9. Independent Predictors for Unplanned 30 Day Readmission				
Variable	**Adjusted Odds Ratio**	**95% CI**		**P**
Female vs. Male	4.28	0.852	21.473	0.078
BMI Class: Obese I vs. Nonobese	0.66	0.067	6.514	0.191
Obese II vs. Nonobese	1.55	0.156	15.347	0.759
Obese III vs. Nonobese	15.64	2.590	94.448	**0.002**
Alcohol	16.93	2.423	118.258	**0.004**
Pulmonary Comorbidity	5.85	0.464	73.669	0.172
Cardiac Comorbidity	0.32	0.069	1.465	0.141
Steroid Use	8.84	0.796	98.234	0.076

Discharge destination and association with postoperative outcome

From the NSQIP database anterior fusion cases with discharge destination data available, 3,182 patients met the inclusion criteria for the study. 2,836 patients (89.1%) were discharged home while 346 (10.9%) were discharged elsewhere. In terms of demographic characteristics (Table 3.10), female sex and elderly age (≥65 years old) were associated with discharge to facilities other than home.

Of the 346 patients discharged to facilities other than home, 67.1% (n=232) were female and 62.4% were ≥65 years old. Both groups did not differ significantly in terms of race distribution, with most patients identifying as white.

In terms of comorbidities, patients discharged to destinations other than home were more likely to be obese, diabetic, have cardiac and pulmonary comorbidities, have partial or total functional dependence, and have used steroids within 30 days prior to surgery. In terms of surgical comorbidities, these patients were more likely to have ASA classification ≥3, have prolonged operation time (≥4 hours), and have their operation in an inpatient setting. In contrast, patients who were discharged home were more likely to have smoked within 30 days of surgery (all $p<0.05$).

Unadjusted analysis

Overall, patients discharged to destinations other than home had significantly higher rates of morbidity and mortality within the first 30-postoperative days (Table 3.11). This included prolonged length of stay, cardiac, pulmonary, renal, and wound complications, venous thromboembolism, urinary tract infections, transfusion, reoperation, and unplanned readmission. $P<0.05$ for all complications listed above.

Multivariate-adjusted analysis

Multivariate logistic regression analysis revealed discharge destinations to facilities other than home to be risk factors for post-discharge wound complications (OR 2.34, CI 1.15-4.76, P=0.0187) and venous thromboembolism (OR 7.23, CI 2.96-17.64, P<0.0001) (Table 3.12). Our analysis, once adjusted for confounding factors, identified non-home discharge to not be associated with mortality or other complications above.

Table 3.10. Bivariate Analysis of Patient Demographic, Preoperative, and Intraoperative Characteristics Following Elective ALF (N=3,182)					
Category	Discharge Home (N)	Discharge Home (%)	Discharge Other Than Home (N)	Discharge Other Than Home (%)	P-value
Sex					
Male	1,321	46.6%	114	32.9%	**<0.0001**
Female	1,515	53.4%	232	67.1%	
Age					
<65	2,210	79.1%	130	37.6%	**<0.0001**
≥65	594	20.9%	216	62.4%	
Race					
White	2,437	86.0%	296	85.6%	0.5735
Other	151	5.3%	21	6.1%	
Black	197	7.0%	26	7.5%	
Hispanic	48	1.7%	3	0.9%	
Obese	1,210	42.9%	173	50.1%	**0.0099**
Diabetes Mellitus	310	10.9%	71	20.52%	**<0.0001**
Dyspnoea	109	3.8%	20	5.8%	0.0843
Functional Status					
Independent	2,785	98.9%	322	93.6%	**<0.0001**
Partially/Totally Dependent	32	1.1%	22	6.4%	
Pulmonary Comorbidity	165	5.8%	34	9.8%	**0.0036**
Cardiac Comorbidity	1,157	40.8%	223	64.5%	**<0.0001**
Renal Comorbidity	4	0.1%	1	0.3%	0.5116
Bleeding Disorder	24	0.9%	4	1.2%	0.5681
Preoperative Transfusion	9	0.3%	2	0.6%	0.4403
ASA Class ≥3	958	33.8%	222	64.2%	**<0.0001**
Operation Time ≥4 hrs	537	18.9%	134	38.7%	**<0.0001**
Operation Year					
2011	433	15.3%	46	13.3%	0.2242
2012	557	19.6%	57	16.5%	
2013	765	27.0%	94	27.2%	
2014	1,082	38.1%	149	43.1%	
Surgery Setting					
Inpatient	2276	97.9%	346	100%	**<0.001**
Outpatient	61	2.1%	0	0%	
Device Intervention	1979	69.8%	245	70.81%	0.6863
Pelvic Fusion	8	0.3%	3	0.9%	0.08
Osteotomy	83	2.9%	14	4.1%	0.2523
Bone Graft	1385	48.8%	193	55.8%	**0.0144**
Pelvic Fusion	8	0.3%	3	0.9%	0.0819
Fusion Length					

Short	2,737	96.5%	311	89.9%	**<0.0001**
Long	100	3.5%	35	10.1%	

Table 3.11. Bivariate Analysis of 30-day postoperative characteristics following Elective ALF (N=1,909)					
Category	Discharge Home (N)	Discharge Home (%)	Discharge Other Than Home (N)	Discharge Other Than Home (%)	p-value
Mortality	2	0.1%	4	1.2%	**<0.0001**
Length of Stay ≥5 Days	502	17.7%	217	62.72%	**<0.001**
Wound Complication	53	1.9%	13	3.8%	**0.0199**
Pulmonary Complication	26	0.9%	17	5.0%	**<0.0001**
Venous Thromboembolism	28	1.0%	12	3.5%	**0.0001**
Renal Complication	1	0.0%	4	1.2%	**<0.0001**
Urinary Tract Infection	27	1.0%	19	5.5%	**<0.0001**
Cardiac Complication	6	0.2%	8	2.3%	**<0.0001**
Intra/Postoperative Transfusion	185	6.5%	85	24.6%	**<0.0001**
Sepsis	17	0.6%	5	1.5%	0.0753
Reoperation	61	2.15%	24	6.94%	**<0.001**
Unplanned Readmission	98	3.45%	25	7.23%	0.0006
Post-discharge Complications					
UTI	13	0.5%	8	3.6%	**<0.001**
Transfusion	1	0.04%	0	0%	0.6513
Sepsis	11	0.4%	1	0.5%	0.9273
Mortality	2	0.1%	0	0%	0.684
Wound Complication	46	1.8%	10	4.7%	**0.0046**
VTE	17	0.7%	4	1.9%	0.0552
Renal Complication	0	0%	1	0.5%	**0.0005**
Cardiac Complication	0	0%	0	0%	N/A
Pulmonary Complication	6	0.2%	2	0.9%	0.0765

Table 3.12. Multivariate Logistic Regression of Discharge Destination Following Elective ALF on 30-day Postoperative Outcomes (N=3,137)			
Outcome	Odds Ratio	Confidence Interval	P-value
Post-discharge wound complications	2.34	1.15-4.76	**0.0187**
Post-discharge VTE	7.23	2.96-17.64	**<0.0001**

Factors associated with the timing of wound complications after ALIF

From the previous results section, we identified that discharge destination was associated with wound complications and venous thromboembolic events. However, few existing studies have investigated whether these complications occur before or after-discharge and the factors that influence this.

From the database and available data, we identified 56 cases of wound complications after ALIF surgery. Of these, 10 cases occurred prior to discharge and 46 cases occurred after discharge.

Upon multivariate-adjusted analysis, history of diabetes was significantly associated with having a wound complication event after ALIF prior to discharge (OR 2.85, 95% CI 1.53-5.29, P<0.001). Preoperative transfusion requirement was significantly associated with having a wound complication after discharge (OR 9.41, 95% CI 3.53-25.07, P<0.001).

Table 3.13. Risk Factors for the Development of Wound Complications Pre- and Post-Discharge Following ALF after multivariate-adjustment

	Pre-Discharge			
Risk Factor	Odds ratio	Lower confidence interval	Upper confidence limit	P-value
Diabetes	2.85	1.53	5.29	<0.001
	Post-Discharge			
	Odds ratio	Lower confidence interval	Upper confidence limit	P-value
Preoperative Transfusion	9.41	3.53	25.07	<0.001

Factors associated with the timing of venous thromboembolism after ALIF

From the NSQIP database, a total of 2682 patients had VTE data available. 2,642 (98.5%) had no VTE and served as the reference. 19 (0.71%) VTEs occurred before discharge and 21 (0.78%) happened after.

Multinomial logistic regression revealed that intraoperative osteotomy (OR=6.26, 1.69-23.17, P=0.006), pulmonary comorbidity (OR=4.92, 1.56-15.57, P=0.007), and operative time ≥4 hours (OR=9.41, 3.53-25.07, P<0.0001) were predictive for development of VTE prior to discharge. While patients developed VTE post-discharge, there were no risk factors that were associated with this outcome (Table 3.14).

Table 3.14. Risk Factors for the Development of VTE Pre- and Post-Discharge Following ALF (N=2682)

	Pre-Discharge			
Risk Factor	Odds	Lower confidence limit	Upper confidence limit	P-value
Osteotomy	6.2561	1.6889	23.1742	0.0061
Pulmonary Comorbidities	4.9223	1.5562	15.5688	0.0067
Operation Time ≥4 hours	9.4129	3.5339	25.0723	<0.0001
	Post-Discharge			
N/A	-	-	-	-

Discussion

Compared with posterior approaches, ALIF is associated with higher return to operating room and prolonged length of stay >5 days

Interbody fusion procedures continue to be an integral component of the management of several spinal pathologies including lumbar degenerative disc disease(2, 3). Despite the development in technologies and approaches for interbody fusion, there remains a scarcity of evidence in the literatures describing the relative benefits and risks of each approach. Both anterior and posterior lumbar fusion involves the removal of the degenerated disc, insertion of a cage or bone between distracted vertebral segments, with the option of further instrumentation to improve spinal stability.

Anterior fusion options include ALIF and LLIF techniques. ALIF allows easier access to the disc space and provides ample distraction to create lordosis(28, 29). However, the anterior approach is associated with risks of injury to the great vessels, the ureter, and causing retrograde ejaculation. The LLIF approach involves accessing the disc space via a lateral retroperitoneal, transpsoas corridor(30). The lateral approach provides excellent disc space clearance and deformity correction, and is particularly used in degenerative deformity cases. Caveats of this approach include risk of injury to psoas muscle and lumbar plexus, particularly at the L4/L5 levels.

There is currently limited multi-centre prospective and direct comparative evidence of anterior versus posterior lumbar interbody fusion directly. To contribute to the literature in this area, 927 matched pairs of anterior versus posterior fusion cases were analysed based on available data in the NSQIP database. Multivariable logistic regression analysis demonstrated that undergoing an anterior procedure was an independent and

strong predictor of both return to OR as well as prolonged length of stay greater than 5 days.

ALIF is in many cases not performed alone but with additional posterior instrumentation, especially in those patients where there is a concern for pseudoarthrosis such as osteoporotic patients, smokers, and the base of long fusion constructs. The observed difference in return to OR and prolonged length of stay may be partially due to planned second stage posterior instrumentation surgery and hence, contributing to a longer LOS. NSQIP is limited in that the reason for return to OR is not defined in the database. Therefore, it was not possible to control for planned second stage operations in the setting of ALIF.

Our results are similar to experiences reported by other centres worldwide. Hacker et al(31) reported one of the earliest comparative analyses comparing 21 ALIF versus 54 TLIF cases in patients with low back pain. Hospital stay was significantly longer in the ALIF group (5.3 days) compared to TLIF (3.5 days). Similarly, Hee et al(32) reported length of stay mean 9 days for ALIF, compared to 5.2 days in the TLIF group. A recent meta-analysis by our group(20) also demonstrated significantly longer hospital stay in the ALIF group by 1.8 days. However, a large propensity-matched study by Huang et al which analysed the Marketscan database did not find significant differences between anterior versus posterior fusion surgery in terms of length of stay, which was 4.3 and 4.5 days, respectively(16).

In terms of 30-day complications, the present study demonstrated no differences between anterior versus posterior fusion matched cohorts, with the exception of return to OR. These results have not been consistent amongst reported studies. Scaduto et

al(19) compared perioperative complications of threaded cylindrical lumbar interbody fusion devices in 31 PLIF patients versus 88 ALIF patients. In this study, all intraoperative complications occurred in the PLIF group, and the relative risk of having a major postoperative complication was 6.8 times higher in the PLIF group compared to ALIF group. In contrast, Huang et al(16) compared 7,460 posterior and 3,481 anterior fusion cases, and demonstrated that the anterior approach was associated with a higher 90-day complication rate (RR 1.24) and higher 2-year reoperation rate (OR 1.43) compared to posterior fusion. However, it is important to note that these two studies did not compare propensity-score matched cohorts, and as such, there may be confounding factors which have not been accounted for.

Obesity and alcohol intake are associated with unplanned readmission following ALIF surgery

In the present study, we specifically explored the readmission rates and risk factors in a population of patients who underwent anterior lumbar interbody fusion surgery. The 30-day readmission rate was determined to be 3.2% from 336 cases of ALIF. Independent risk factors for readmission included being morbidly obese and higher alcoholic consumption. Furthermore, patients who were readmitted had a significantly higher proportion of complications including wound, pulmonary complications, UTIs, sepsis and graft failure.

The reported rates of readmissions in the present study for ALIF are similar to prior reports in spinal and orthopaedic populations. Deyo et al(33) retrospectively analysed Medicare claims of 31,543 cases of lumbar stenosis, one of the largest studies of its

kind. The authors reported a 30-day readmission rate of 9.1%, which increased to 17.2% at 4-year follow-up. Following subgroup analysis according to procedure type, the authors found that readmissions after laminectomy was significantly lower compared to complex fusion surgery (7.8% vs 13%).

Pugely et al(34) conducted a multicentre clinical registry and assessed 15,668 patients undergoing lumbar spinal surgery. Of these, 695 patients required hospital readmissions within 30-days (4.4%), similarly to rates reported in the present study. Follow-up subgroup analysis according to procedure type, it was found that the readmission rate for discectomy was significantly lower compared to that following deformity operations (3.3% vs 9.0%). However, subgroup analysis according to type of fusion approach was not conducted. After adjustment for confounding factors, it was found that age >80 years, African-American race, recent weight loss, pulmonary disorder, cancer history, long operative procedures, and prolonged hospital stay were independently associated with 30-day readmission to hospital. These results differ from our study, we focused on a different surgical population and demonstrated that only morbid obesity and alcoholic intake as predictors of readmissions in anterior lumbar fusion surgery. This is supported by existing evidence in the literature(35), which suggests that morbid obesity is associated with significantly higher complication rates and costs in spinal fusion surgery, which may partly explain the present results.

Whilst the majority of studies exploring spinal surgery readmission rates have been derived from multicentre or national database, these are often limited by the lack of clinical detail available. These details are often offered in single-institutional studies where clinical data may be collected to a higher degree of granularity. Akamnonu et al(36) retrospectively analysed a hospital administrative database from 2011 to 2013.

The authors found a 3.3% 90-day readmission rate. This was predominantly due to surgical site infections and wound complications, similarly to results reported in the present study. Wang et al reported a slightly higher rate of 7.2% following lumbar decompression alone or 9.7% for lumbar decompression with fusion(37).

We also found that morbid obesity was a strong independent risk factor for readmissions in ALIF. This result is supported by a number of prior studies. Higgins et al(38) conducted a single-institutional retrospective analysis of patients undergoing instrumentation for degenerative spinal disease. The authors found that obesity was associated with 2.8 times higher rate of wound complications, 2.5 higher rates of major medical complications and $9,078 increase in overall cost of care. Kalanithi et al analysed spinal fusions that were performed in California from 2003-2007, and found a higher mortality rate in patients who were obese. Furthermore, average hospital costs were also significantly higher ($108,604 vs. $84,861 US) in additional to prolonged length of stay(35). These trends were more significant in those undergoing lumbar fusions compared to cervical fusion. The above results are further supported by other studies(39-41).

Analysis of the NSQIP data offered a unique opportunity to exam risk factors for 30-day readmission rates based a single type of fusion procedure, anterior lumbar interbody fusion surgery. Strategies to optimise BMI and diet and to reduce alcohol intake will likely reduce short-term readmissions.

Discharge to non-home destination is associated with post-discharge wound complication and venous thromboembolism

Discharge destination following ALIF surgery, whether to home, a skilled nursing facility (SNF), or rehabilitation, is another major consideration for post-operative care. However, there is little literature investigating the impact this decision has on outcomes. Effective discharge planning is complex and requires multidisciplinary cooperation between many healthcare professionals. Many factors go into the decision including age, preoperative health, availability of home care, surgical success, and length of hospital stay(42). Understanding risk factors for patient discharge following surgery is an essential step to help improve patient recovery, physician workflow and reduce financial burden on the healthcare system.

Our analysis of the NSQIP database identified female sex and age ≥65 years were associated with being discharged to a destination other than home in our study. The association between age and discharge destination is likely multifactorial(33, 43-45). Degenerative aging processes like frailty, cardiovascular decline, impaired immune function, and decreased perioperative reserve exaggerate the reserve lost due to surgery in elderly patients compared to younger patients(46, 47). It is reasonable to connect how these high-risk patients would require addition care postoperatively after discharge at a facility other than home. Even then, these facilities cannot significantly mitigate the cardiac, pulmonary, urologic, and wound complications associated with increased age (47-50).

Like elderly age, the association between female sex and discharge destination is also multifactorial. In a study of 14,326 patients looking at factors influencing discharge

destination after total hip arthroplasty, Schwarzkopf et al. found that male gender was the only factor that lowered the risk of discharge to extended care facilities(51). Males in this study were more likely to be married and have a caregiver at home, thus decreasing the odds that they would require additional care from other discharge facilities. In another study of 1518 patients looking at the influence of gender on patient-oriented outcomes following spine surgery, Pochon et al. found that women present with a significantly worse preoperative Core Outcome Measures index (COMI) score than men(52). The worse preoperative assessment is likely to persuade surgeons to take extra precaution, resulting in more females being discharged to destinations other than home for more acute postoperative care.

Our analysis also demonstrated that patients who were discharged to non-home facilities tended to have more complications, including prolonged length of stay, cardiac, pulmonary, renal, and wound complications, VTE, UTIs, transfusion, reoperation, and unplanned readmission. However, following adjustment for potential confounding variables, we found that discharge to a non-home destination was independently associated with post-discharge wound complications and venous thromboembolism, but not 30-day follow-up mortality. The reason why mortality and other complications were not found significant to non-home discharge could be multifactorial. Although one complication by itself may not be independently associated with non-home discharge, patients who are discharged to non-home facilities often have at least one, and often multiple, perioperative risk factors that may together result in the significant associations that were shown with univariate analysis. Prolonged operative time requires additional anaesthesia time and is associated with more complex cases, increased need for transfusion, and increased complications.

The current study contributes to the limited existing literature investigating associations with discharge to non-home facilities after spinal or orthopaedic surgery. Two retrospective studies of 15,092 patients following surgical spinal fusion by Aldebeyan et al(24). and 9,973 patients following revision total joint arthroplasty by Keswani et al.(53) correlated multiple operative factors to discharge to a facility other than home including ASA class >1, prolonged operative time, multilevel surgery, and non-elective surgery. These two studies also correlated multiple medical comorbidities to non-home discharge destinations including obesity, diabetes, cardiopulmonary decline, renal failure, bleeding disorders, and hypertension. In addition, elderly patients who are discharged to non-home environments have an increased risk of developing delirium, postoperative complications, morbidity, and mortality following orthopaedic procedures of the knee and spine(54-58).

The relationship between discharge destination and postoperative morbidity and mortality is clinically relevant because medical teams in charge of patient care can utilize this information to create better, more efficient discharge planning procedures for patients that are due to undergo ALIF. Rapid recognition of these risk factors via an algorithm or other type of administrative tool can help identify patients that are more likely to experience postoperative medical complications and allow for action to prevent or treat them more effectively. Initiatives such as these could potentially result in more timely appropriate discharge, reduced postoperative complications and associated healthcare costs, and also increased satisfaction with care among patients and healthcare professionals.

Diabetes and preoperative blood transfusions associated with wound complications after ALIF

The prior results chapters have demonstrated risk factors for postoperative complications following ALIF surgery. In particular, non-home discharge destination was an independent predictor of wound complications. However, prior studies have not examined the timing of wound complications, and whether there are patient factors which predispose to complications arising before or after discharge. Understanding such a relationship would inform areas of improvement in facilitating patient recovery, with potential benefits of improving workflow in and reducing financial strain on the healthcare system. Targeting how risk factors vary in predicting timings of wound complications would allow health professionals to tailor postoperative care for the patient, which in turn can reduce length of hospital stay and related healthcare costs.

Following adjusted analysis, it was found that diabetes history was independently associated with pre-discharge wound complications. This is not surprising, given that patients with diabetes have poor wound healing capacity which are slow to heal, and poor distal microvasculature which predisposes to infections, foot ulcers, and neuropathy(59-61).

Multivariate analysis also found that having preoperative transfusions correlated with wound complications post-discharge. Allogenic blood transfusions are known to have an immunosuppressive effect, which may have resulted in the increased risk of infections in the pre-discharge period. A study by Jensen et al.(62) found that natural killer cell function was significantly impaired in patients transfused with whole blood up to 30 days after elective colorectal surgery. While such the effect of such

immunosuppression has not been well explored in spinal surgeries, perioperative blood transfusions has been found to be significantly associated with increased postoperative infectious or septic complications as well as mortality in studies concerning abdominal, hip and cardiac surgeries(63-68). Consequently, this association provides evidence that patients who require preoperative blood transfusions should receive enhanced postoperative monitoring for potential wound-related complications.

The implications of these results are that medical teams in charge of patient care can utilize the findings of this study to form efficient and improved postoperative care procedures for patients due to undergo ALIF. These risk factors could help identify patients likely to experience postoperative medical complications whilst considering pre-discharge or post-discharge timings of such complications to inform effective preventative or treatment strategies. Initiatives such as these would potentially reduce postoperative complications and as such, promote more suitable patient discharge times while decreasing associated healthcare costs.

Prolonged operation duration, osteotomy and pulmonary comorbidity are associated with increased risk of venous thromboembolism before discharge

Venous thromboembolism is a well-known complication and includes pulmonary emboli (PE) and deep venous thrombosis (DVT). These are preventable complications associated with high morbidity and mortality despite advances in diagnosis and treatment. If not promptly identified and managed, this may lead to thromboembolic complications, such as lower extremity DVT, PE, myocardial infarction, and cerebral

infarction. Ultimately, this may lead to severe malfunction of the extremities, heart, and brain, and even death.

The current literature is limited, in part the low incidence rates of thromboembolic events, which means that studies large sample sizes to detect a true difference in incidence between 2 cohorts. Risk factors for VTE after spinal surgery has been studied, but the specific risks following ALIF surgery and whether this is different for VTE events before versus after discharge is not well established.

In our analysis of the NSQIP database, we found that prolonged surgery time, osteotomy (and by implication, increased complexity of surgery) and pulmonary comorbidities to be significant predictors of VTE events. Specifically, these predicted VTE events prior to discharge. We did not find any significant parameters associated with post-discharge VTE. Our findings are similar to those reported by Schoenfield et al(69), who retrospectively analysed 27,730 spinal surgery cases and reported a VTE rate of 1%. In their cohort, body mass index > 40kg/m^2 and prolonged operation time were significantly associated with VTE. Zhang et al(70) performed a meta-analysis of twenty-six studies involving 3,216,187 patients. The total incidence of VTE after spinal surgery was 0.35% (0.15–29.38%). In their pooled analysis, VTE following spinal surgery was particularly associated with higher age, female sex, chronic kidney disease, non-ambulatory preoperative activity status, and D-dimer level. Additionally, similar to our study, Zhang et al found that prolonged operative duration, fusion surgery as opposite to simple decompression procedures, and cases requiring blood transfusion all increased the odds of having a postoperative VTE event. However, upon subgroup analysis comparing anterior lumbar interbody fusion vs posterior intervertebral fusion /translaminar lumbar interbody fusion, the authors did not find any significant

differences in VTE rates. However, for this subgroup analysis, the authors were only able to include 3 studies with data, and thus the analysis is not sufficiently powered.

The implications of our findings are that clinical VTE risk assessment may improve with increased focus toward select high-risk patients with pulmonary comorbidities, as well as those undergoing prolonged surgery or with more complex spinal surgery procedures.

Limitations

The ACS-NSQIP databased provided the perioperative patient data for the retrospective analysis performed in this study. It is a national outcomes-based initiative and collaboration between hundreds of institutions. Using the aggregated data of over 150 variables, hospitals have followed current trends of adverse events in selected surgical specialties, and significantly decreased short-term complications and mortality, and improved patient outcomes in both the military and civilian sector. However, there are several limitations with utilizing this database, especially when it comes to orthopaedics-specific complications.

The above analyses are constrained by several limitations. Firstly, outcomes reported were limited to 30-day follow-up, there may be differences at long-term follow-up which would not be detected by the present analysis. Secondly, other relevant outcomes such as radiographic parameters were not recorded in the NSQIP database, which should be taken into consideration when comparing anterior versus posterior approaches. Prior reports(29, 71) have demonstrated that anterior lumbar fusion techniques are associated with significantly superior restoration of disc height, segmental lordosis and lumbar lordosis in comparison to lumbar approaches. Patient-

reported disability and functional outcomes were also not associated in the present study, as well as other parameters of note such as worker's compensation status(72, 73), economic cost(74), surgeon experience and learning curve(75). Furthermore, outcomes could not be differentiated by ALIF levels, given limitations in the data points collected by NSQIP. From a surgical perspective, the L5-S1 level is the easiest and less morbid of all levels.

The ACS-NSQIP database classifies cases based on CPT codes, so variations in procedural techniques cannot be recorded and their effect on postoperative outcomes cannot be addressed. It is also recognized that the database contains information submitted from hospitals that are participating in the ACS-NSQIP and thus does not contain a statistically representative sample of spine patients who underwent ALF. Furthermore, there are likely to be more approach –specific complications, e.g. vascular injury for ALIF, lumbar plexus and nerve injury for LLIF, dural tears and nerve root injury for TLIF/PLIF, which were not captured by the NSQIP database. Although this is one of the largest existing national databases in the United States which capture spine surgery perioperative outcomes, it could be argued that the low rate of complications means that potentially that a greater sample size is required to identify clinically significant risk factors.

The present study is non-randomized and therefore susceptible to potential selection bias. However, we have minimized the influence of this on outcomes by propensity score-matching to ensure no baseline differences in demographics and comorbidities when examining ALIF versus PLIF outcomes and conducting multivariable analyses to adjust for any differences.

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Chapter 4

Radiological follow-up of anterior lumbar interbody fusion with titanium-coated PEEK integrated cages

Preface and objectives

In the previous chapters, it was demonstrated how the short-term and long-term outcomes following ALIF can be influenced by patient demographic factors, comorbidities as well as perioperative factors such as length of surgery and discharge destination.

Whilst the previous chapters have focused on the effect of demographic and clinical comorbidities on ALIF clinical outcomes, the effectiveness of surgery is also significantly influenced by whether successful bony fusion is achieved. Thus, in this Chapter there is a shift in focus in determine how long-term radiological fusion can be achieved based on optimal choice of cage implant material.

Increasing the rate of fusion has been the major goal when selecting materials and surface modification of implants used in ALIF. There has been considerable interest in the combination of materials to achieve enhanced osseointegration with the use of titanium at the endplate junction, with the benefits of the modulus of elasticity of PEEK within the body of the implant. An option to address this issue is to engineer PEEK device with surface modification with a layer of Ti which offers the advantages of both materials. However, there remains a lack of long-term radiological data to support its effectiveness in lumbar fusion.

Therefore, the objectives of this chapter are to assess the 24-month radiographic follow-up of Ti-coated PEEK integrated cages in ALIF surgery. The author contributions statement is appended.

Acknowledgements

The current study would not be possible without the efforts of my supervisor A/Prof Mobbs, who was the primary surgeon involved in each of the cases assessed and analysed in this chapter. His supervision and vision in this field allowed this study to be possible. The author contributions statement is included below.

Background

Achieving solid radiographic fusion as become one of the main assessment endpoints of successful spinal fusion surgery. Although radiographic fusion does not always directly correlate with improved clinical outcome(1-5), in a significant proportion of patients, correction of structural abnormality and stabilisation across the intervertebral segment prevents further unnecessary and painful motion(6). Thus, there are ongoing innovative efforts in interbody cage design and biomaterials choice to provide an optimal environment to promote arthrodesis to provide segment stability and improve patient clinical and functional outcomes.

Choice of biomaterial for spinal implants is an important consideration. When designing an implant and choosing an ideal biopolymer for material choice, the ideal properties include:

- being strong yet matching the elastic modulus of bone
- inert
- biocompatible
- amenable to osseointegration with bone for long-term fusion

Traditionally, titanium (Ti) and Ti alloy cages were used. Used in orthopaedic surgery since the 1940s, Ti is a robust material with corrosion resistance and excellent strength under physiological loads(7-9). Ti can undergo further surface modification to improve its bioactivity and osseointegration ability to achieve long-term fusion(10, 11). However, Ti alloy cages had several disadvantages. These include a higher rate of subsidence into adjacent vertebral endplates(12), higher stiffness which reduces mechanical stimulation of the surrounding bone and shielding the bone graft(13), lack

of radiolucency which hinders optimal radiographic evaluation, and subject to *in vivo* corrosion and hydrogen embrittlement(14).

Poly[aryl-ether-ether-ketone] (PEEK) biomaterials were introduced in the 1980s and became more widely available in the 1990s with the introduction of the Brantigan cage(15). The popularity of PEEK increased during this time as surgeons pivoted towards materials with lower modulus of elasticity to match implant stiffness with bone to be integrated with. The elastic modulus of PEEK is 4.3GPa, which is closer to cortical bone (18.6GPa) compared to titanium (110GPa)(16). It was thought that implant-bone elastic modulus mismatch was a major contributor to implant subsidence(17). Additionally, PEEK has lower stiffness than titanium alloy, which allows better transfer of loading forces to the bone graft whilst minimizing stress shielding compared to solid titanium implants. PEEK also has excellent *in vitro* and *in vivo* biocompatibility(18, 19) and has been shown to be safe, non-cytotoxic, and non-mutagenic(20, 21). From a technical workflow point of view, PEEK material has excellent radiolucency which allows easier interpretation of radiographic imaging intraoperative and assessment of fusion postoperatively.

Despite the above advantages of PEEK over titanium, implant subsidence due to poor osseointegration of PEEK remains a significant concern. *In vitro* studies have shown that osteoblasts differentiate to a lesser degree when cultured on PEEK versus titanium surfaces, suggesting that the former has a lower level of support for osteogenic tissues(8). There are multiple clinical reports of PEEK cages used for anterior cervical discectomy and fusion (ACDF) which showed slow or incomplete body fusion(22, 23). In one study of patients who received standalone PEEK implants, most patients did not achieve radiographic fusion by 18-month follow-up(24). When the authors compared

patients who did not achieve radiographic fusion compared with those who did, the prior group had poorer functional outcome and symptom improvement. This issue is a particular problem when strong anchoring to bone is required, such as in lumbar interbody fusion.

There has been considerable interest in the combination of materials to achieve enhanced osseointegration with the use of titanium at the endplate junction, with the benefits of the modulus of elasticity of PEEK within the body of the implant(7). It is likely that success in osseointegration between the interbody implant with surrounding bone will facilitate fusion thus improving implant longevity by limiting subsidence as well as stress shielding and associated complications. Although Ti and PEEK have been commonly used as interbody implants in the last 25 years, the unaltered state and surfaces of these materials provide limited bioactivity. Currently, alteration of implant surfaces into bioactive areas is routinely performed on interbody implants in hopes of achieving bony on- and in-growth. Surface treatments are now routinely performed to create a strong implant-bone interface to achieve structural, biochemical and functional stability also known as osseointegration.

To address the above limitations, more recent changes in cage designs have involved surface biomodification of implant materials to improve osseointegration and thus fusion rates(7). In particularly, Ti-coated PEEK implants have received considerable attention. Bioactive surface modification with titanium at the endplate should promote osseointegration, in-growth and on-growth whilst the PEEK body of the implant maintains ideal properties of providing appropriate flexibility and resisting excessive motion. Walsh et al have demonstrated that application of plasma-sprayed Ti coating to

PEEK spacers facilitates direct bone on-growth at cortical and cancellous sites using an ovine model system(25).

We have previously described this problem based on CT imaging and histological analysis(26). In this case, we described a patient who underwent L4/L5 ALIF surgery who received a standard PEEK implant and graft. CT images were captured at 12-month follow-up to assess for any evidence of poor osseointegration. The method for histomorphometric analysis has been previously described by Professor Bill Walsh(25). In brief, tested implants were placed in a line-to-line manner in cortical bone and cancellous bone of adult sheep tibia using an established ovine model. The extent of osseointegration between the PEEK/composite material and cortical and cancellous implantation sites was then determined on histology. We demonstrated and termed the "PEEK-Halo" effect, which describes a halo effect between the PEEK implant and the bone graft on CT imaging (Figure 4.1.1). This phenomenon is secondary to poor osseointegration of PEEK implants. In comparison, a second patient underwent L5/S1 ALIF surgery with a Ti-coated PEEK composite implant (Ti-bond; Spinal Elements, Carlsbad, CA, USA). As seen at 12-month radiographic follow-up in Figure 4.1, the PEEK-Halo effect is not observed due to improved osseointegration of composite implants with the surrounding vertebral bone and bone graft placed within the cage device. The above differences were confirmed histologically in Figure 4.2, where distinguishable fibrous tissue layer and gap has formed across the PEEK/BONE interface of the inserted PEEK implants, corresponding to a radiolucent "Halo" observed on CT.

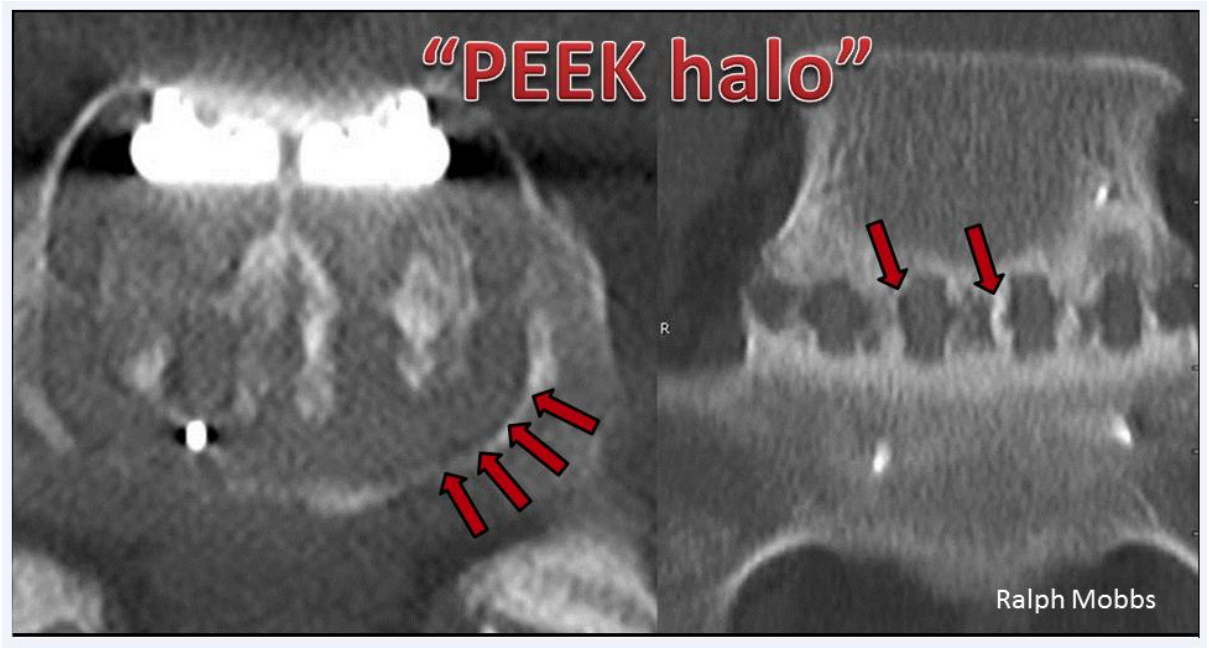

Figure 4.1. Computed tomography (CT) image showing 12 months postop L4/5 ALIF. A. Mid-sagittal CT. B. Coronal CT. Fine cut CT imaging demonstrating adjacent endplate sclerosis and the absence of radiolucency at the Ti/Bone endplate interface (Arrows). Figure reproduced from Phan et al(26).

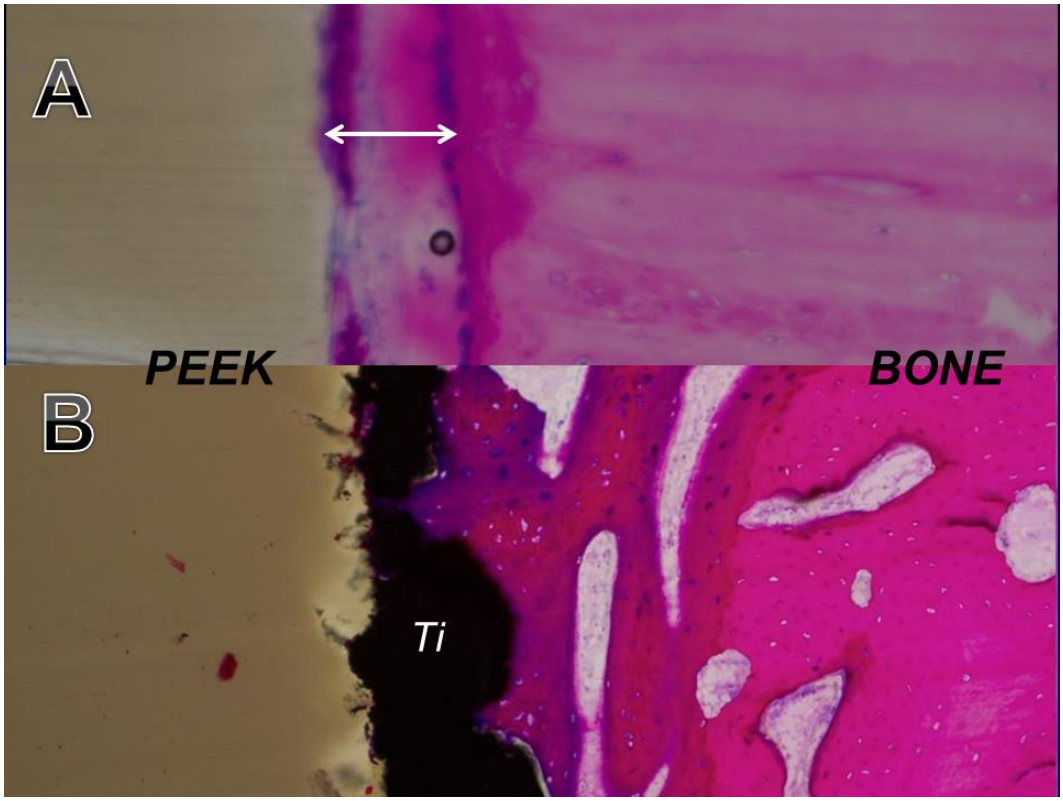

Figure 4.2. Histology of PEEK/Bone interface at 4 weeks post implantation into sheep tibia model. A PEEK/Bone interface: At 4 weeks there is a well-established rim of fibrous tissue (white arrow) between the PEEK implant and adjacent bone – the rim of fibrous tissue results in the HALO effect seen on CT imaging. B. In contrast, a comparator analysis of PEEK/Ti/BONE interface demonstrates on-growth and ingrowth of bone at the Ti/BONE interface – with no radiolucent rim evident on CT imaging. Adapted from Walsh et al.(25)

Our above *in vitro* findings have been corroborated with findings from a number of other authors. Cheng Yao et al studied osteoblast adhesion on PEEK coated with Ti compared with uncoated PEEK and found that the former increased osteoblast adhesion and spreading via changed surface wettability and increased adhesion to the nanometre surface roughness(27). Ha and colleagues(28) studied vacuum-plasma-sprayed Ti on carbon fibre-reinforced PEEK substrates which were chemically treated with sodium hydroxide. When immersed in simulated body fluid (SBF) containing ions, these specimens developed a carbonate-containing calcium phosphate layer, in contrast to untreated PEEK specimens which did not develop a surface precipitate. As such, these *in vitro* studies support surface modification of PEEK with Ti as a technique to enhance implant surface cellular response.

The effect of Ti surface modification of PEEK implants have been studied in animal models. These studies have come to similar conclusions, supporting improved bone on-growth with Ti surface modification of PEEK implants. Han et al(29) used electron beam deposition to coat PEEK cages with Ti. Using a rabbit tibial defect model, they found that the level of proliferation and differentiation of osteoblast precursor MC3T3-E1 cells more than doubled after the implant was Ti-coated, as well as a significantly higher bone-to-implant contact ratio. Walsh et al(30) conducted a randomized study evaluating the *in vivo* response of promoting new bone growth and bone apposition in three types of implants in defects in cancellous bone (distal femur and proximal tibia) of four mature sheep. In Group 1, Ti was coated over the entire PEEK cylindrical dowel including apertures, in Group 2 Ti-coating was applied only over the apertures, and Group 3 was the control group with no surface coatings. At 8-week follow-up, significant new bone formation in the apertures were noted in implants with Ti coating

whereas these were empty in the PEEK group, as objectively quantified using volumetric CT analysis. On histology, newly formed woven bone was found along the surface of the titanium in the apertures whereas PEEK only implants had nonreactive fibrous tissue inside the apertures at follow-up. It is important to note that these animal trials used non-functional models which are non-dynamically loaded. These do not replicate the complex physiological and biomechanical conditions of a typical implant in an intervertebral joint, and does not account for anatomical variance, differing physiological preloads and complex joint kinematics.

As such, there is promising early data which suggests that Ti-coated PEEK cages may offer potential advantages of improved osseointegration and improved radiographic fusion. There is limited evidence investigating the long-term outcome of patients undergoing lumbar interbody surgery with Ti-coated PEEK implants. As such, the objectives of this Chapter are to further add to the literature by reporting our clinical experience and longer-term radiological outcomes of ALIF with an integrated Ti-coated PEEK cage in a prospective study.

Methods

Data source and patient selection

Approval for this study was obtained from the South Eastern Sydney Local Health District-Northern Sector (SESLHD-NS) ethics committee, Ref: HREC 11/183.

Over a 7-month period in 2017-2018, consecutive patients who underwent ALIF surgery with a composite Ti-PEEK integrated cage implant (Figure 4.3) by a single surgeon (supervisor A/Prof Ralph Mobbs) were recruited for this study. Inclusion criteria was persistent back pain and/or radiculopathy, unresponsive to prolonged conservative treatment and pain specialist review who deemed that ongoing pain management and injection therapies were not appropriate. Specific indications for surgery included re-recurrent (multiple) disc herniation, isthmic spondylolisthesis, degenerative scoliosis, and discogenic low back pain. Paediatric cases, cases with surgical indications for trauma and malignancy, and anterior surgery performed at non-lumbar levels were excluded.

Surgical procedure

All procedures were performed by a single surgeon (A/Prof Ralph Mobbs). All implants used in this study were Titanium / PEEK ALIF “Redmond” x3 screw device (A-Spine ASIA / Taiwan) (Figure 4.3). An open ALIF surgical technique was used, with an anterior approach to the lumbosacral spine. A vascular surgeon (Dr Andrew Lennox) was present in all cases and assisted in exposure, mobilisation of vascular structures and closure. Heparin was not used during the procedure.

The ALIF surgical technique used for this study has been previously described by us(31) and is summarised here. The patient is placed in a supine position. For the L5/S1 exposure, a transverse incision (mini-Pfannenstiel) is performed between the umbilicus and the symphysis pubis. For other lumbar levels (L2/L3, L3/L4, L4/L5) and multi-level operations, a midline vertical incision used. Diathermy is used for dissection of skin and soft tissues, with an inferior and superior flap raised to give the vertical exposure. The linea alba is exposed and divided using monopolar diathermy. The rectus sheath muscles are elevated and retracted using tissue forceps, to allow access to the retroperitoneal plane.

The retroperitoneum is approached with blunt dissection. The inferior epigastric vessels are visualised, preserved, and retracted anteriorly. The psoas muscle and the genitofemoral nerve are visualised. As the vessels are identified (left common iliac artery and vein), a low profile narrow ring-based retractor blade system is positioned (Synframe, Synthes, USA). The iliac arteries and veins are then exposed and retracted laterally to reveal the lumbar intervertebral disc space, with the median sacral vessels double clipped and divided. In all cases, the left ureter was identified and retracted medially. Major anterior vessels (Aorta and iliac veins/arteries) were mobilised and retracted.

The level of pathology was confirmed with X-ray prior to disc removal, and endplates prepared. The anterior disc space dissection is performed with peanut dissectors to avoid diathermy injury to the sympathetic nerves (that cross the L5/S1 disc) to reduce the risk of retrograde ejaculation. The discectomy is approached with an annulotomy spanning the full anterior aspect of the intervertebral disc. Decortication of the vertebral endplates is then performed to optimise the bone-graft interface. Using a Cobb elevator,

the plane between the bony and cartilaginous endplate is developed. Using a rotatable distractor the disc height elevation is provided for efficient disc removal with a piecemeal approach using a pituitary rongeur. A microscope can now be used for visualization of the Posterior Longitudinal Ligament, with further disc removal of sequestered fragments in the canal to complete the decompression.

During preparation of the disc space and decompression of the neural elements, the bone graft material is prepared. Once the disc space is prepared, trial implants are inserted in order to select for the best size fit. The depth, position and lordosis is confirmed with X-ray imaging. A stand-alone A-Spine Ti/PEEK ALIF cage (Figure 4.3) is packed with bone graft, inserted and fixated with integral screws. Correct placement is confirmed radiographically. The site is then washed with antibiotic irrigation prior to closure.

Following haemostasis, the retractors are removed. The peritoneum returns to its position. The linea alba is closed with heavy PDS, with standard subcutaneous and skin closure.

Figure 4.3. Ti/PEEK Integral fixation 3-screw ALIF Implant. Porous Titanium endplates with PEEK forming the body of the implant. X3 screw integral fixation. (Redmond-L Implant, A-Spine ASIA, Taiwan).

Interbody graft

Allograft Supercritical CO2 (SCCO2) sterilized "crunch" from a local supplier, ("Allovance", Australian Biotechnologies, Sydney, Australia), was used along with BMP-2 (INFUSE, Medtronic) and included collagen sponge. A small dose (4.2 mg rhBMP-2) was used for each level performed. The BMP-2 was mixed evenly throughout the Allograft preparation. 4 patients had a combination of SCCO2 Allograft & DBM Fibers (Australian Biotechnologies, Sydney, Australia), without BMP based on patient preference to avoid perceived issues with Bone Morphogenic Proteins.

Outcome measures

Radiographic fusion was assessed by the surgeon (RJM) and an independent radiologist as part of routine clinical care. Plain radiographs were performed at Day 1 postoperative and 6 weeks postoperative to check for implant failure or migration from implantation position. CT scan imaging was performed at 4-6 months follow-up to assess fusion status, and again at 18-24 months if no fusion was present on the initial CT scan. Fusion was considered successful if bridging bone incorporating the graft and adjoining Ti endplates was apparent, with additional loss of radiolucency, restoration of interbody space and no hardware failure.

For clinical outcome at follow-up, patients were asked to quantify their overall pain on a Visual Analogue Scale (VAS) for low back pain ranging from 0 (no pain/discomfort) to 10 (worst pain/discomfort imaginable) pre- and post-operatively. Functional outcome was measured using the Oswestry Disability Index (ODI). Patients were also assessed according to Odom's criteria(32) for their overall clinical outcome. Patient satisfaction

with their procedure was elicited using the Patient Satisfaction Index (PSI) as described by Palit et al(33) at final follow up.

Statistical analysis

Descriptive data are represented as means ± standard deviation (range, minimum–maximum). All data sets were tested for normality with the D'Agostino and Pearson omnibus normality test. Nonparametric data was analysed using the Mann-Whitney U test and parametric unrelated data with the unpaired t test for comparison of the results between the Plated and Non-Plated Groups. A paired t test was used for comparison between pre- and postoperative continuous variables within patient groups. Statistical significance was set at level of $P<0.05$. All analyses were generated using a commercial software package (GraphPad Prism version 5.01, GraphPad Software, Inc., USA).

Results

Demographics of Ti-PEEK ALIF cohort

Over a 7-month time period, 17 patients with 20 ALIF levels performed, were operated and data prospectively collected. There were 15 patients who had stand-alone ALIF with integral fixation, and 2 with additional posterior percutaneous pedicle screw fixation. There were 10 males and 7 females, with a mean age of 54 years (range, 31-79). There were 2 smokers, 3 diabetics (Type-2) and 1 workers compensation case.

Specific indications for surgery included: 3 re-recurrent (multiple) disc herniation (17.6%), 3 isthmic spondylolisthesis (17.6%), 2 with degenerative scoliosis (11.8%) and 9 with discogenic low back pain (52.9%). Representative cases of preoperative and postoperative imaging for degenerative disc disease (Figure 4.4), recurrent disc herniation (Figure 4.5), multi-level fusion (Figure 4.6), spondylolisthesis requiring posterior fixation with pedicle screws (Figure 4.7), and isthmic spondylolisthesis (Figure 4.8) are shown. All patients presented with a combination of mechanical back pain, and/or radiculopathy related to foraminal stenosis or re-recurrent disc herniation. The mean preoperative symptom length was 16 months (range, 5 - 57 months).

The average length of stay was 4.3 days (range 1-7 days). Average operative time was 79 minutes, with an average blood loss of 90cc.

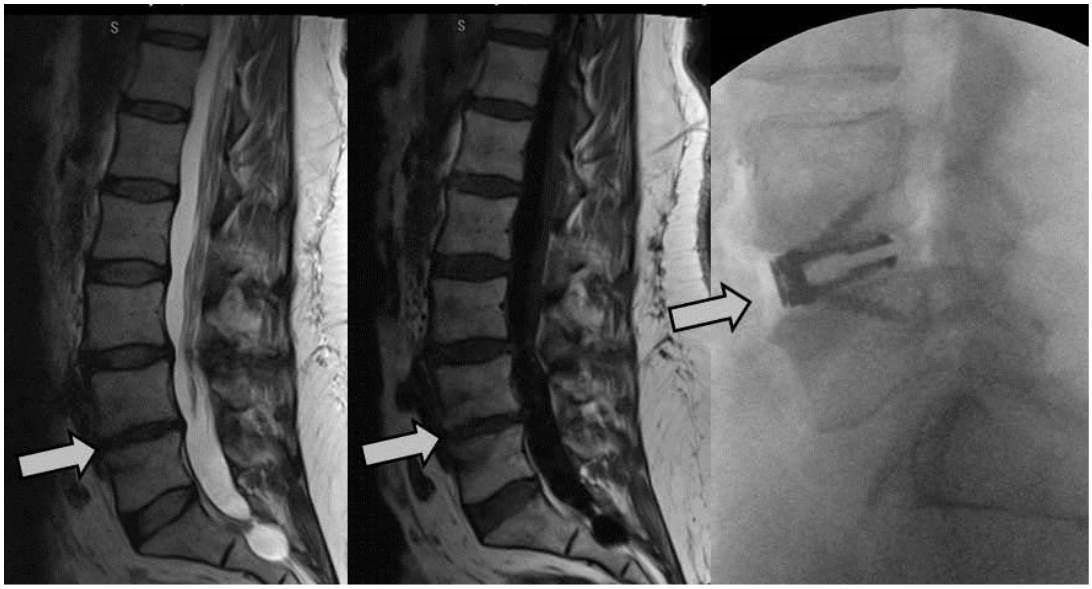

Figure 4.4. L4/5 ALIF for degenerative disc disease, managed with integral fixation composite Ti-PEEK ALIF implant. White arrows point towards level of pathology, and location of implanted cage.

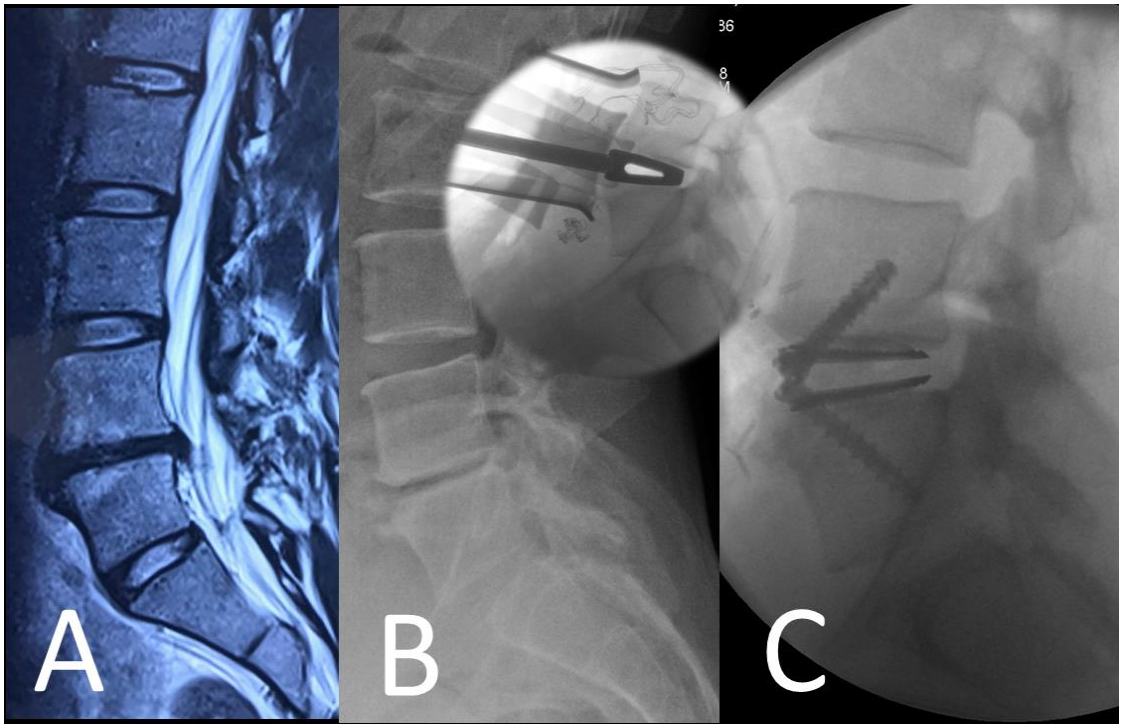

Figure 4.5. L4/5 ALIF. (A) Recurrent disc herniation following multiple microdiscectomy procedures with progressive disc height loss, foraminal stenosis with clinical symptoms of discogenic low back pain and L4 radiculopathy. (B) Pre-operative lateral Xray. (C) L4/5 ALIF with Ti/PEEK device. (Insert) Intraoperative trial prosthesis.

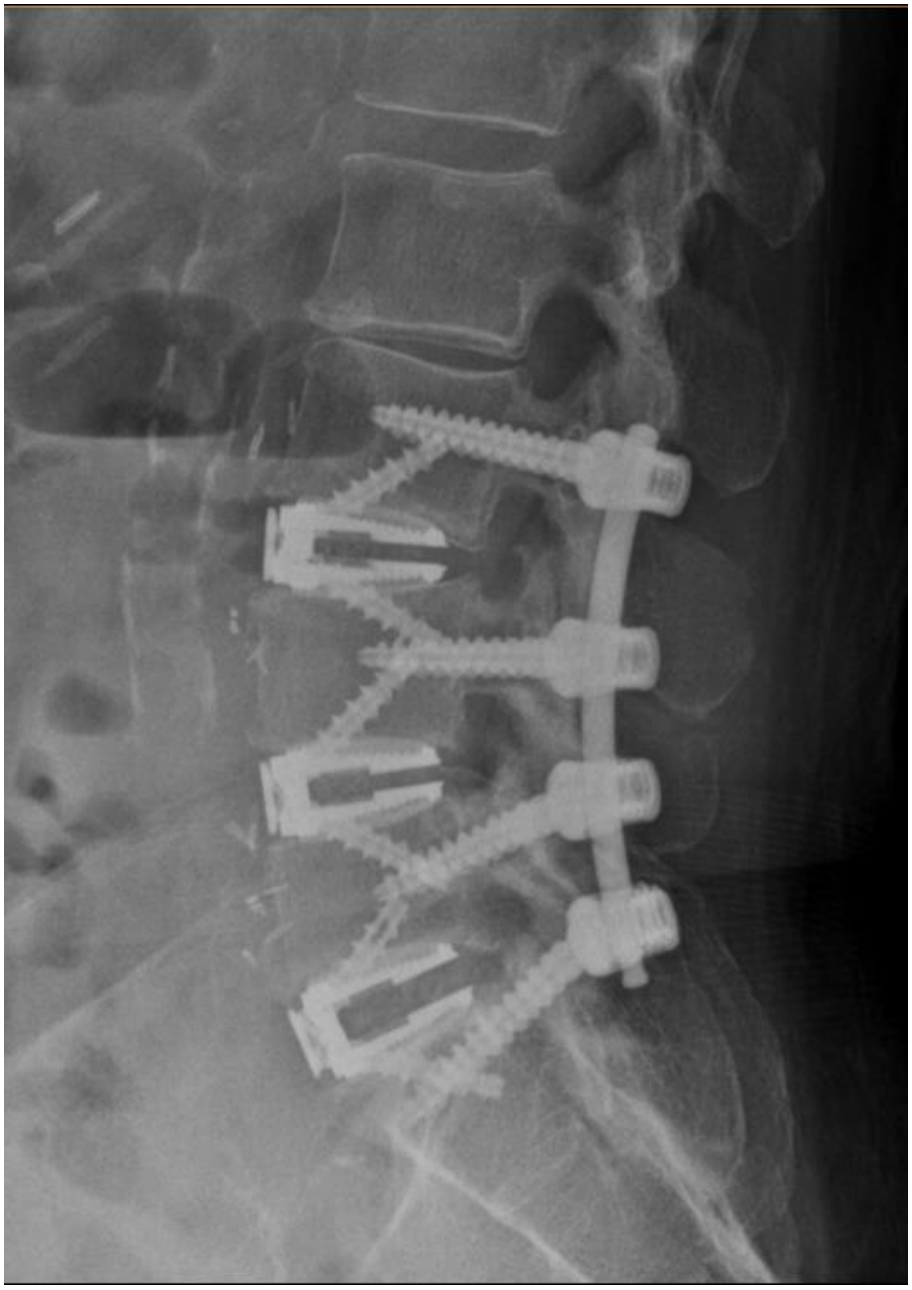

Figure 4.6. Multilevel ALIF Implant with unilateral percutaneous pedicle screw fixation. Posterior fixation of long constructs is recommended to increase fusion rate.

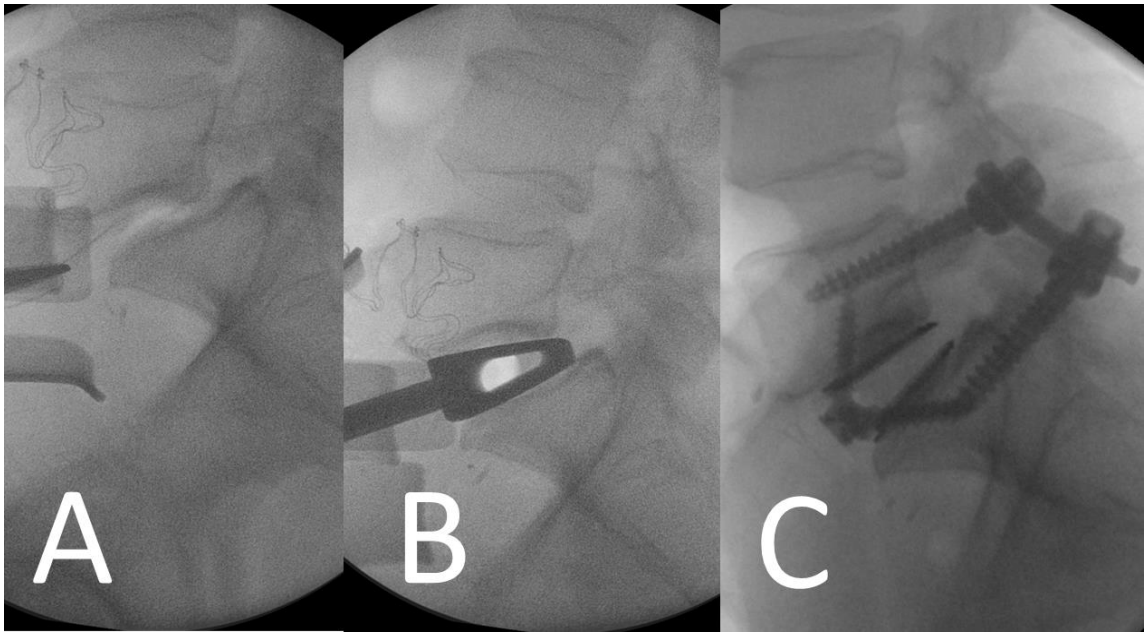

Figure 4.7. ALIF with Percutaneous Pedicle Screw Fixation. (A) Intraoperative level check. (B) Trial prosthesis to confirm position and restoration of foraminal volume. (C) Percutaneous fixation to assist with posterior tension band.

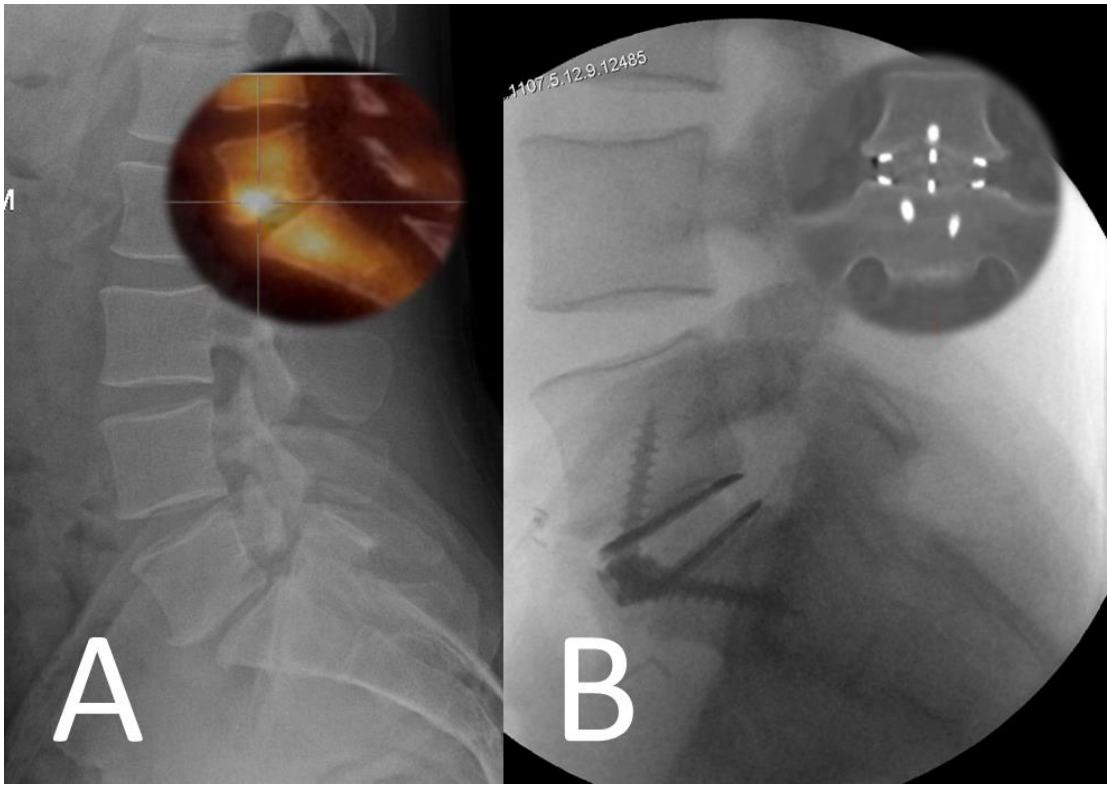

Figure 4.8. Stand-alone ALIF for Isthmic Spondylolisthesis. (A) Standing X-Ray. Degenerative Disc Disease with low grade spondylolisthesis and pars defect. Insert. Discovertebral uptake on bone scan. (B) 6-month postoperative X-ray and (Insert) CT demonstrating restoration of disc height with no subsidence, no lucency and evidence of early integration of graft material.

Radiological outcomes

An 85% radiographic fusion rate (17/20 implants) was achieved at 6 months postoperatively, and 95% (19/20 implants) at 24 months. The non-union patient was deemed to have a 'locked non-union' with improvement in preoperative clinical symptoms and therefore no further surgery was necessary. Representative CT imaging demonstrating fusion at 6-month follow-up (Figure 4.8, Figure 4.9) and 12-month follow-up (Figure 4.10) are shown.

3/20 ALIF implants (15%) demonstrated graft subsidence of 2-3mm. There were no cases of graft or implant migration, and no screw back-out or breakage.

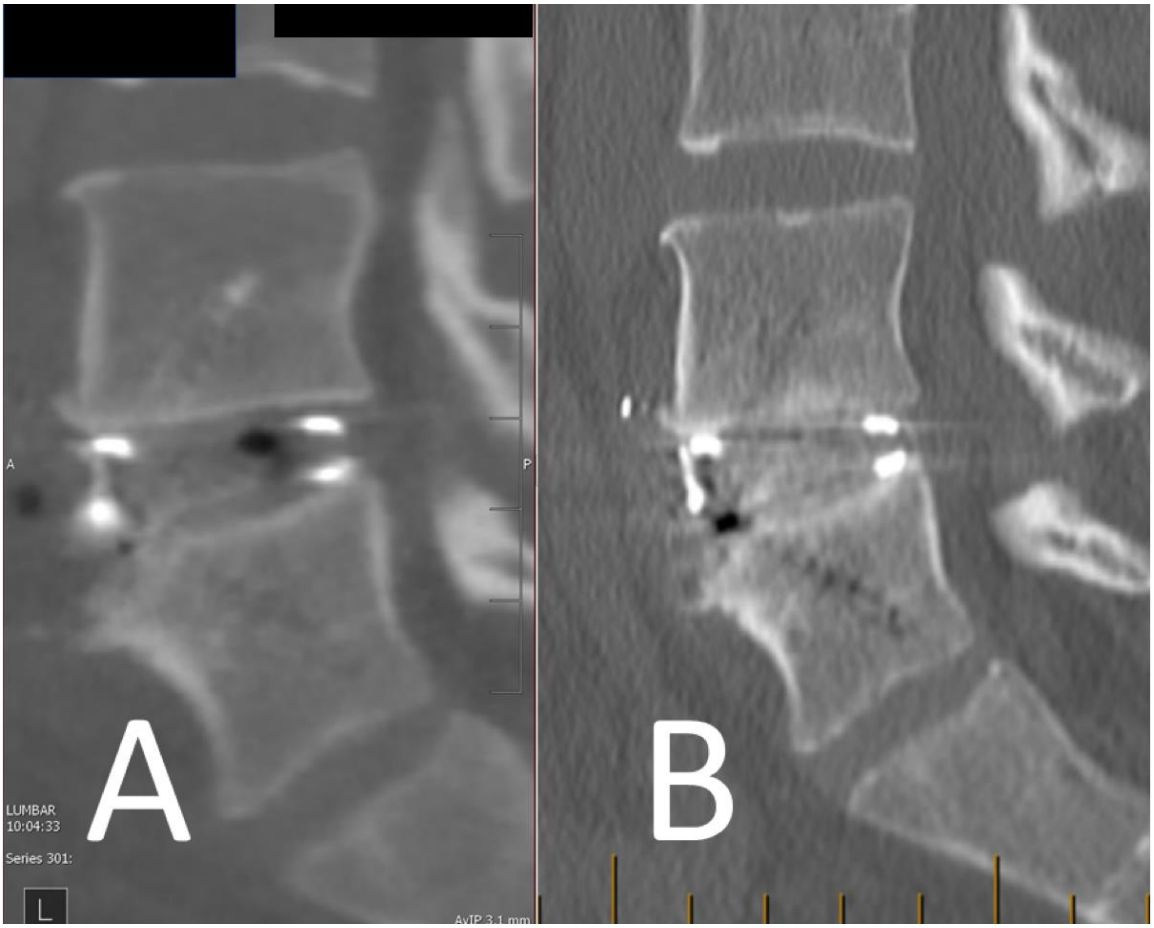

Figure 4.9. L4/5 ALIF: Solid fusion at 6 months postop using Allograft and Fibermatt DBM graft. A. Day-1 Postop CT. B. 6-month Postoperative CT with osseointegration through and behind the ALIF implant. No halo/lucency at Titanium/bone junction consistent with incorporation of the titanium into the bone endplate. No subsidence is noted.

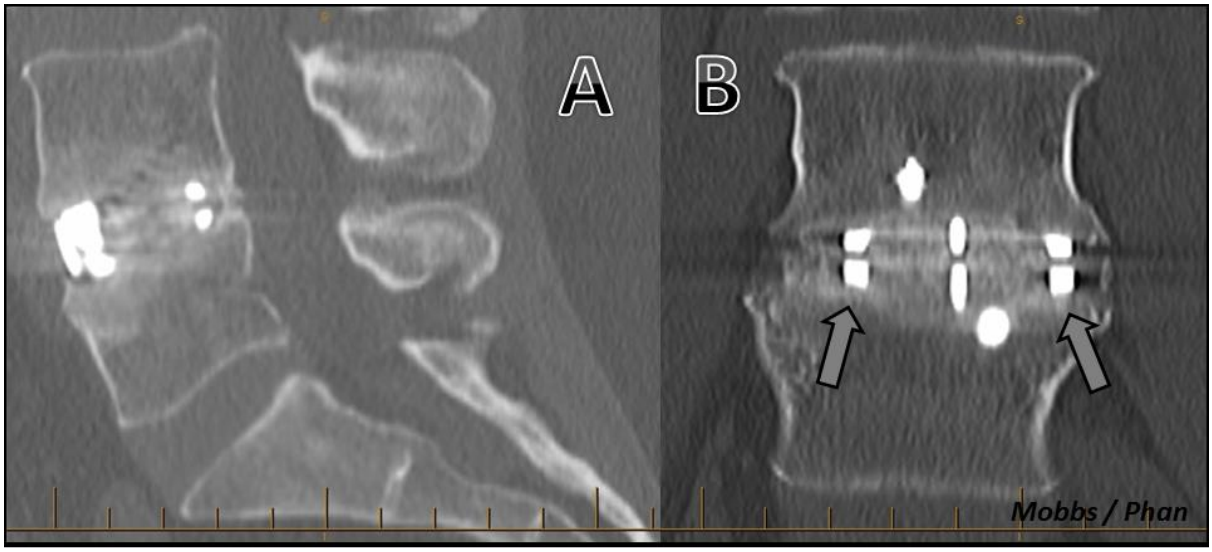

Figure 4.10. Computed tomography (CT) image showing 12 months postop L4/5 ALIF. A. Mid-sagittal CT. B. Coronal CT. Fine cut CT imaging demonstrating adjacent endplate sclerosis and the absence of radiolucency at the Ti/Bone endplate interface (Arrows).

Patient reported clinical outcomes

Overall pain scores as measured by VAS showed significant improvement ($P<0.0001$) when compared with the preoperative scores. Overall combined back/leg pain improved on average from 7.9 preoperatively to 1.8 postoperatively, with a mean improvement of 6.1±2.1 (range, 1-9).

In terms of the PSI scores, at 6 months postop, 13/17 patients (76.5%) achieved either excellent or good outcomes according to the PSI criteria, and 15/17 patients (88.2%) by 24 months. 2/17 patients (11.8%) self-classified as a poor outcome due to significant postoperative complications related to cardiac issues, and hip pathology in another patient that was identified post ALIF.

Complications

There were no cases of retrograde ejaculation in the male cohort. Ileus was experienced in 2 patients, both with 2 level ALIF procedures. There were no wound related complications, and no blood transfusions were necessary. A single patient had a myocardial infarct post-surgery and required further cardiac management.

Discussion

Longer-term follow-up of our cohort of patients undergoing ALIF with Ti-coated PEEK implants with Allograft and BMP-2 suggests it is effective in achieving radiographic fusion. Follow-up imaging in fused patients demonstrate no lucency around the Ti endplates, significant improvement in patient-reported clinical outcomes. Supercritical CO_2 Allograft provided an osteoconductive scaffold and combined well with BMP-2 to facilitate fusion.

Both animal studies and evolving human data on rapid osseointegration of bioactive implant surfaces is promising and may one day lead to implant technology relying on the device alone, without with addition of bone grafting. It is likely that achieving bone integration with the interbody implant will aid in fusion and improve implant longevity by limiting subsidence as well as stress shielding and associated complications. Surface modification and/or conversion of implant surfaces into bioactive areas is intended to improve ingrowth and on-growth, bringing with it associated clinical benefits. There are a number of factors to consider, including interbody cage material choice, interbody graft choice and implications in terms of requiring further additional posterior fixation.

Interbody cage properties

PEEK, a radiolucent semi-crystalline polyaromatic linear polymer and thermoplastic material, consists the properties of high molecular weight, whilst being biologically inert and non-resorbable(23), with long clinical history(22). Using a host in a rat air pouch model, Moore and Rhoad demonstrated PEEK elicits minimal cytotoxicity and

inflammatory response(34). Additionally, other biomechanical properties of PEEK include resistance to radiation and chemical damage, compatibility with various reinforcing agents (e.g. titanium and carbon fibre) and reasonably greater strength (per mass basis) than many metals(22). Hence, PEEK cages provide a hard frame which can withstand spinal loading. The elastic modulus of PEEK is 3.5 GPa, which is comparable to that of cortical bone in the range of 15-20 GPa and cancellous bone at 1 GPa(35), which is likely to minimize graft subsidence(36). Despite remodelling of bone graft within the implant cavity, spinal alignment can be maintained. However, some studies have described suboptimal osseointegration of PEEK at the adjacent vertebral endplate following implant insertion. We have observed a "PEEK-Halo" effect was seen on computed tomography (CT) at up to 12 months following an ALIF procedure, delineated by a radiolucent rim on axial view(26). The peri-implant halo likely indicates the presence of fibrous tissue interface surrounding the PEEK implant(25).

Ti has the propensity to be altered to improve both osseointegration. On-growth of bone refers to the direct apposition of bone onto implant surface; while ingrowth requires a 3-dimensional structure with pores connecting the outside, allowing bone growth and interlocking 'into' the surface of an implant. Additional modifications of implants are targeted at influencing the way tissues incorporate and interact with the implant material. The combination of these two biomaterials has the advantage of the modulus of elasticity of PEEK with the on-growth benefits of porous Titanium. In vitro studies have demonstrated that Ti-PEEK implants have superior cell attachment, proliferation and osteoblastic differentiation compared to pure PEEK substrates(25, 29). It was suggested that Ti-PEEK implants may provide better biocompatibility compared to pure PEEK substrates. Bone on-growth to titanium is well-established(37) as well as titanium

coated PEEK(22, 30). This study further supports this combination of these biomaterials to assist in the fusion process following the ALIF procedure when used in combination with allograft and an inductive factor BMP-2.

Interbody graft material

Autograft is still widely considered as the gold standard in lumbar fusion(38). A Cochrane systematic review concluded that fusion techniques utilizing autograft yielded higher fusion rates than allograft and synthetic bone substitute techniques, however other outcomes were not able to be assessed due to the lack of standardized outcome measures within the literature(39). Hence, donor site morbidity associated with autograft has fuelled the growing interest in alternative bone grafting materials(40), namely ceramics, as fusion substrates for lumbar arthrodesis. This study demonstrates that a combination of a Ti-coated PEEK cage with allograft and BMP-2, proved to be an effective and safe materials combination, resulting in acceptable fusion at follow-up and improvements in patient pain and function.

Posterior stabilization and fixation

The use of posterior fixation may further reduce micromotion between the graft-host interface, promoting graft settling, however increasing operative time, risks and costs(41). Whilst posterior fixation with facet and pedicle screws is commonly employed to stabilise fusions, there have also been reports of associated morbidity, namely instrumentation failure(42). We believe there is a role for additional posterior

fixation in pathologies such as isthmic spondylolisthesis, osteoporosis and multilevel procedures(43, 44).

It is expected that with bioactive endplate technologies, cage integration with the adjacent endplate is more rapid as compared with PEEK cages alone, therefore reducing the necessity for additional posterior fixation. In the present series, there was one case of L5/S1 low grade spondylolisthesis with bilateral pars defects managed with integral fixation alone (Figure 4.8), and another case of spondylolisthesis Grade 1+ requiring percutaneous fixation with pedicle screws. The combination of a large implant (Redmond-L, A-Spine ASIA, 43 x 32mm dimensions), with rigid initial fixation and porous Titanium endplates resulted in an excellent early radiological and clinical result, avoiding the need for additional posterior fixation in the majority (15/17) of cases.

Comparison with prior experiences using Ti- PEEK implants

In order to assess the effectiveness of Ti-PEEK implants in terms of osseointegration and clinical improvement, prospective clinical studies should be performed with ongoing follow-up. There is currently very limited long-term clinical evidence comparing outcomes of Ti-PEEK composite implants versus PEEK implants for degenerative spinal disease. In one of the earliest reports, Schnake et al in 2013(45) conducted a randomized study PLIF patients who received either Ti-coated PEEK or non-coated PEEK cages. The surgery included posterior fixation with pedicle screws and 2 cages per level. At 12-month X-ray and CT follow-up, there was no cage migration in the Ti-PEEK cage group compared with 2.8% migration rate in the non-coated PEEK group. Fusion rates was similar in terms of bone-cage contact in >50% of

CT slices (74% vs 66.6%), bone growth through cage pores (96.3% vs 94.4%), and higher for bone growth outside cage pores (81.5% vs 58.3%). Clinical outcomes in terms of ODI and VAS low back pain scores were not significantly different. Benneker et al(46) reported 2-year experience with carbon fibre-reinforced PEEK (Carbon/PEEK) interbody fusion cage used in 42 patients undergoing TLIF or PLIF. The authors reported solid fusion in all but one patient, albeit this study had no comparator control group.

There are also few reports of Ti-PEEK cages used specifically in ALIF. Sclafani et al(47) reported their early experience via a retrospective observational analysis of 44 subjects who under ALIF with a plasma-sprayed Ti-coated PEEK implant. At average follow-up of 7.3 months, 96% of cases demonstrated radiographic union with bridging bone formation across the interbody space. No differences were found in terms of follow-up VAS low-back pain. Our present cohort of cases demonstrates a similar fusion rate (95%) at 24-month follow-up, further providing support for the effectiveness of Ti-PEEK ALIF implants.

A summary of key literature on the use of Ti-coated PEEK cages or Ti-PEEK composite cages in lumbar interbody fusion adapted from Assem et al(48) is shown in Table 4.1. As observed, there is a scarcity in the literature reporting long-term radiographic and clinical outcomes following Ti-coated PEEK cages in lumbar fusion. There is only one other study which reports outcomes using Ti-coated PEEK cages in ALIF(47) with average follow-up of 7.3 months, compared to up to 24-month follow-up in the current study.

Limitations

A chief limitation of this study is the relatively small numbers involved. Assessment of interbody fusion and the integration of the Ti endplate remains a challenge. As there are no universally accepted criteria for determining radiological fusion, it is often difficult to arrive at a true assessment of fusion based on plain radiography alone particularly when synthetic cages are utilised. Fine-cut CT scans with reconstruction has been shown to be more reliable and sensitive for the detection of pseudoarthrosis than plain radiography(49, 50), therefore this technique was instituted in all patients.

Conclusions

In this study, we have found that using a Ti-coated PEEK interbody cage containing Allograft and 4.2mg BMP-2 per level, in one and two level ALIF procedures, proved to be an effective treatment for degenerative spine/disc disease, low grade lumbar isthmic spondylolisthesis, spondylotic radiculopathy and discogenic low back pain. There were no cases of lucency or halo adjacent to the Ti endplates at the 6-month postoperative mark, consistent with bone/porous Ti incorporation. Bioactive conversion of PEEK cages with porous Ti alloy endplates is likely to assist with early integration of the prosthesis with the surrounding bone / vertebral endplate.

Table 4.1. Summary of key results extracted on studies reporting outcomes of Ti-PEEK implants in lumbar fusion surgery. A = Control cohort (PEEK cages), B = Experimental cohort (PEEK/Ti cages), Pts = patients, M = Months, NSS = No Statistical Significance, * = Conference Abstract, PLIF - Posterior Lumbar Interbody Fusion, TLIF – Transforaminal lumbar interbody fusion, NA = Not Applicable. Adapted from Assem et al(48).

Author, Level of Evidence	**Surgery**	**Patient Nº/ Group**	**Radiological Outcome**	**Clinical Outcomes**	**Conclusions**
Schnake, et al. (2013) * Level II , RCT	PLIF (12 pts with 2-levels of fusion)	60 pts A – 36 B – 27	12 M follow up – <u>Migration –</u> A 2.8% B 0 <u>Bone-cage contact in >50% of CT slices (%)</u> A 66.6 B 74 <u>Bone growth through cage pores (%)</u> A 94.4 B 96.3 <u>Bone growth outside the cages (%)</u> A 58.3 B 81.5	<u>Oswestry-score</u> *Pre-op* A 22 B 21 *Post-op* A 15 B 10 <u>VAS (low back pain)</u> *Pre-op* A 4.7 B 5.9 *Post-op* A 2.4 B 1.8 <u>VAS (leg pain)</u> *Pre-op* A 2.8 B 2.5 *Post-op* A 0.7 B 0.8	Both groups had similar clinical outcomes and fusion rates at 12-month follow-up.
Rickert, M, et al. (2014) * Level II, RCT	TLIF (10 pts had two level fusion)	40 pts A – 26 S B – 24 S	<u>Functional radiograph – fusion rate (%)</u> 12M A 91.7 B 91.7 (22/24 S)	NA	Both groups had similar clinical outcomes and fusion rates at 12-month follow-up.
Kulling, et al. (2013) *	TLIF	18 pts	<u>Fusion (Bony trabeculation)</u> 12 M	<u>SF-36</u> <u>(Median % improved)</u>	All patients demonstrated 12-month

Level III-3, retrospective study		(All patients in group B)	100% <u>Subsidence</u> 0% (No sign of subsidence or radiolucency in any of the patients)	*Bodily pain* 70.3 *Health* 54% <u>ODI (Median % improved)</u> *Pain* 300 *Neurogenic Symptoms* 100 *Function* 93	fusion following TLIF with Ti-coated PEEK cages.
Benneker, et al. (2014) * Level III – 3, retrospective study	TLIF and PLIF	42 pts (All patients in group B)	<u>Grade 1 fusion</u> 18 M 94% of patients <u>Neighbouring segment degeneration</u> 4.3% - 2pts	NA	After 2 years only 1 patient did not achieve solid fusion, with a low complication rate (87% pts had a good or perfect result).
Sclafani et al. (2017) Level III – 3, retrospective study	ALIF	44 pts (All in group B)	<u>Fusion</u> 7.3 months – 96%	<u>VAS low back pain</u> B – improved by 4.5 points <u>VAS leg pain</u> B – improved by 4.1 points	Plasma-sprayed Ti on zero-profile PEEK cage demonstrated good radiographic and clinical outcomes at follow-up <1 yr

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Chapter 5

Conclusions

Anterior lumbar interbody fusion (ALIF) remains one of the mainstay surgical approaches in treating painful degenerative disc disease with or without segmental instability in the lower spine. The anterior approach allows for more complete resection of the degenerative disc, improved access to and preparation of the vertebral endplates, ability to insert larger implants and therefore the potential for greater restoration of disc height, foraminal height, lumbar lordosis, and disc angle, all whilst avoiding the spinal canal, cauda equine and nerve roots. However, the risks of the anterior approach are related in the manipulation of major abdominal organs and anterior vascular structures such as the aorta.

Although several surgical approaches exist for fusion in the lower lumbar spine, including anterior, lateral, posterior, oblique, and transforaminal approaches, there are limited clinically robust studies which compare clinical and radiological outcomes between these approaches. Although there is a considerable amount of literature reporting clinical outcomes following ALIF surgery, few have focused on patient demographic and surgical risk factors are associate with functional improvement and complications following ALIF. Given that the anterior approach transverses abdominal and vascular anatomy that differs from lateral and posterior approaches, it is expected that the risk factors and complication profile for ALIF differs significantly from other established fusion techniques.

Although determining long-term outcomes after ALIF is important in establishing its efficacy, insight into the short-term perioperative outcomes is of significant important too and must not be understated. It is a significant contributor to the rising financial burden of healthcare in the western world, given that complications are the strongest indicator of in-hospital costs per patient. Particularly in the United States, hospitals may be penalised for higher readmission rates and postoperative complications as per the Affordable Care Act. Thus, it is more important than ever to understand which complications are associated with ALIF in the postoperative period, and to determine both patient and surgical factors that are associated with these complications.

Therefore, the goal of the first part of this thesis is to establish the factors associated with long-term clinical outcome (Chapter 2) and short-term perioperative outcomes (Chapter 3) following ALIF. The goals of the second part of the thesis (Chapters 4) are to establish biomaterial and cage design alternatives to further improve radiographic outcome and ease of operation during ALIF surgery, namely titanium(Ti)-coated PEEK integrated cages. Collectively, this thesis highlights the importance of personalising the care of an ALIF surgery patient, through identification and optimization of individual risk factors for short-term and long-term outcomes, as well as through choice of biomaterials and implant designs.

ALIF is an effective fusion technique with excellent follow-up clinical and radiographic outcomes

For long-term clinical and radiographic outcomes, a cohort of 147 patients who underwent ALIF surgery was examined, all implanted with a single type of integrated

cage to minimize heterogeneity. A fusion rate of 91.2% was achieved at follow-up at 6-12 months and determined via assessment with a senior neurosurgeon. Delayed cage subsidence occurred in 10.2% of cases. Significant corrections in anterior disc height, posterior disc height and lumbar lordosis were achieved. ALIF proved to be clinical efficacious in our cohort, with significant reductions in VAS and ODI scores as well as increases in SF-12 scores that were maintained at 12-month follow-up.

Influence of age, obesity and smoking on clinical and radiographic outcomes following ALIF

Subgroup analysis was then performed based on three key demographic characteristics of patients who often present for lumbar fusion for various pathologies: age group, weight group and smoking status. With advances in surgical techniques and anaesthesia, there has been an increasing demand for operations in higher risk candidates. However, the guidance on what age limit, if at all, constitutes high risk of complications and morbidity for spinal fusion remains conflicted. Our study provides evidence that for ALIF specifically, elderly age (≥64 years old) results in increased rate of subsidence but does not affect clinical outcomes. All other short-term and long-term postoperative outcomes and complication rates in our prospective cohort did not differ according to age group. Our results suggest that age alone should not be a contraindication to ALIF.

Our analysis also suggested that obesity was not associated with postoperative complications or in follow-up patient-reported outcomes. Our data suggests that being overweight or obese should not be the sole contraindication for performing ALIF in this population. The technical difficulty of access and exposure in our study was in part

mitigated by enlisting the experience of a senior vascular surgeon who has significant expertise in such exposures, as well as the use of a retractor system which comprises a ring placed around the surgical site. However, we did note that the obese group had lower fusion rates compared to the normal weight group. Only 60% of obese patients achieved successful bone fusion, compared with 76% of overweight patients, and 88.2% of normal-weight patients.

However, the rate of failed fusion was significantly higher for smokers, and smokers were significantly more likely than non-smokers to experience postoperative complications such as pseudoarthrosis. From this, we recommend that all patients undergoing ALIF surgery should fully cease smoking if possible, or at least within a timeframe prior to operation.

ALIF is associated with prolonged length of stay and higher rate of return to operating theatre compared to PLIF

To assess risk factors for perioperative complications and readmission after ALIF, the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database was analysed. Based on a propensity score-matched analysis, it was found that the rate of return to the operating room as well as total length of stay >5 days was higher for ALIF compared with PLIF, but no differences in any other 30-day complication. Contributors to the risk of return to the operating theatre included being dependent prior to surgery, neuromuscular injury, steroid use and operative duration >4 hours. Predictors of prolonged length of stay>5 days for ALIF were ASA scores ≥3 and prolonged operative time >4hours.

Obesity and alcohol intake is associated with 30-day readmissions following ALIF

I next examined factors associated with readmission to hospital following ALIF. Patients who were readmitted had a higher proportion of any complications, wound complications, pulmonary complications, septic shock, graft failure, return to operating room and unplanned reoperations. A multivariable logistic regression model was performed to determine independent risk factors for readmissions in anterior lumbar interbody fusion. Being morbidly obese and alcohol intake independently predicted unplanned 30-day readmission. However, sex, pulmonary comorbidity, cardiac comorbidity and steroid use were not found to be significant independent predictors.

Discharge to non-home destination following ALIF is independent associated with wound complications and venous thromboembolism

Discharge destination following ALIF surgery, whether to home, a skilled nursing facility (SNF), or rehabilitation, is another major consideration for post-operative care. It was identified that female sex and age ≥65 years were associated with being discharged to a destination other than home in this study. In terms of comorbidities, patients discharged to destinations other than home were more likely to be obese, diabetic, have cardiac and pulmonary comorbidities, have partial or total functional dependence, and have used steroids within 30 days prior to surgery. In terms of surgical comorbidities, these patients were more likely to have ASA classification ≥3, have prolonged operation time (≥4 hours), and have their operation in an inpatient setting.

Overall, patients discharged to destinations other than home had significantly higher rates of morbidity and mortality within the first 30-postoperative days. This included

prolonged length of stay, cardiac, pulmonary, renal, and wound complications, venous thromboembolism, urinary tract infections, transfusion, reoperation, and unplanned readmission. Following multivariate adjustment, discharge to destinations other than home was an independent risk factor for wound complications and venous thromboembolism.

The relationship between discharge destination and postoperative morbidity and mortality is clinically relevant because medical teams in charge of patient care can utilize this information to create better, more efficient discharge planning procedures for patients that are due to undergo ALIF.

Patients with diabetes tend to develop wound complications prior to discharge, whereas those requiring transfusions tend to develop post-discharge wound complications

From the previous results section, we identified that discharge destination was associated with wound complications and venous thromboembolic events. However, few existing studies have investigated whether these complications occur before or after-discharge and the factors that influence this. Upon multivariate-adjusted analysis, history of diabetes was significantly associated with having a wound complication event after ALIF prior to discharge. Preoperative transfusion requirement was significantly associated with having a wound complication after discharge. These risk factors could help identify patients likely to experience postoperative medical complications whilst considering pre-discharge or post-discharge timings of such complications to inform effective preventative or treatment strategies.

Osteotomy, pulmonary comorbidities and prolonged operation time >4 hours are associated with venous thromboembolism prior to discharge

Multinomial logistic regression revealed that intraoperative osteotomy, pulmonary comorbidity, and operative time ≥4 hours were predictive for development of VTE prior to discharge. While patients developed VTE post-discharge, there were no risk factors that were associated with this outcome. The implications of our findings are that clinical VTE risk assessment may improve with increased focus toward select high-risk patients with pulmonary comorbidities, as well as those undergoing prolonged surgery or with more complex spinal surgery procedures.

Radiological follow-up of anterior lumbar interbody fusion with Ti-PEEK integrated cages

For the final part of the thesis, we focused on newer biomaterials and implant cage designs which aim to further augment and improve outcomes following ALIF surgery. One such outcome is achieving solid radiographic fusion. Although radiographic fusion does not always directly correlate with improved clinical outcome, in a significant proportion of patients, correction of structural abnormality and return to baseline stabilisation across the intervertebral segment prevents further unnecessary and painful motion.

There has been considerable interest in the combination of materials to achieve enhanced osseointegration with the use of titanium at the endplate junction, with the benefits of the modulus of elasticity of PEEK within the body of the implant. An option to address this issue is to engineer a composite Ti-PEEK material device which offers

the advantages of both: a device with sufficient compliance and fusion similar to that of PEEK, coupled with the ability of appropriate flexibility and resistance in excessive motion once implanted.

Chapter 4 reported the outcomes of a series of 17 patients who had stand-alone ALIF using a Ti-coated PEEK implant. Excellent radiographic follow-up was achieved, with 85% radiographic fusion rate was achieved at 6 months postoperatively, and 95% at 24 months. 15% of cases demonstrated graft subsidence, but there were no cases of graft or implant migration, nor screw backout or breakage. Significant improvements in VAS scores were measured at follow-up. Therefore in our experience, a Ti-coated PEEK cage, with Allograft and BMP-2, achieves rapid interbody and progression to fusion, and is an effective implant for use in anterior lumbar surgery with high early fusion rates, no lucency around the Ti endplates, with promising longer-term results.

Final remarks

This thesis represents a body of work of several studies which addresses distinct research and clinical questions in the field of ALIF surgery. Risk factors for short-term and long-term clinical outcomes and complications, postoperative discharge destination, and timing of wound complications and VTE were identified. This information can be used to inform hospital policy and develop predictive models to determine which patients require more close monitoring and anticipate discharge planning. Long-term radiographic follow-up outcomes with an integrated Ti-coated PEEK ALIF cage used with allograft and BMP-2 were reviewed, demonstrating efficacy and safety of this novel composite biomaterial.