



The impact of BMI on operating room time, blood loss, and hospital stay in patients undergoing spinal fusion

Alan Villavicencio^{a,b}, E. Lee Nelson^a, Sharad Rajpal^{a,b}, Niketna Vivek^c, Sigita Burneikiene^{a,b,*}

^a Boulder Neurosurgical Associates, Boulder, CO, United States

^b Justin Parker Neurological Institute, Boulder, CO, United States

^c University of Colorado Boulder, Boulder, CO, United States

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ABSTRACT

Objective: Obesity affects not only the health of an individual but society as a whole and especially the healthcare system. Healthcare providers are faced with challenges to deliver adequate care in this resource-limited environment, assure safety, and accommodate the increasing population of overweight patients. The effects of increased body mass index (BMI) on clinical outcomes, complications, health care resource utilization, effectiveness of minimally invasive approaches, and perioperative parameters in spine surgeries have all been previously studied, but the majority of these findings are conflicting rather than conclusive. The main objective of this study was to analyze the impact of BMI on perioperative outcomes in patients undergoing one- to two-level elective TLIF procedures for degenerative spine conditions and to identify the need to modify internal hospital operational planning, team organization, and patient flow processes to accommodate patients who are overweight.

Patients and methods: A single-center retrospective case-review study was completed. The study included 172 consecutive patients who underwent elective one- or two-level transforaminal lumbar interbody fusions (TLIF). The patients were categorized as obese if they had BMI value that was equal to or greater than 30 kg/m². Outcome measures included surgical and non-operative operating room (OR) time, length of stay (LOS), and estimated blood loss (EBL). Multiple regression analyses were performed to determine if BMI had an effect on perioperative parameters while controlling for independent variables.

Results: BMI did not have a statistically significant effect on surgical ($p = 0.13$) and non-operative OR time ($p = 0.82$). Obese patients remained hospitalized on average 0.45 ± 0.25 days longer ($p = 0.037$) and lost 71.8 ± 26.3 mL more blood ($p = 0.007$).

Conclusions: Obesity is associated with longer hospitalization and more intraoperative blood loss, but may have no impact on surgical and non-operative OR times in patients undergoing one- and two-level TLIFs.

1. Introduction

According to Centers for Disease Control and Prevention, the prevalence of obesity is 36.5% among adults in the U.S. with even higher rates among middle age and older adults [1]. Obesity affects not only the health of an individual but the society as a whole and especially the healthcare system. An annually economic impact was estimated to be 2 trillion dollars globally [2] and more than \$190 billion in the U.S [3]. Healthcare providers are faced with challenges to deliver adequate care in this resource-limited environment, assure safety, and accommodate the increasing population of overweight patients [4–7]. A 33% increase in obesity prevalence is expected by 2030 [8].

Samartzis et al. [9] have previously studied the role of obesity and

five pathomechanisms responsible for low back pain in overweight patients, including excessive compressive loading, vascular insufficiency, inflammatory response, metabolic disorder, and gene-environment interaction. Overweight patients therefore have a higher prevalence of low back pain [10,11] and spinal conditions that require multiple surgeries [12].

The effects of increased BMI on clinical outcomes [13–17], complications [13,14,18–22], utilization of health care recourses [23], the effectiveness of minimally invasive approach [24,25], and perioperative parameters [14,16,17,22,26–30] in spine surgeries have been previously studied. However, the majority of these findings are conflicting rather than conclusive. The main objective of this study was to analyze the impact of BMI on perioperative outcomes in patients

* Corresponding author at: Boulder Neurosurgical Associates, 4743 Arapahoe Avenue, Suite 202, Boulder, CO, 80303, United States.

E-mail address: sigitab@bnasurg.com (S. Burneikiene).

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undergoing one- to two-level elective TLIF procedures for degenerative spine conditions and to identify the need to modify internal hospital operational planning, team organization, and patient flow processes to accommodate patients who are overweight.

2. Patients and methods

A single-center retrospective case-review study was completed and included 172 consecutive patients who underwent elective one- or two-level TLIFs between 2011 and 2018 at a community hospital in Colorado. Only lumbar spine (L1 – S1) surgeries performed for a diagnosis of symptomatic degenerative disc disease conditions, including spinal stenosis and spondylolisthesis, were included. All patients underwent open TLIF procedures with bilateral pedicle screw placement using three-dimensional image guidance.

The patients were categorized as obese if they had BMI value that was equal to or greater than 30 kg/m². The other variables analyzed in this study include age, gender, previous surgeries, American Society of Anesthesiologists (ASA) score, number of fusion levels, complications, surgical and non-operative OR time, EBL, and LOS. Surgical time was defined as incision to closure time and non-operative OR time included patient arrival, positioning, preparation, anesthesia time, and time through the patient leaving the operating room.

2.1. Statistical analysis

Chi-square analysis was used to compare categorical values and Student's *t*-test was performed to differentiate between continuous variables. Multiple regression analysis was performed to determine if BMI had an effect on the outcomes of interest including surgery and non-operative OR time, EBL, and LOS while controlling for independent variables.

3. Results

A group comparison and selected baseline demographic and clinical characteristics are presented in Table 1. Fifty-three (30.8%) patients had BMI ≥ 30, including 30 patients who were moderately obese (30–35), 15 severely obese patients (35–40), 7 very severely obese patients (40–45), and one morbidly obese patient (45–50). In the comparison group of 119 (69.2%) patients, one patient was severely underweight (15–16), one patient was underweight (16–18.5), 63 patients had healthy weight (18.5–25), and 54 patients were overweight (25–30).

Table 1

Selected demographic, clinical parameters, and surgical characteristics. Values are presented as means with standard deviations or percentage in parentheses. Student *t*-tests were used for all calculations comparing the two groups except where noted (*), in which a chi-square test was performed. ASA - American Society of Anesthesiologists; BMI – body mass index; F- female; M – male, TLIF – transforaminal lumbar interbody fusion.

	Total	BMI < 30	BMI ≥ 30	P-value
Patients (n)	172	119 (69.2%)	53 (30.8%)	
BMI	27.9 ± 5.9 (15–47)	24.8 ± 3.1	34.9 ± 4.5	< 0.0001
Age	64.0 ± 12.2	65.0 ± 11.4	64.0 ± 12.1	0.61
F/M ratio	83/89	56/63	27/26	0.74*
ASA score	2.4 ± 0.61	2.21 ± 0.58	2.74 ± 0.52	< 0.0001
Previous surgeries				
None	136 (79.1%)	91 (76.5%)	45 (84.9%)	0.37*
Decompression	30 (17.4%)	24 (20.2)	6 (11.3%)	
Fusion	6 (3.5%)	4 (3.3%)	2 (3.8%)	
TLIF levels	1.5 ± 0.5	1.5 ± 0.5	1.4 ± 0.5	0.52
One-level	91 (52.9%)	61 (51.2%)	30 (56.6%)	0.62*
Two-level	81 (47.1%)	58 (48.7%)	23 (43.4%)	
Intraoperative complications	2 (1.2%)	1 (0.8%)	1 (1.9%)	0.52*
Surgery time	178.4 ± 50.9	177.5 ± 52.6	180.4 ± 47.2	0.74
Non-operative OR time	60.3 ± 17.7	59.3+/-16.8	62.7 ± 19.6	0.26
EBL	197.2 ± 152.9	179.0 ± 120.8	238.1 ± 203.1	0.019
LOS	3.0 ± 1.65	2.7 ± 1.5	3.6 ± 1.9	0.003

Table 2

Multiple regression analysis - surgery time. ASA - American Society of Anesthesiologists; BMI – body mass index; SEM - standard error of the mean.

	Estimate (min)	SEM	T value	P value
BMI	10.6	7.0	1.5	0.13
Age	-0.3	0.3	-1.0	0.33
Female gender	-3.2	5.8	-0.6	0.58
Previous decompression	0.07	8.1	0.01	0.99
Previous fusion	21.8	16.7	1.3	0.19
Two-level surgeries	59.0	6.0	9.7	< 0.00001
Complications	13.8	26.9	0.5	0.61
ASA score 2	5.6	12.9	0.4	0.67
ASA score 3	4.2	14.4	0.3	0.77
ASA score 4	-52.1	31.3	-1.7	0.09
Surgeon	-62.7 – 163.0	6.8 – 37.6	-1.7–5.9	< 0.0001–0.2

The two groups were comparable in terms of demographic and clinical patient parameters with the exception of ASA scores, which were highly statistically significant (*p* < 0.0001). Although BMI is directly reflected in ASA scores, obese patients had a significantly higher comorbidity burden. Student *t*-tests revealed that EBL (*p* = 0.019) and LOS (*p* = 0.003) were significantly higher in the BMI ≥ 30 kg/m² compared with the BMI < 30 kg/m² patient group. However, non-operative OR and surgical times were not different between the groups.

Multiple regression analyses were also performed to determine if BMI had an effect on surgical (Table 2) and non-operative OR time (Table 3), LOS (Table 4), and EBL (Table 5) while controlling for age, gender, previous surgeries, the number of fusion levels, complications, ASA scores, and surgeon.

BMI did not have a statistically significant effect on surgical time (*p* = 0.13) as surgeries on obese patients lasted an average of 10.6 ± 7 min longer compared to non-obese patients (Table 2). The following factors were found to be statistically significant: two-level surgeries (< 0.00001) added an average of 59 ± 6 min and surgical times varied significantly (*p* < 0.00001 to *p* = 0.2) depending on the surgeon: -62.7 ± 37.4–163.0 ± 37.6 min. Although not statistically significant, previous fusion surgeries added 21.8 ± 16.7 min to surgery time (*p* = 0.19) and patients with ASA scores of 4 tended to have shorter surgeries by 52.1 ± 31.3 min on average (*p* = 0.09).

Similarly, BMI did not have a statistically significant effect (*p* = 0.82) on non-operative OR time (Table 3), however, depending on the surgeon it varied from -24.6 ± 15.7 min to 11.5 ± 8.0 min

Table 3
Multiple regression analysis - non-operative OR time. ASA - American Society of Anesthesiologists; BMI – body mass index; SEM - standard error of the mean.

2:08 PM	Estimate (min)	SEM	T value	P value
BMI	-0.7	2.9	-0.2	0.82
Age	-0.0	0.1	-0.0	0.98
Female gender	0.0	2.4	0.1	0.99
Previous decompression	-2.9	3.4	-0.9	0.39
Previous fusion	7.5	7.0	1.1	0.28
Two-level surgeries	2.3	2.6	0.9	0.36
ASA score 2	-0.6	5.4	-0.1	0.91
ASA score 3	8.6	6.0	1.4	0.16
ASA score 4	15.9	13.1	1.2	0.23
Surgeon	-24.6 – 11.5	2.8 – 15.7	-1.5–4.8	< 0.00001–0.64

Table 4
Multiple regression analysis - LOS. ASA - American Society of Anesthesiologists; BMI – body mass index; LOS – length of stay; SEM - standard error of the mean.

	Estimate (days)	SEM	T value	P value
BMI	0.45	0.25	1.8	0.037
Age	0.01	0.01	0.9	0.36
Female gender	0.52	0.21	2.5	0.013
Previous decompression	-0.70	0.29	-2.4	0.017
Previous fusion	-0.09	0.60	-0.2	0.88
Two-level surgeries	0.92	0.22	4.3	< 0.00001
Complications	4.82	0.96	5.0	< 0.00001
ASA score 2	0.23	0.46	0.5	0.61
ASA score 3	0.77	0.51	1.5	0.13
ASA score 4	4.09	1.12	3.7	0.0003
Surgeon	-0.77 – 0.99	0.24 – 1.34	-0.7 – 3.4	0.0009 – 0.57

Table 5
Multiple regression analysis - EBL. ASA - American Society of Anesthesiologists; BMI – body mass index; EBL – estimated blood loss; SEM - standard error of the mean.

	Estimate (mL)	SEM	T value	P value
BMI	71.8	26.3	2.7	0.007
Age	1.5	1.0	1.5	0.14
Female gender	10.2	21.7	0.5	0.64
Previous decompression	28.0	30.5	0.9	0.36
Previous fusion	160.0	62.6	2.7	0.008
Two-level surgeries	110.7	22.8	4.9	< 0.00001
Complications	-84.5	100.7	-0.8	0.40
ASA score 2	-14.4	48.1	-0.3	0.77
ASA score 3	-14.7	53.8	-0.3	0.79
ASA score 4	-134.3	117.2	-1.2	0.25
Surgeon	-63.1 – 219.6	25.4 – 140.8	-0.9 – 1.9	0.05 – 0.54

($p < 0.00001$ to $p = 0.64$). ASA scores of 4 added 15.9 ± 13.1 min on average but this was not statistically significant ($p = 0.23$).

Obese patients remained hospitalized an average of 0.45 ± 0.25 days longer than non-obese patients (Table 4), which was statistically significant ($p = 0.037$). The longest increase in LOS was noted for patients with complications (4.82 ± 0.96 days, $p < 0.00001$), followed by ASA score of 4 (4.09 ± 1.12 days, $p = 0.0003$), two-level surgeries (0.92 ± 0.22 days, $p < 0.00001$), individual surgeon preferences (-0.77 ± 1.33 to 0.99 ± 0.29 days, $p = 0.0009$ to $p = 0.57$), and female gender (0.52 ± 0.21 days, $p = 0.013$).

Multiple regression analysis demonstrated that the effect of BMI on

EBL was statistically significant ($p = 0.007$) and obese patients lost on average 71.8 ± 26.3 mL more blood compared to non-obese patients. Other factors also played a significant role, including two-level TLIFs (110.7 ± 22.8 mL, $p < 0.00001$), and to some degree surgeon (-63.1 ± 25.4 – 219.6 ± 139.9 mL, $p = 0.05$ to $p = 0.54$), or previous fusion surgeries (160 ± 62.6 mL, $p = 0.008$).

4. Discussion

The population in the Boulder area has the lowest obesity rates (12.4%) among the metropolitan statistical areas [31] and Colorado is the least-obese (22.3%) state in the country [1]. Regardless, 31% of our patients who were undergoing fusion surgery were obese, which is consistent with the fact that obesity represents a risk factor for back pain associated with degenerative disc disease.

We analyzed perioperative outcomes in a well-defined patient population undergoing one- to two-level TLIF surgeries for symptomatic degenerative disc disease conditions including spinal stenosis and spondylolisthesis. Statistical analysis revealed that BMI did not have any effect on surgical or non-operative OR time, rather other factors were responsible for the increase including two-level surgeries, surgeon, or ASA scores. Surgical OR times were significantly shorter for procedures performed by spine fellowship-trained surgeons. Although other authors reported contradicting results demonstrating that higher BMI does increase surgical times, they analyzed microdiscectomies, ¹⁶ anterior lumbar interbody fusions [29], included various surgical procedures, or did not differentiate between open and minimally invasive approach [14,17,28], did not control for surgical procedures or the number of levels [30], or comprised a very small cohort of patients [24,30]. Several studies did, however, utilize large databases [14,20,32] and reported that BMI was associated with significant increases in surgical time.

Multiple regression analysis demonstrated a statistically significant increase in EBL and LOS when comparing obese and non-obese patients. Controlling for other sources of variability revealed that EBL was also affected by surgeon and the number of surgical levels, whereas LOS was affected by complications, ASA scores, the number of surgical levels, individual surgeon preferences, and even female gender. Some studies were in agreement that higher BMI increases LOS and EBL [14,16], but these authors mainly focused on clinical outcomes or complications and did not account for potential confounding variables. Interestingly, the authors that specifically analyzed LOS and EBL in obese patients undergoing spinal surgeries reported no differences. Andreshak et al. [26] reported no statistically significant differences in EBL or LOS for obese compared with non-obese patients undergoing lumbar fusion surgeries: 1027 mL vs. 1064 mL and 6.5 vs. 6.4 days, respectively. However, the authors did not account for potential confounding factors, the most important being surgical levels, which may have caused an underestimation of the effect. In addition, the reported EBL and LOS values significantly exceeded values reported in our study. Similar results with very high amounts of blood loss and no statistically significant differences were presented by Vaidya et al. [30] but the authors compared obese vs. morbidly obese patients.

4.1. Limitations

The main limitation of our study was that although we analyzed a well-defined patient cohort consisting of 172 patients, the study might still be underpowered to detect the surgical and non-operative time differences, especially since only 30.8% of patients in our study were obese with a mean BMI of 34.9. The small number of severely obese patients adds further caution regarding the generalizability of these findings. In addition, other factors that were not analyzed in this study may influence the outcomes including the pathology itself, grade of the spinal canal or foramen stenosis, severity of listhesis, bone density for screw placement, or intervertebral distraction during cage placement.

Notwithstanding the limitations and that generalizability of these results to other spine procedures and the impact to cost and resource utilization should be explored further, the results of this study provide a comprehensive evaluation of the effect that BMI imposes on perioperative outcomes.

5. Conclusions

Obesity was associated with longer hospitalization and more intraoperative blood loss, but may have no impact on surgery and non-operative OR times in patients undergoing one- and two-level transforaminal lumbar interbody fusions.

Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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References

- [1] C.L. Ogden, M.D. Carroll, C.D. Fryar, K.M. Flegal, Prevalence of obesity among adults and youth: United States, 2011–2014, *NCHS Data Brief* (219) (2015) 1–8.
- [2] R. Dobbs, C. Sawers, F. Thompson, J. Manyika, J.R. Woetzel, P. Child, S. McKenna, A. Spatharou, *Overcoming Obesity: An Initial Economic Analysis*, McKinsey Global Institute, Jakarta, Indonesia, 2014.
- [3] J. Cawley, C. Meyerhoefer, The medical care costs of obesity: an instrumental variables approach, *J. Health Econ.* 31 (1) (2012) 219–230.
- [4] R.N. Uppot, D.V. Sahani, P.F. Hahn, D. Gervais, P.R. Mueller, Impact of obesity on medical imaging and image-guided intervention, *AJR Am. J. Roentgenol.* 188 (2) (2007) 433–440.
- [5] S.D. Choi, K. Brings, Work-related musculoskeletal risks associated with nurses and nursing assistants handling overweight and obese patients: a literature review, *Work* 53 (2) (2015) 439–448.
- [6] S.G. Khoo, N. Rajaretnam, Surgical tracheostomy in morbidly obese patients: technical considerations and a two-flap technique for access, *J. Laryngol. Otol.* 126 (4) (2012) 435–438.
- [7] A.E. Telfeian, G.T. Reiter, S.R. Durham, P. Marcotte, Spine surgery in morbidly obese patients, *J. Neurosurg.* 97 (1 Suppl) (2002) 20–24.
- [8] E.A. Finkelstein, O.A. Khavjou, H. Thompson, et al., Obesity and severe obesity forecasts through 2030, *Am. J. Prev. Med.* 42 (6) (2012) 563–570.
- [9] D. Samartzis, J. Karppinen, J.P. Cheung, J. Lotz, Disk degeneration and low back pain: are they fat-related conditions? *Glob. Spine J.* 3 (3) (2013) 133–144.
- [10] D. Samartzis, J. Karppinen, D. Chan, K.D. Luk, K.M. Cheung, The association of lumbar intervertebral disc degeneration on magnetic resonance imaging with body mass index in overweight and obese adults: a population-based study, *Arthritis Rheum.* 64 (5) (2012) 1488–1496.
- [11] R. Shiri, J. Karppinen, P. Leino-Arjas, S. Solovieva, E. Viikari-Juntura, The association between obesity and low back pain: a meta-analysis, *Am. J. Epidemiol.* 171 (2) (2010) 135–154.
- [12] M.S. Walid, N. Zaytseva, History of spine surgery in older obese patients, *Ger. Med. Sci.* 9 (2011) Doc05.
- [13] M. Djurasovic, K.R. Bratcher, S.D. Glassman, J.R. Dimar, L.Y. Carreon, The effect of obesity on clinical outcomes after lumbar fusion, *Spine* 33 (16) (2008) 1789–1792.
- [14] M. Flippin, J. Harris, E.W. Paxton, et al., Effect of body mass index on patient outcomes of surgical intervention for the lumbar spine, *J. Spine Surg.* 3 (3) (2017) 349–357.
- [15] B. Knutsson, K. Michaelsson, B. Sanden, Obesity is associated with inferior results after surgery for lumbar spinal stenosis: a study of 2633 patients from the Swedish spine register, *Spine* 38 (5) (2013) 435–441.
- [16] J.A. Rihn, M. Kurd, A.S. Hilibrand, et al., The influence of obesity on the outcome of treatment of lumbar disc herniation: analysis of the Spine Patient Outcomes Research Trial (SPORT), *J. Bone Joint Surg. Am.* 95 (1) (2013) 1–8.
- [17] J.A. Rihn, K. Radcliff, A.S. Hilibrand, et al., Does obesity affect outcomes of treatment for lumbar stenosis and degenerative spondylolisthesis? Analysis of the Spine Patient Outcomes Research Trial (SPORT), *Spine* 37 (23) (2012) 1933–1946.
- [18] A.I. Mehta, R. Babu, I.O. Karikari, et al., Young Investigator Award winner: the distribution of body mass as a significant risk factor for lumbar spinal fusion postoperative infections, *Spine* 37 (19) (2012) 1652–1656.
- [19] N. Patel, B. Bagan, S. Vadera, et al., Obesity and spine surgery: relation to perioperative complications, *J. Neurosurg.* Spine 6 (4) (2007) 291–297.
- [20] M.F. Shamji, S. Parker, C. Cook, R. Pietrobon, C. Brown, R.E. Isaacs, Impact of body habitus on perioperative morbidity associated with fusion of the thoracolumbar and lumbar spine, *Neurosurgery* 65 (3) (2009) 490–498 discussion 498.
- [21] S. Yadla, J. Malone, P.G. Campbell, et al., Obesity and spine surgery: reassessment based on a prospective evaluation of perioperative complications in elective degenerative thoracolumbar procedures, *Spine J.* 10 (7) (2010) 581–587.
- [22] J. McClendon Jr., T.R. Smith, S.E. Thompson, et al., The impact of body mass index on hospital stay and complications after spinal fusion, *Neurosurgery* 74 (1) (2014) 42–50 discussion 50.
- [23] P.A. Kalanithi, R. Arrigo, M. Boakye, Morbid obesity increases cost and complication rates in spinal arthrodesis, *Spine* 37 (11) (2012) 982–988.
- [24] S.J. McAnany, D.C. Patterson, S. Overley, D. Alicea, J. Guzman, S.A. Qureshi, The effect of obesity on the improvement in health state outcomes following minimally invasive transforaminal interbody fusion, *Glob. Spine J.* 6 (8) (2016) 744–748.
- [25] A. Tomasino, K. Parikh, J. Steinberger, J. Knopman, J. Boockvar, R. Hartl, Tubular microsurgery for lumbar discectomies and laminectomies in obese patients: operative results and outcome, *Spine* 34 (18) (2009) E664–672.
- [26] T.G. Andreshak, H.S. An, J. Hall, B. Stein, Lumbar spine surgery in the obese patient, *J. Spinal Disord.* 10 (5) (1997) 376–379.
- [27] R. De la Garza-Ramos, M. Bydon, N.B. Abt, et al., The impact of obesity on short- and long-term outcomes after lumbar fusion, *Spine* 40 (1) (2015) 56–61.
- [28] K.J. McGuire, M.A. Khaleel, J.A. Rihn, J.D. Lurie, W. Zhao, J.N. Weinstein, The effect of high obesity on outcomes of treatment for lumbar spinal conditions: subgroup analysis of the spine patient outcomes research trial, *Spine* 39 (23) (2014) 1975–1980.
- [29] C.W. Peng, J.A. Bendo, J.A. Goldstein, M.M. Nalbandian, Perioperative outcomes of anterior lumbar surgery in obese versus non-obese patients, *Spine J.* 9 (9) (2009) 715–720.
- [30] R. Vaidya, J. Carp, S. Bartol, N. Ouellette, S. Lee, A. Sethi, Lumbar spine fusion in obese and morbidly obese patients, *Spine* 34 (5) (2009) 495–500.
- [31] residents B.
- [32] D. Burneikis, G. Morris-Stiff, S. Chalikhonda, Time attributable to obesity in surgery: a multi-specialty report on day-of-surgery resource utilization from 189,264 cases, *World J. Surg.* 42 (October (10)) (2018) 3125–3133, <https://doi.org/10.1007/s00268-018-4599-5>.