

The impact of spinopelvic morphology on the short-term outcome of pedicle subtraction osteotomy in 104 patients

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OBJECTIVE Pedicle subtraction osteotomy (PSO) is commonly performed for correction of spinal sagittal plane deformities. The PSO results in complex, multiple changes of the spinopelvic alignment. The influence of the variability of individual pelvic morphology has not been fully analyzed in previous outcome studies of sagittal imbalance. The aim of this study was to define radiological variables affecting the outcome after PSO in adult spinal deformities, with special emphasis on the variability of pelvic morphology.

METHODS Clinical and radiographic outcomes were analyzed in a retrospective analysis of 104 patients who underwent a PSO at a single center. The radiographic variables studied were sagittal vertical axis (SVA), T1SPI (T-1 spinopelvic inclination), lumbar lordosis (LL), thoracic kyphosis (TK), pelvic incidence (PI), pelvic tilt (PT), and sacral slope (SS). To control for the individual variation of pelvic morphology, the LL/PI, PT/PI, and SS/PI ratios were calculated. Clinical outcome was assessed using the visual analog scale for pain, Oswestry Disability Index, and EQ-5D preoperatively and at a minimum 1-year follow-up. Correlation coefficients were calculated between each individual radiographic variable and the outcome measures. The importance of LL mismatch to TK, reflecting the importance of a harmonious spine, was analyzed by comparing the outcome of patients with a TK+LL+PI \leq 45° to those with a sum > 45°.

RESULTS SVA and T1SPI demonstrated the strongest correlation with the clinical outcome scores (r = 0.4-0.5, p < 0.001). LL correlated weakly with the clinical outcome (r = 0.2-0.3, p < 0.003). Mismatch of LL to PI, however, did not correlate significantly with the outcome. Similarly, only weak and inconsistent correlation was observed between PT, SS, PT/PI, SS/PI, and functional outcome. Patients with a TK+LL+PI $\leq 45^{\circ}$ had a significantly lower ODI score (33 vs 44) and a significantly higher EQ-5D score (0.64 vs 0.40) than patients with a sum > 45° (LL is a negative value).

CONCLUSIONS PSO resulted in a substantial correction of sagittal imbalance and improved outcome in most patients in this study. Correction of the global sagittal balance appears to be a necessary precondition for a good outcome. A harmonious spine with a TK and an LL of similar magnitude seems to add to a positive outcome.

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KEY WORDS pedicle subtraction osteotomy; spinopelvic parameters; sagittal imbalance; adult spine deformity; surgical technique

The normal standing posture with least energy expenditure needs a good balance between spine and pelvis.¹³ Numerous radiographic parameters have been introduced to define this intricate balance (see Table 2). Pelvic incidence (PI), pelvic tilt (PT), and sacral

slope (SS) signify the morphology and spatial orientation of the pelvis, whereas thoracic kyphosis (TK) and lumbar lordosis (LL) define the sagittal orientation of the spine. Sagittal vertical axis (SVA) and T-1 spinopelvic inclination (T1SPI) are the most often used radiographic parameters

ABBREVIATIONS ASD = adult spinal deformity; HRQOL = health-related quality of life; LL = lumbar lordosis; ODI = Oswestry Disability Index; PI = pelvic incidence; PSO = pedicle subtraction osteotomy; PT = pelvic tilt; SS = sacral slope; SVA = sagittal vertical axis; T1SPI = T-1 spinopelvic inclination; TK = thoracic kyphosis; VAS = visual analog scale.

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TABLE 1. Patient-reported outcome measures

Clinical Tools	Description & Score Range
VAS back	Back pain: 0–100
ODI	Pain & function in daily life: 0–100
EQ-5D index	Questionnaire w/ maximum score = 1.00, representing perfect HRQOL
Global assessment	Patient satisfaction at final follow-up classified as much better, better, unchanged, or worse

to describe global sagittal balance.¹⁰ The aging process leads to degenerative loss in lordosis, moving the spine forward. In an attempt to maintain global spinal balance, so that the head remains centered over the pelvis, compensatory changes such as pelvic retroversion and knee flexion shift the pelvis posteriorly.¹¹ These compensations, however, come at the cost of huge muscle energy expenditure. Failure of this compensatory cascade leads to deformity, global malalignment, and disability.¹⁴ The quantum of these compensations or appearance of decompensation can be identified radiologically by measuring the SVA, PT, SS, and PI-LL mismatch. Schwab et al. proposed radiological parameter thresholds predictive of worse clinical symptoms and poorer quality of life, and concluded that PT of 22° or more, SVA of 47 mm or more, and PI - LL of 11° or more were associated with severe disability (Oswestry Disability Index [ODI] score > 40).²³ In a recent study, however, the ideal spinopelvic values were found to increase with the age of the person, and the authors concluded that the operative realignment goals need to be tailored to the age of the patient.8

The pedicle subtraction osteotomy (PSO) is a widely used method for correcting spinal deformities in the sagittal plane. The major impact of the PSO on the sagittal profile of the spine brings about multiple changes in the spinopelvic alignment.^{9,12,16,25} Several radiological variables have been reported to affect outcome after surgical attempts to restore sagittal balance.⁵ The relative importance of these changes for the outcome is still not fully understood.

It has been demonstrated that a single-level PSO can provide a major correction of the global sagittal alignment.^{3,4,15} Several authors have reported that the clinical outcome following a PSO depends on whether the global sagittal balance is normalized.^{3,5,9,16,22} It has been recommended that for a better outcome, the PSO should be planned in such a way that the LL obtained after PSO surgery should be within 10° of that patient's PI. In addition, it has been reported that a PT exceeding 20° is strongly correlated with a negative outcome.^{17,22}

Each normal individual has his or her unique PI, and a corresponding tilt of the pelvis. Surgical correction of sagittal imbalance tends to decrease pelvic retroversion, and to optimize spinopelvic balance one would assume that the PT should be adapted to each patient's PI. However, except for the relation of LL to PI, previous studies have not controlled for the effect of the individual variation of PI on PT. The retroversion of the pelvis can be measured alternatively as the PT or the SS: they mathematically reflect each other, i.e., if one increases the other decreases, and vice versa.

To determine whether individualized spinopelvic variables affect the outcome, we performed a retrospective analysis of 104 patients who underwent a PSO at our center over a 5-year period. A correlation was sought between individualized radiological and clinical outcome. The aim was to determine which, if any, radiological spinopelvic parameter predicts the outcome of PSO in patients with sagittal imbalance.

Methods

Study Population

One hundred and four consecutive patients operated on using a PSO were identified by a retrospective analysis of the inpatient medical records on spinal procedures at Sahlgrenska University Hospital, Gothenburg, Sweden, from 2007 to 2012. All PSOs were performed for symptomatic sagittal plane deformity of multiple etiologies. There were 76 patients with a diagnosis of spinal deformity and 28 patients with a diagnosis of flat-back syndrome after previous lumbar fusion, as presented in the report on the clinical outcome.

Data Collection

Preoperative patient characteristics were documented. Clinical outcomes were assessed by validated outcome measures, i.e., the visual analog scale (VAS) for back pain, ODI for functional disability, and the EQ-5D for healthrelated quality of life (HRQOL) preoperatively and at a minimum of 1-year follow-up. In addition, the patients rated their own global assessment of the outcome at the time of follow-up as much better, better, unchanged, or worse

TABLE 2.	Radiographic	measurements
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Radiographic Measurement	Definition
SVA	The distance btwn C-7 plumb line & superior posterior part of S-1 vertebra
LL	The angle btwn superior endplates of L-1 & S-1
TK	The angle formed by upper endplate of T-4 vertebra & lower endplate of T-12 vertebra
PI	The angle btwn perpendicular to sacral plate at its midpoint & line connecting this point to middle axis of femoral heads
SS	The angle btwn superior plate of 1st sacral vertebra & horizontal line
PT	The angle btwn line connecting midpoint of sacral plate to axis of femoral heads & vertical line
T1SPI	The angle formed by vertical line & line from center of T-1 to middle of bicoxofemoral axis



FIG 1. Left: Preoperative standing radiograph of a 61-year-old woman with degenerative scoliosis and severe sagittal imbalance (SVA 204 mm). **Right:** Postoperative standing radiograph of the same patient after an L-3 PSO and fusion (T-4 to pelvis) with normalized sagittal balance postoperatively. Figure is available in color online only.

than their preoperative state (Table 1). Preoperative scores were available for all patients except in 4. The final follow-up scores were available for 87% (90 patients).

All patients had a standardized full-length standing radiograph taken before surgery, immediately following surgery, and at a minimum of 1-year follow-up. The radiological variables were measured using Surgimap Spine by a single observer⁴ (Table 2).

Outcome Variables

The outcomes of patients were compared according to the degree of SVA (< 50 mm, 50-100 mm, and > 100

TABLE 4. Pearson correlation coefficient (r) between the
changes in radiological measurements and clinical outcome

	VAS	Back	EQ-5	D Index	C	DDI
Measurement	r	p Value	r	p Value	r	p Value
SVA	0.19	0.19	-0.23	0.11	0.05	0.71
SS	-0.09	0.55	0.04	0.76	0.04	0.76
PT	0.03	0.85	0.04	0.77	-0.03	0.85
LL	-0.01	0.93	0.04	0.74	-0.07	0.52

mm). In addition, the outcomes of patients with a lordosis matched for the PI, defined as $LL = PI \pm 15^{\circ}$, were compared with the outcomes of patients with a mismatch of PI and LL. Lumbar and thoracic PSOs were also analyzed separately because their effect on LL often is the opposite, i.e., a lumbar PSO increases LL whereas a thoracic PSO decreases it; the need for compensatory increased lordosis is diminished in the latter case. L-1 was operationally considered "thoracic," because it normally is not a part of LL.

The sum of TK, LL (negative value), and PI was calculated to test the hypothesis as suggested by Rose et al.¹⁶ that a sum $\leq 45^{\circ}$ is predictive of a positive outcome after a PSO.

Correlation coefficients were calculated between all documented radiographic variables and the outcome scores preoperatively and at follow-up. As generally accepted, the variations in the normal PI among individuals affect the LL, SS, and PT.¹³ To control for these variations in PI we calculated the ratio between PI and LL (LL/PI), between PI and SS (SS/PI), and between PI and PT (PT/PI), and correlated these ratios with the outcome measures. In addition to the observed outcome preoperatively and at follow-up, we also correlated the change in radiographic variables with the clinical outcome.

Statistical Analysis

All statistical analysis was performed using SPSS (version 21, IBM SPSS, Inc.) Normally distributed variables were described using means and standard deviations. For normally distributed variables, parametric tests were used. And for nonnormally distributed variables, nonparametric tests were used. The significance level was set at p = 0.05. Differences between outcome variables (ODI, VAS for back pain, VAS for leg pain, and EQ-5D) according to

TABLE 3. Radiographic measurements preoperatively and at follow-up after PSO

	Preop		Pos		
Measurement	$Mean \pm SD$	Range	$Mean \pm SD$	Range	p Value
SVA (mm)	74 ± 59.9	-45 to 215	49 ± 54.5	-90 to 178	0.03*
TK (°)	31.4 ± 22	2–104	36.0 ± 17.4	1–68	0.02*
LL (°)	-29.9 ± 18.9	-83 to 17.7	-42.0 ± 19.8	-85 to 18.4	0.001*
PSO angle (°)	6.4 ± 13.8	-23 to 57	-20.8 ± 13.1	-47 to 30	0.001*
PI (°)	52.0 ± 16.3	15–88	49.0 ± 15.4	14.3 to 82	0.61
SS (°)	25.0 ± 11.6	2–55	31.0 ± 13.1	6–61	0.001*
PT (°)	27.0 ± 14.6	-14 to 64	19.0 ± 12.3	-6 to 53	0.001*

* The mean difference was significant at the 0.05 level.

	VAS	VAS Back		ODI		D Index
Parameter	r	p Value	r	p Value	r	p Value
SVA	0.23	0.04*	0.24	0.038*	-0.2	0.18
PT	-0.10	0.39	0.01	0.94	0.03	0.78
SS	-0.01	0.95	-0.1	0.43	0.12	0.28
LL	0.16	0.10	0.18	0.07	-0.32	0.001*
T1SPI	0.12	0.31	0.18	0.13	-0.12	0.29
Coronal Cobb angle	-0.10	0.38	0.07	0.55	-0.14	0.21
TK	-0.04	0.72	-0.1	0.40	0.11	0.33

TABLE 5. Preoperative correlation of radiographic parameters and clinical outcome scores

* Correlation significant at the 0.05 level (2-tailed test).

the degree of SVA were compared by ANOVA. Global assessment was compared between the SVA groups by chisquare analysis.

Results

Among the 104 patients there were 33 men and 71 women. The mean age at surgery was 55 years (range 48–67 years). There were 70 patients with a lumbar osteotomy, 30 with a thoracic osteotomy, and 4 patients underwent a PSO at 2 levels. The most common level of PSO was L-3 (42%) and L-2 (23%). The mean correction obtained at the osteotomy site was 27.2° (Fig. 1).

Compared with the preoperative scores there were significant improvements of the mean scores in all the outcome measures. The VAS, ODI, and the EQ-5D Index improved by 33 points, 16 points, and 0.31 points, respectively. Similarly, all radiographic variables had a statistically significant improvement (Table 3). However, for all radiological variables there was no significant correlation between the degree of change in radiographic measurement and the change in outcome scores (Table 4).

The mean preoperative SVA was 74 mm, which was corrected to 49 mm at follow-up. The mean LL increased from 29° to 42° in the total group. However, in the lumbar PSO subgroup it increased from 25° to 42°. As expected, there was no significant change observed in PI. The mean

TABLE 6. Follow-up correlation of radiographic parameters	and
clinical outcome scores	

	VAS	VAS Back ODI		EQ-5I	D Index	
Parameter	r	p Value	r	p Value	r	p Value
SVA	0.41	0.001*	0.58	0.00*	-0.55	0.00*
PT	-0.18	0.15	0.02	0.89	-0.05	0.68
SS	-0.24	0.06	-0.29	0.02*	0.31	0.01*
LL	0.19	0.07	0.29	0.01*	-0.3	0.003*
T1SPI	0.46	0.00*	0.56	0.00*	-0.5	0.00*
Coronal Cobb angle	-0.01	0.96	0.04	0.78	-0.06	0.66
TK	0.21	0.11	0.27	0.04*	-0.23	0.08

* Correlation significant at the 0.05 level (2-tailed test).

TABLE 7. Clinical outcome according to SVA at follow-up

	I	Mean SVA (mm)			
Outcome	<50	50-100	>100	Value*	
VAS back	29	48	55	0.002	
VAS leg	22	53	45	0.003	
ODI	29	51	55	0.001	
EQ-5D index	0.62	0.43	0.26	0.000	

* Obtained by ANOVA.

PT decreased from 27° to 19° (p = 0.001) and the mean SS increased from 25° to 31° (p = 0.001; Table 3)

Preoperatively, the SVA was the only spinopelvic parameter that showed a significant correlation with outcome measures (r = 0.2-0.3, Table 5). It also showed the strongest correlation at follow-up (r = 0.4-0.6; Table 6). In addition, the clinical outcome scores were clearly correlated with the degree of sagittal imbalance as observed in subgroups of SVA (Tables 7 and 8). The alternative measurement of the global spinal balance, T1SPI, also showed a significant correlation with all the outcome scores at follow-up, with r values ranging from 0.46 to 0.56 (Table 6). Similar results were obtained when lumbar PSOs were analyzed separately (Table 9).

The LL was weakly, but significantly, correlated with the EQ-5D preoperatively and also at follow-up (r = 0.3). There was no statistically significant difference in the outcome between groups in whom there was an LL versus PI mismatch as compared with those in which the LL matched the PI (LL = PI ± 15°). There was a slight but significant change in mean TK from 31.4° to 36.0°, which had a weak, but, again, significant correlation (r = 0.27) to the ODI at follow-up. Similarly, the SS was weakly, but significantly, correlated (r = 0.2-0.3) with the outcome scores at follow-up (Table 6), whereas the PT showed no correlation with the outcome.

Significant correlations were observed between the PT/ PI and SS/PI ratios and EQ5D scores at follow-up (r = 0.3). However, none of the other outcome scores were found to be significantly correlated with these ratios (Table 10). Patients with a sum of TK, LL, and PI $\leq 45^{\circ}$ showed a statistically better outcome than patients with a sum > 45° (Table 11).

Discussion

In the present study we found that the PSO resulted in a significant improvement of all spinopelvic variables, accompanied by an improvement of all outcome scores. The

TABLE 8. Global assessment according t	o SVA	at 1	year
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Global Assessment		SVA (mm)	
(%)	<50	50–100	>100
Much better	27.9	40.0	12.5
Better	48.8	20.0	12.5
Unchanged	14.0	20.0	37.5
Worse	9.3	20.0	37.5

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TABLE 9. Correlation between radiographic parameters and
clinical outcome scores postoperatively in the lumbar PSO
subgroup analyzed separately*

	VAS Back		ODI		EQ-5D Index	
Parameter	r	p Value	r	p Value	r	p Value
SVA	0.44	0.01†	0.62	0.00†	-0.50	0.001†
PT	-0.15	0.36	-0.04	0.82	0.00	0.99
SS	-0.38	0.02†	-0.38	0.02†	0.38	0.02†
LL	0.22	0.09	0.27	0.04†	-0.3	0.035

* Lumbar PSO defined as L-2 and below.

† Correlation significant at the 0.05 level (2-tailed test).

observed SVA, LL, SS and PT/PI at follow-up correlated with the outcome measures. However, only the global sagittal balance, as measured by SVA or T1SPI, showed a consistent and moderately close correlation to clinical outcome. Other radiographic measures were inconsistently and only weakly correlated with outcome. This was also true after controlling for the individual variation in PI affecting the LL, PT, and SS.

Our results are in accordance with previous studies^{6,7,10} showing that the coronal imbalance has limited effect on outcome. Several authors^{5–7,10} have reported that the most crucial factor for a good outcome is the global sagittal balance, measured as SVA or T1SPI. Lafage et al.¹⁰ in a prospective study on 125 patients with adult spinal deformity (ASD) found that among more than 100 spinopelvic measures, global sagittal balance, i.e., SVA and T1SPI, had the strongest correlation with the HRQOL, with correlation coefficients ranging from 0.42 to 0.55. Accordingly, we found a similar degree of association, with correlation coefficients between 0.41 and 0.58. The similar result, despite using different outcome measures in the 2 studies, underlines the relationship between global sagittal balance and patients' symptoms.

Rose et al.¹⁶ tested 3 hypotheses in their data of 40 patients, to determine whether PI, TK, or a combination of the two could be used to predict the LL necessary to regain ideal sagittal balance following PSO. They observed that PI and TK in isolation had a poor predictive value on the desired LL. However, in combination, PI and TK displayed the greatest sensitivity in predicting LL associated with good sagittal correction (SVA < 5 cm). This led them to conclude that the sum of TK, LL (taken as a negative value), and PI predicted the outcome of surgery in ASD. A sum \leq 45 was reported to predict a successful clinical outcome after a PSO. Our results are in agreement with those of Rose et al., showing a clearly better outcome for

TABLE 11. Clinical outcome in patients with a sum of TK, LL, and PI below and above 45° $\,$

Questionnaire	≤45° (mean)	>45° (mean)	p Value
VAS back	32.8	42.6	0.14
ODI	32.6	44.1	0.02*
EQ-5D index	0.64	0.40	0.00*

* Correlation significant at the 0.05 level.

patients with TK and LL of equal magnitude, PI being on average around 45° in most patients. The sum of TK, LL, and PI indicated consistent and clinically important differences between patients with values below as opposed to above 45°. The results of the study suggest that rather than correcting each variable to a fixed angle, the correction of sagittal balance should be aimed toward a harmonious spinal configuration. Thus, in addition to a normal global sagittal balance, the results of the study support the concept of achieving a harmonious spine to limit pain and functional disability.

In agreement with our study, several authors have reported a correlation between disability and lack of lordosis.^{18–20} Accordingly, we found a correlation between LL and disability scores both prior to surgery and following a PSO. However, compared with the findings of Schwab et al.²⁴ we found a weaker and less consistent correlation between LL and outcome, which was true even after controlling for the individual variability in PI.

Because the normal LL varies among individuals, a rough guide to estimate LL has been $LL = PI \pm 9^{\circ}.^{21}$ However, we failed to demonstrate any significant difference in the outcome between patients in whom there was a significant mismatch between the LL and PI, and those in whom the LL was within $\pm 15^{\circ}$ of PI, as well as within $\pm 10^{\circ}$. This was true even after exclusion of the patients who underwent a thoracic PSO. Also, somewhat in contrast to our study, Boissière et al.² reported that the ratio LL/PI was a predictor for the need of an osteotomy, whereas we found that the LL/PI ratio did not correlate with the outcome.

We hypothesize that the reason for this discrepancy with other studies is because the measurement of complete L1–S1 lordosis is too crude a variable to reflect normal lordosis. The total LL could be the sum of a compensatory low lumbar hyperlordosis and a high lumbar kyphosis, or even vice versa (Fig. 2). Each patient has a unique sagittal profile, and each level in the spine affects every other level in a unique way, rendering any recommendation on specific degrees of correction uncertain.

In contrast to other authors²⁴ we found only a weak and

TABLE 10. Correlation of SS, PT, and LL normalized for individual PI with outcome scores

	VAS	Back	ODI		EQ-5D		GA	
Ratio	r	p Value						
SS/PI	-0.54	0.68	-0.22	0.08	0.28	0.029*	-0.11	0.34
PT/PI	0.56	0.66	0.23	0.07	-0.30	0.016*	0.10	0.42
LL/PI	0.06	0.61	-0.0	0.97	0.04	0.70	-0.00	0.97

* Correlation significant at the 0.05 level.



FIG 2. Left: Preoperative standing radiograph of a 65-year-old man with posttraumatic kyphosis and functionally disabling back pain. Right: Postoperative standing radiograph of the same patient after PSO at L-1 and fusion from T-10 to L-4, which normalized the preoperative compensatory-decreased TK, as well as the increased low LL.

nonconsistent correlation between PT and SS, on one hand, and outcome, on the other hand. This was true even when PT and SS were adjusted for PI (Table 10), as well as for the crude measurement (Table 6). Such adjustments, which logically should improve the sensitivity of the analysis, have not been reported previously. Lafage et al.¹⁰ observed a moderate correlation between the patients nonadjusted PT and outcome scores, with correlation coefficients ranging from 0.28 to 0.43 in different subscore analyses, but no significant correlation between SS and any outcome measure. A general recommendation to aim for a correction of PT to less than 20° was given. In contrast, we found no significant correlation between the PT and any of the outcome scores, but some limited correlation between SS and the outcome. We cannot explain the reasons for this difference, but the limited precision in the assessment of pelvic parameters may affect the results.

Because the PT as well as the SS equally reflects pelvic retroversion, one would expect both variables to correlate with outcome to the same extent. Both variables vary with the PI, increasing in magnitude with increasing PI, as PI = SS + PT. The PI is a stable pelvic parameter and does not change after a PSO. However, the PI directly affects the degree of SS, PT, and LL. Since the PI varies widely among individuals and affects their SS and PT, it seems obvious that the absolute magnitude of PT, or SS, is a suboptimal reflection of a normal pelvic retroversion in the individual patient. In this study we therefore controlled for the impact of different degrees of PI. Despite this, with the exception of PT/PI that showed a significant, but limited, correlation with outcome, we found little evidence for any major effect of pelvic retroversion on outcome. The improved methodology in the present study may be of importance in explaining the difference in results compared with previous studies.

There are several limitations of this study. Although the outcome data were prospectively collected, the study design is retrospective with its inherent limitations, particularly loss of some radiological as well as outcome data. The short follow-up time is another limitation; it is rather likely that a longer follow-up would result in some recurrence of sagittal imbalance. However, the aim of the study is not compromised by this fact. The advantage of the study is the high follow-up rate (87%) of a large number of consecutive patients undergoing a PSO. Another advantage is the individualized analysis of pelvic parameters, with adjustment of PT and SS for different PIs, not accounted for in previous studies.

Our results suggest that the most important factors for a good outcome are the restoration of the SVA and harmonizing the TK with the LL. Although this secondarily results in normalization of the pelvic parameters, the data do not support a strong influence of this phenomenon per se on the outcome. Although the reason for this cannot easily be explained, theoretically one would accept such a relationship. The limited precision in measurements of pelvic parameters—for example, the definition of the center of the femoral head—may be a contributing explanatory factor.

Conclusions

PSO results in a substantial correction of sagittal imbalance and improved outcome in most patients. Correction of the global sagittal balance seems to be a necessary precondition for a good outcome. A harmonious spine with a TK and an LL of similar magnitude appears to add to a positive outcome.

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Disclosures

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

Author Contributions

Conception and design: Sharma, Hedlund. Acquisition of data: Sharma, Eskilsson, Johansson. Analysis and interpretation of data: all authors. Drafting the article: Sharma, Eskilsson, Hedlund. Critically revising the article: Sharma, Hedlund. Reviewed submitted version of manuscript: Sharma. Approved the final version of the manuscript on behalf of all authors: Sharma. Statistical analysis: all authors. Study supervision: Hedlund.

Supplemental Information

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