Delayed presentation to a spine surgeon is the strongest predictor of poor postoperative outcome in patients surgically treated for symptomatic spinal metastases

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Abstract

Background: Symptoms associated with spinal metastases are often non-specific and resemble non-cancer-related. Therefore, patients with spinal metastases are at risk for delayed referral and treatment. Delayed presentation of symptomatic spinal metastases may lead to the development of neurological deficits, often followed by emergency surgery.

Objective: The aim of this cohort study was to analyze the effect of delayed referral and treatment of spinal metastases on clinical outcome.

Methods: We included all patients surgically treated for spinal metastases at our tertiary care center. Based on the (in)ability to undergo elective surgery, patients were identified as timely treated or delayed. Patient- and tumor-characteristics, surgical variables, and postoperative variables such as complication rate, the ability to return home and length of hospital stay were recorded and compared between the two groups.

Results: Based on the urgency of treatment at admission, 206 patients were identified as timely treated and 98 as delayed. At baseline, the two groups did not differ significantly except for the extent of neurological symptoms. Timely treated patients underwent less invasive procedures (52.9% vs 13.3% percutaneous pedicle screw fixations), less median blood loss (200cc vs 450cc), shorter median admission time (7 vs 13 days), lower complication rate (26.2% vs 48.0%) and higher chances of being discharged home immediately (82.6% vs 41.1%) compared to delayed patients. Using multivariate regression models these correlations remained present independent of tumor prognosis, preoperative mobility and ASA-score.

Conclusion: The delayed presentation of patients with spinal metastases to a spinal surgeon is strongly and independently associated with worse surgical and postoperative outcome parameters. Improvements in referral patterns could potentially lead to more scheduled care, negating the detrimental effects of delay.

Keywords: Spinal metastases, spine surgery, delay, emergency surgery, patient outcome

Introduction

Symptomatic spinal metastases are an increasing problem in oncology. Currently, spinal metastases occur in approximately 20% of all oncological patients.[1,2] However, due to the superior effects of new systemic anti-cancer therapies on overall survival, the prevalence of patients with spinal metastatic disease is increasing.[3,4] Unchecked growth of spinal metastases can cause mechanical instability of the spine, with or without compression on neural structures.[5] Intuitively, timely treatment of patients may be an important factor in achieving acceptable treatment outcomes.

A major challenge in the early identification of patients with spinal metastases is that patients often present with symptoms resembling non-cancer-related back pain, which is one of the most common conditions in the middle-aged population.[6] More alarming symptoms (e.g. neurological deficits) may only develop later in the disease process, putting patients at risk for delayed diagnosis, referral and treatment. As a result, symptomatic spinal cord compression occurs in 25%-50% of all patients with spinal metastases.[7,8] At this stage, patients commonly require emergency surgical intervention in an attempt to deter progression and/or reverse neurological symptoms.[9–11] The short preparation time available before emergency surgery might hamper adequate patient work-up and limit the availability of preferred spinal implants and qualified staff, potentially leading to adverse clinical outcomes.[12,13] Furthermore, an impaired neurological status has also been linked to a reduction in both postoperative clinical parameters and Quality of Life (QoL).[14–17]

The exact effects of delayed presentation and treatment of patients with spinal metastases however remains to be quantified. We hypothesized that earlier treatment of patients with spinal metastases lead to more favorable surgical and postoperative clinical outcomes. The primary aim of this study was therefore to assess the relationship between delayed presentation to a spine surgeon and surgical and postoperative parameters for patients with symptomatic spinal metastases. The secondary aim was to investigate how each aspect of delayed presentation to the spine surgeon (i.e.

neurological deficits, emergency surgery, etc.) correlates to the aforementioned parameters independent of other prognostic factors.

Materials and methods

Our institutional review board approved a waiver of informed consent for this study. Data for all consecutive patients referred to a single tertiary spine center for surgical treatment of symptomatic spinal metastases between March 2009 and December 2017 were collected. Patients with spinal involvement of multiple myeloma were also included for analysis due to similarities in clinical presentation and initial treatment. Tumor histology was analyzed from intra-operative transpedicular biopsies and categorized into three groups based on median overall survival as previously described by Bollen *et al.* and updated in consultation with our medical oncology department (<18 months: unfavorable, 18-36 months: moderate, >36 months, favorable).[18] Unknown primary tumors were classified as unfavorable. Patients with a life expectancy of at least three months were deemed eligible for surgical treatment.[19] Indications for surgery were either mechanical pain, radiographic (imminent) spinal instability and/or neurological deficits. The surgical technique was chosen by the treating spine surgeon.

The population was split into two groups: The first, timely treated group consisted of patients who, in the absence of alarming symptoms, could be scheduled for surgery more than 3 days after initial presentation at the spinal surgery department. The second, delayed group consisted of patients who, in the presence of alarming symptoms (e.g. neurological deficits, signs of gross mechanical instability), required urgent or emergency surgery within 3 days after initial presentation at our department. The 3-day cutoff for elective or non-elective surgery was chosen in accordance with the criteria of the Global Spine Tumor Study Group (GSTSG).[20] The delayed patient group could be further split up into patients requiring surgery within 24 hours and patients requiring surgery after 24 hours but within three days ("intermediate" patients). Sensitivity analyses were performed to assess the effect of excluding these intermediate patients from the analyses.

All parameters were extracted from medical records and included demographic data such as age, sex, ASA-classification (American Society of Anesthesiologists, a physical status classification system)[21] and tumor characteristics. Preoperative neurological status, Karnofsky Performance Score (KPS), surgical urgency, Tomita[22] scores and Tokuhashi[23] scores were assessed and recorded by the treating spine surgeon. Predefined surgical data including surgical technique, duration of surgery, blood loss and instrumented levels as well as postoperative data including duration of admission, complications, destination after discharge and postoperative neurological status were submitted to the GSTSG database for further processing.[20] All the involved surgeons adhered to the same basic principles, using SINS (Spinal Instability Neoplastic Score)[24] for spinal stability, KPS for general patient condition and ASIA/Frankel (American Spinal Injury Association) classification for neurological status, and combining these in a uniform way, similar to the NOMS-guidelines (Neurologic, Oncologic, Mechanical and Systemic) to determine the adequate type and timing of treatment for each patient.[10,24]

Statistical analysis.

For continuous data, means, standard deviations (SD), medians and interquartile range (IQR) were used, based on their distribution. Normality was checked graphically using histograms and Q-Q plots. For categorical data frequencies were used. To compare timely treated and delayed patients at baseline, Chi-squared tests for categorical data, unpaired t-tests for normally distributed continuous data and Mann Whitney U tests for continuous data with non-normal distribution were used. Log transformation was applied in case of non-normal distribution of dependent continuous variables in regression analyses. To assess the relationship between the timing of treatment and continuous surgical/postoperative outcome measures (surgery duration, blood loss during surgery and number of days spent in the hospital), independently of potential confounders (i.e. pre-operative mobility score, KPS, preoperative ASA classification, preoperative tumor favorability and patient age), multiple linear regression analyses were used. Binary logistic regression analysis was used for dichotomous surgical/postoperative outcome variables (the occurrence of complications and the ability to return home) associations were reported using odds ratios (OR). Due to collinearity of preoperative mobility scores and the KPS, the independent parameters included in both types of regression analyses were preoperative mobility (on a 3-point Likert-scale: unassisted (reference value), assisted and unable), preoperative ASA classification (reference value: 1), preoperative tumor favorability (reference value: favorable) and patient age. Collinearity of these factors was assessed using variance inflation factors (VIF's) with a VIF exceeding 1.5 advocating in favor of collinearity. All analyses were performed using IBM SPSS Statistics for Macintosh, Version 24.0 (Armonk, NY: IBM Corp).

Results

The cohort consisted of 206 timely treated and 98 delayed patients. At baseline, no significant differences between the two groups were found for age, gender, ASA-classification, tumor favorability, the number of affected levels, VAS-pain scores and mean Tomita score. Delayed patients had a higher prevalence of neurological deficits and lower outcome parameters related to neurological status such as KPS, mobility score, urinary sphincter control and Tokuhashi score (**Table 1**).

Delayed patients had to undergo more open surgical procedures, had a longer median surgery duration and more median blood loss during surgery than timely treated patients (**Table 2**). Six patients had an isolated vertebroplasty or vertebral body stent without further instrumentation, all in the timely treated group. None of the patients underwent multiple procedures during the same hospital admission due to multi-regional metastatic disease. Postoperatively, delayed patients spent more time in the hospital, had a higher risk of complications, fewer cases were able to return home and had more outspoken neurological symptoms (**Table 3**).

Adjusted multivariate analysis was used to estimate the association between delayed treatment and five different outcome parameters, adjusted for potential confounders (i.e. preoperative mobility score, ASA-score, tumor favorability and age). None of these remaining potential confounders showed collinearity. The analyses showed that delayed treatment was associated with an increase in duration of hospital stay (+ 2.93 days, p<0.001), blood loss (+ 628 ml, p<0.001) and surgery duration (+ 0.46 hours, p<0.001) independent of preoperative mobility, ASA-score, tumor prognosis and patient age. Delayed treatment was also independently associated with a lower probability to return home with an OR of 0.203 (0.110 to 0.376, p<0.001) and a higher risk of complications with an OR of 2.094 (1.156 to 3.795, p<0.001) (Table 4).

Sensitivity analysis of the influence of "intermediate" patients requiring surgery after 24 hours but within 3 days after presentation showed differences in terms of surgery duration and blood loss during surgery. Omitting the "intermediate" patients from the delayed patients led to a slightly higher risk of complications (63.8% vs 48%) and a slightly lower probability of returning home (31.1% vs 41.1%). In the multivariate analyses, the association between delayed treatment and hospital stay, surgery duration and the probability of returning home showed no meaningful differences. The added effect on blood loss was higher (1623 ml vs 628 ml) and the effect on the risk for the occurrence of complications was higher (OR of 3.526 vs 2.094) after omitting the "intermediate" patients from the analyses. (**Supplementary materials, online only**).

Discussion

In this study, 304 patients were included, of which 206 received timely treatment and 98 delayed treatment for symptomatic spinal metastases. The results show worse surgical and postoperative outcome for delayed patients compared to timely treated patients. Considering the two groups did not differ in demographic characteristics such as age, gender, primary tumor type and ASA-classification, the observed differences in patient outcome are presumably caused by delayed recognition of the presence and (often) relentless progression of spinal metastatic disease. Although delayed patients had much more extensive neurological deficits, the negative impact of delayed treatment remained present after correction for other potential confounding factors such as postoperative mobility scores, comorbidities, tumor histology and KPS.

In patients with advanced cancer, the spinal column is the preferred skeletal location for the formation of metastases.[9] In these patients, QoL is frequently used as an outcome parameter for the assessment of treatments. One previous study showed that emergency surgery in patients with spinal metastases was associated with lower postoperative EQ-5D scores, as well as lower survival rates.[25] Because of these lower survival rates, less postoperative QoL data are available for analysis in this patient category. This could mean that the negative effect of emergency surgery on postoperative QoL is underestimated. Therefore, to properly assess the direct effects of delayed treatment on patient outcome, direct postoperative outcome measures available for most patients, similar to those in the current study, can be used.

An important factor to take into consideration when interpreting the differences in postoperative outcome between timely treated and delayed patients is the difference in preoperative neurological status. In the timely treated patients, 84,5% scored Frankel E (no sensorimotor deficit), as opposed to 19.4% in delayed patients. A study by Lo *et al.* showed that surgery within 48 hours showed a trend towards better neurological recovery than after 48 hours.[26] These findings justify the need for rapid surgical intervention when patients present with neurological deficits, but further compromise the ability of health-care providers to perform a comprehensive patient work-up in the emergency setting. Several studies however show a direct correlation between neurological deficit and reduced postoperative outcome, QoL and survival.[14–17,27] Indirectly, one study also found that patients requiring decompressive surgery and fixation of the spine experienced a smaller increase in EQ-5D scores at three months postoperatively compared to patients only requiring spinal fixation.[15] More extensive, open decompressive surgical techniques are generally preferred over percutaneous techniques in the case of compression on neural structures. This is also reflected in the current population, where open decompressive surgical procedures were utilized in 47.1% of the timely treated patients as opposed to 86.7% of the delayed patients, potentially contributing to a reduction in postoperative outcome.[16] Surgery duration was significantly longer in delayed patients and median intraoperative blood loss was more than twice that compared to patients treated in a timely fashion, likely to be due to the extent of open surgical procedures in both groups.[28,29] As a result, delayed patients had a higher chance of requiring a blood transfusion compared to timely treated patients. Previous research suggested postoperative blood transfusions have a negative impact on survival rates, especially in oncological patients, independent of other factors affecting survival and this effect is directly correlated with the number of units transfused.[30] The study by Pereira et al. did not detect a similar effect specifically in patients with spinal metastases, however, as the authors readily concurred, this study was at risk for a type 2 statistical error.[31] To assess the effect of the total tumor load on the results, sub-analyses were performed for patients with four or more affected levels between timely treated and delayed patients. However, these results did not differ from the overall study for any of the outcome measures both in significance levels and effect sizes.

In this study a 48.0% complication rate was found among delayed patients, compared to a 26.2% complication rate in timely treated patients. A previous study by Dea *et al*. on serious adverse events (SAE's) in emergency oncological spine surgery reported a much higher complication rate of 76.2%.[14] This discrepancy can be partly explained by differences in baseline characteristics (e.g. 58.4% neurological deficits compared to 36.5% in our population) but is more likely caused by the robust, prospective design of their study specifically aimed at assessing (all) complication rates through daily rounds by a dedicated research nurse. They identified several factors contributing to the number of SAE's such as a higher patient age, lower surgeon caseload and myelopathy or radiculopathy as the presenting complaint. Timely treated patients were almost exclusively operated on by spinal surgeons dedicated to spinal oncological procedures. In contrast, delayed patients often presented outside office hours and would undergo surgical intervention by the spinal surgeon on-call, potentially leading to differences in indications, surgical technique and/or approach. Another potential reason for more complications in delayed patients is the fact that they spend more time in the hospital, which is known to also increase the risk of complications.[32]

Symptomatic spinal metastases require specialized care, mostly available in tertiary care centers. Consequently, health-care providers familiar with the management of spinal metastatic disease are often involved late in the decision making. For timely patient presentation (particularly before the onset of neurological deficits), tertiary care centers and specialized health-care providers have to rely on efficient referral patterns within the primary and secondary health-care centers in their respective catchment area. The mean time between the onset of any symptoms and the onset of neurological deficits has been noted to be as little as seven weeks.[33] Although these neurological deficits may be the first presenting symptom of cancer, for the majority of patients a history of malignancy is known and preceding symptoms indicative of pending neurological deficits such as atypical back pain aggravated by movement, radicular pain or ataxia, may have been present for some time. Few studies have previously looked into delay for spinal metastatic patients. Husband *et al.* described a median total delay (time from onset of complaints until treatment) of 73,5 days.[34] Levack *et al.* found a slightly higher median total delay of 90 days.[35] Several factors were identified placing patients at risk for delayed treatment such as initial presentation at a general practitioner or the absence of a prior cancer diagnosis. Both studies claim that in order to improve patient outcome, earlier diagnosis is required.[34,35] Our results confirm the negative consequences of delays in identification and referral of patients with neurological deficits on short-term clinical outcome. With the overall prevalence of spinal metastatic disease increasing, referral patterns for patients with spinal metastases need to be addressed as neurological damage resulting from spinal cord and cauda equina compression can be irreversible and may have great impact on the further course of the disease.

The current study has some limitations. First, the process of deciding if a patient requires treatment within or after three days may be subject to some variability. In the authors institution all spine surgeons are member of a formal "spine unit" and adhere to basic principles. Examples are:

refrain from operative intervention if life expectancy is less than three months; practice shared-decision making with the goal of optimizing QoL; practice expeditious intervention in case of rapid progression of neurological deficits. Furthermore, we use a common and appropriate technical language (SINS for spinal stability, KPS for general patient condition and ASIA/Frankel classification for neurological status)[18] when tasked with the care for patients with symptomatic spinal metastases. As a result, the decision process is evidence-based, while simultaneously reflecting the realistic day-to-day practice at a tertiary referral center.[19] Second, the definition of "delayed presentation" in this study is not a resultant of actual timing of the referral, but rather of patients' surgical urgency. The authors argue that this is a suitable proxy for the timing of their presentation, however ideally actual time since the onset of symptoms should be utilized. Third, some patients might have experienced so much delay that their condition has declined to a point where they are now deemed unfit for surgery. This may result in an underestimation of the negative effects of delayed presentation on outcome parameters.

Conclusion

In conclusion, the results from our study show that delayed referral and treatment of patients with symptomatic spinal metastases reduces short term clinical outcome. We emphasize the need for early identification of patients with spinal metastases at risk of neurological deficits and optimization of referral patterns to prevent or minimize delayed surgery in the future.

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Tables

Table 1. Baseline characteristics for both patient groups			
	Timely Treated n=206	**Delayed** n=98	**P-value**
Mean age, years (SD)	61.9 (11.7)	62.3 (11.0)	0.789
Gender, male (%)	106 (51.5%)	56 (57.1%)	0.474
ASA, n (%)			0.122
1	36 (17.5%)	7 (7.2%)	
2	111 (53.9%)	55 (56.7%)	
3	59 (28.6%)	35 (36.1%)	
Tumour Histology, n (%)			0.001
Bladder	4 (1.9%)	1 (1.0%)	
Breast	42 (20.4%)	16 (6.3%)	
Cervicouterine	4 (1.9%)	1 (1.0%)	
Gastrointestinal	11 (5.3%)	11 (11.2%)	
Lung	25 (12.1%)	17 (17.3%)	
Lymphoma	7 (3.4%)	8 (8.2%)	
Melanoma	4 (1.9%)	0 (0.0%)	
Myeloma	30 (14.4%)	13 (13.1%)	
Plasmacytoma	4 (1.9%)	5 (5.1%)	
Prostate	16 (7.8%)	13 (13.3%)	
Renal	26 (12.6%)	6 (6.1%)	
Sarcoma	2 (1.0%)	0 (0.0%)	
Thyroid	1 (0.5%)	0 (0.0%)	
Other	12 (5.8%)	2 (2.0%)	
Unknown	14 (6.8%)	3 (3.1%)	
Tumour favorability*, n (%)			0.686
Favorable	48 (24.0%)	27 (28.4%)	
Moderate	66 (33.0%)	30 (31.6%)	
Unfavorable	86 (43.0%)	38 (40.0%)	
KPS (SD)**	68.6 (14.5)	56.3 (16.0)	<0.001
Frankel on entry, n (%)			<0.001
A	0 (0.0%)	3 (3.1%)	
B	0 (0.0%)	7 (7.1%)	
C	4 (1.9%)	25 (25.5%)	
D	28 (13.6%)	44 (44.9%)	
E	174 (84.5%)	19 (19.4%)	
Mobility on entry, n (%)			<0.001
Normal	146 (70.9%)	32 (32.7%)	
Uses one crutch	2 (1.0%)	1 (1.0%)	
Uses walker or two crutches	13 (6.3%)	7 (7.1%)	
Confined to wheelchair	13 (6.3%)	6 (6.1%)	
Confined to bed	32 (15.5%)	52 (53.1%)	
Urinary sphincter control			<0.001
Incontinent	1 (0.5%)	8 (8.2%)	
Impaired	11 (5.3%)	32 (32.7%)	
Normal	194 (94.2%)	58 (59.2%)	
Number of affected levels n (%)			0.878
1	99 (48.1%)	45 (45.9%)	
2	34 (16.5%)	15 (15.3%)	
3	27 (13.1%)	11 (11.2%)	
≥4	46 (22.3%)	27 (27.6%)	
VAS pain, mean (SD)	4,9 (2.4)	4.6 (2.5)	0.285
Tomita, mean (SD)	4.7 (2.7)	5.0 (2.9)	0.363
Tokuhashi, mean (SD)	9.5 (2.8)	8.0 (2.9)	<0.001

*Median survival > 36 months (favorable), 36 months ≥ 18 months (moderate) and < 18 months (unfavorable). **Karnofsky Performance Score.

Table 2. Differences in surgical parameters between timely treated and delayed patients.

	Timely Treated n=206	Delayed n=98	P-value
Surgial technique, n (%)			<0.001
Open surgery	97 (47.1%)	85 (86.7%)	
Percutaneous surgery	109 (52.9%)	13 (13.3%)	
Surgical approach			<0.001
Anterior	1 (0.5%)	0 (0.0%)	
Combined	8 (3.9%)	2 (2.0%)	
Posterior	197 (95.6%)	96 (98.0%)	
Median surgery duration, hours (IQR)	2.0 (1.0-2.0)	2.0 (2.0-3.0)	<0.001
Median blood loss, ml (IQR)	200 (50-500)	450 (200-800)	<0.001
Level of instrumentation			<0.001
Cervical	19 (9.2%)	1 (1.0%)	
Cervicothoracic	26 (12.6%)	10 (10.2%)	
Thoracic	78 (37.9%)	57 (58.2%)	
Thoracolumbar	34 (16.5%)	17 (17.3%)	
Lumbar	34 (16.5%)	7 (7.1%)	
Lumbosacral	5 (2.4%)	0 (0.0%)	

Table 3. Differences in postoperative parameters between timely treated and delayed patients.

	Timely Treated n=206	Delayed n=98	P-value
Median hospital time, days (IQR)	7 (5-12)	13 (7-20)	<0.001
Occurrence of complications, n (%)			0.001
Yes	54 (26.2%)	47 (48.0%)	
No	152 (73.8%)	51 (52.0%)	
Discharge to, n (%)			<0.001
Home	166 (82.6%)	39 (41.1%)	
Other institution	19 (9.5%)	26 (27.4%)	
Different hospital/ward	16 (8.0%)	30 (31.6%)	
Mobility at discharge, n (%)			<0.001
Normal	122 (60.7%)	11 (11.8%)	
Assisted	75 (37.3%)	71 (76.3%)	
Confined to bed	4 (2.0%)	11 (11.8%)	
Frankel at discharge, n (%)			<0.001
A	0 (0.0%)	2 (2.0%)	
B	3 (1.5%)	3 (3.1%)	
C	1 (0.5%)	17 (17.3%)	
D	26 (12.6%)	42 (42.9%)	
E	171 (83.0%)	31 (31.6%)	

Table 4. Multivariate analyses of the association between the treatment category and hospital stay, blood loss, surgery duration, the ability to return home and the occurr
mobility score, ASA-score, tumor type favorability and patient age

		Multiple linear regression						
		Hospital stay*	n=293	**Blood loss***	n=283	**Surgery duration***	n=294	**Return home**
		Days (CI)	p-value	ml (CI)	p-value	Hours (CI)	p-value	Odds ratio
Intercept		7.01 (4.33 to 11.37)	**<0.001**	566 (266 to 1207)	**<0.001**	2.25 (1.71 to 2.96)	**<0.001**	
Treatment category	Timely treated	*Reference*		*Reference*		*Reference*		*Refer*
	Delayed	2.93 (1.24 to 4.98)	**<0.001**	628 (324 to 1034)	**<0.001**	0.46 (0.19 to 0.77)	**0.001**	0.203 (0.110 to 0
Mobiliy score	Unassisted	*Reference*		*Reference*		*Reference*		*Refer*
	Assisted	1.52 (-0.29 to 3.85)	0.105	-109 (-253 to 102)	0.269	-0.03 (-0.32 to 0.29)	0.826	0.683 (0.298 to 1
	Unable	3.19 (1.23 to 5.61)	**0.001**	6 (-155 to 231)	0.950	0.14 (-0.13 to 0.45)	0.328	0.285 (0.143 to 0
ASA	1	*Reference*		*Reference*		*Reference*		*Refer*
	2	-0.78 (-2.14 to 0.96)	0.352	-235 (-340 to -79)	**0.006**	-0.29 (-0.55 to 0.01)	0.054	0.888 (0.320 to 2
	≥3	-0.438 (-2.01 to 1.64)	0.649	-268 (-372 to -121)	**0.003**	-0.40 (-0.67 to -0.08)	**0.015**	0.708 (0.240 to 2
Tumor prognosis	Favorable	*Reference*		*Reference*		*Reference*		*Refer*
	Moderate	-0.72 (-1.94 to 0.78)	0.321	-102 (234 to 82)	0.242	-0.09 (-0.34 to 0.19)	0.504	1.529 (0.702 to 3
	Unfavorable	-0.93 (-2.05 to 0.45)	0.175	-168 (-276 to -20)	**0.029**	-0.10 (-0.34 to 0.16)	0.443	1.155 (0.567 to 2
Age	Per year	0.02 (-0.03 to 0.07)	0.410	-3 (-9 to 4)	0.426	0 (-0.01 to 0.01)	0.858	0.970 (0.943 to 0

**Statistics were performed on log-transformed dependent variables due to non-normal distribution*