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Association of Medical Comorbidities With Objective Functional Impairment in Lumbar Degenerative Disc Disease

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Abstract

Study Design: Analysis of a prospective 2-center database.

Objectives: Medical comorbidities co-determine clinical outcome. Objective functional impairment (OFI) provides a supplementary dimension of patient assessment. We set out to study whether comorbidities are associated with the presence and degree of OFI in this patient population.

Methods: Patients with degenerative diseases of the spine preoperatively performed the timed-up-and-go (TUG) test and a battery of questionnaires. Comorbidities were quantified using the Charlson Comorbidity Index (CCI) and the American Society of Anesthesiology (ASA) grading. Crude and adjusted linear regression models were fitted.

Results: Of 375 included patients, 97 (25.9%) presented at least some degree of medical comorbidity according to the CCI, and 312 (83.2%) according to ASA grading. In the univariate analysis, the CCI was inconsistently associated with OFI. Only patients with low-grade CCI comorbidity displayed significantly higher TUG test times ($p = 0.004$). In the multivariable analysis, this effect persisted for patients with CCI = 1 ($p = 0.030$). Regarding ASA grade, patients with ASA = 3 exhibited significantly increased TUG test times ($p = 0.003$) and t-scores ($p = 0.015$). This effect disappeared after multivariable adjustment ($p = 0.786$ and $p = 0.969$). In addition, subjective functional impairment according to ODI, and EQ5D index was moderately associated with comorbidities according to ASA (all $p < 0.05$).

Conclusion: The degree of medical comorbidities appears only weakly and inconsistently associated with OFI in patients scheduled for degenerative lumbar spine surgery, especially after controlling for potential confounders. TUG testing may be valid even in patients with relatively severe comorbidities who are able to complete the test.

Keywords

objective functional testing, functional impairment, degenerative disc disease, lumbar spinal stenosis, lumbar disc herniation, comorbidity

Introduction

During the past decades, outcome of interest in medical research have shifted from surrogate measures of success such as radiological parameters and physician-based outcome assessment toward subjective patient-reported outcome measures (PROMs).[1] Recently, frequently used subjective measures of success (e.g. PROMs such as the Oswestry Disability Index [ODI]) have been complemented by objective functional testing, through which the presence and degree of objective functional impairment (OFI) can be evaluated.[2-4] These tests[4] include the timed-up-and-go (TUG),[2] 6-minute-walking (6WT),[5] or 5-repetition sit-to-stand (5R-STS).[3] Their aim is

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to capture symptoms and signs that cannot be registered by well-established PROMs, such as mobility restrictions resulting from foot drop and limping.[6,7] Overall, the quick execution, high reliability and straight-forward interpretation of OFI tests have the potential to be of great benefit when used alongside PROMs.[8-11]

Medical comorbidities such as chronic-obstructive pulmonary disease (COPD), cardiovascular disease, diabetes mellitus, asthma, morbid obesity or malnutrition among others are not uncommon in patients scheduled for surgery for lumbar degenerative disc disease (DDD).[12,13] These are possibly linked to sarcopenia,[14] functional dependency,[15] discharge disposition,[16] postoperative delirium,[17] higher onset of post-operative complication[18-20] and mortality rates.[18-21] Overall, they contribute to a poorer functional status and TUG performance in normative populations.[22,23] Other tests for OFI like the 5R-STS are even commonly used to grade comorbidity, e.g. in COPD.[24] A strong influence of medical comorbidities on TUG test performance would mean that—in the presence of severe comorbidities such as COPD—any amount of OFI could also just as well be explained by the comorbidity instead of DDD, and would thus lower the value of objective functional testing. The association of medical comorbidities with OFI as assessed by the TUG is not yet scientifically investigated.[2]

The goal of this study consequently was to quantify the extent of association among medical comorbidities and OFI in a population of patients with degenerative lumbar spine disease.

Materials and Methods

Overview

This study was a secondary analysis of a prospective 2-center database. The study was approved by the Institutional Review Board (IRB) of the University of Geneva (IRB No. 14-079) and the Ethics Committee St.Gallen (IRB No. 14/049). All patients gave written informed consent. All objective functional testing took place during preoperative consultations.

Study Population

All enrolled patients were candidates for elective surgery. They were assessed preoperatively during outpatient consultations or upon admission for surgical treatment. Inclusion criteria were the presence of lumbar disc herniation (LDH), lumbar spinal stenosis (LSS), or any type of lumbar DDD requiring surgical treatment. Only patients 18 years or older were included. Pregnant patients or those with severe functional disability unrelated to the spine disease but unable to walk and perform the TUG test were excluded.

Baseline Variables

Alongside objective functional testing, a battery of PROMs were collected as stated previously.[2] Specifically, patients were asked to complete questionnaires containing baseline sociodemographic data, as well as numeric rating scales: visual analogue scale (VAS) for back and leg pain severity, validated German and French versions of the Oswestry Disability Index (ODI), Roland-Morris Disability Questionnaire (RMDQ), the Short-Form 12 questionnaire physical component summary score (SF12 PCS), and EuroQOL-5D (EQ-5D) questionnaire—containing the EQ-5D index and visual analogue scale (EQ-VAS).

Medical comorbidities were quantified by neurosurgeons and anesthesiologists using standardized protocols according to the Charlson Comordbidity Index[25] (CCI) and the American Society of Anesthesiology (ASA) grading,[26] respectively. The CCI allows for robust estimates of mortality from comorbid disease by assigning 1, 2, 3 or 6 points for a standardized list of comorbidities (see Supplementary Material 1). The ASA grading stratifies patients into normal/healthy (ASA 1), into those with mild (ASA 2) or severe systemic disease (ASA 3). Those graded higher are in constant threat to life (ASA 4), are not expected to survive without (ASA 5) or even with the intended surgical procedure (ASA 6).

The Timed-Up-and-Go (TUG) Test

All patients performed the TUG test as described previously.[2] In brief, on the words "Three, Two, One—Go!" patients got up from a chair with an arm rest, walked as fast as possible (without running) to a line in 3-m distance. Then, they would turn around by 180° and return—again, as fast as possible—to the chair and sit down. The time between getting up from the chair and sitting back down was recorded using the "TUG app."[10] Patients were encouraged to wear their regular shoes and use a walking aid, if required. Raw TUG test times (in seconds) were transformed into OFI T-scores, based on age- and sex-adjusted normative data, with T-scores > 123 representing values that exceed the 99th percentile of the normal population and are thus indicative of OFI.[2] T-scores indicate how much a numerical value deviates from the population mean. As a transformation of Z-scores—the number of standard deviations that a value deviates from the population mean—T-scores are easier to compare with other tests, and were derived according to Gautschi et al.[2]

Statistical Analysis

Continuous variables are reported as means $\pm$ standard deviations (SD), and categorical variables as numbers and percentages. The severity of OFI at baseline was graded according to the previously described severity stratification.[2,11] Levene's test was used to check for equality of variance. We assessed intergroup differences using 1-way analysis of variance (ANOVA). Subsequently, linear regression models were fitted to evaluate the influence of the severity grading on TUG performance, with CCI $= 0$ or ASA $= 1$ as the reference category. Crude and multivariate regression models, adjusted for age, sex, body mass index, paresis, surgical procedure, and index level were constructed to correct

Table 1. Basic Demographic and Disease-Specific Data.

Characteristic		Value N = 375
Age [yrs]		58.9 ± 15.7
Female sex, n (%)		162 (43.2)
Ability to work, n (%)		
	Working	154 (41.1)
	Retired	149 (39.7)
	Unable	62 (16.5)
	Invalid	10 (2.7)
BMI [kg/m^2]		27.1 ± 4.6
Active smoker, n (%)		96 (25.6)
Paresis, n (%)		102 (27.2)
BMRC Grade of Paresis, n (%)		
4		80 (21.3)
3		17 (4.5)
2		4 (1.1)
1		1 (0.3)
Procedure, n (%)		
	Discectomy	189 (50.4)
	Decompression	135 (36.0)
	Fusion	51 (13.6)
Number of index levels, n (%)		
	1	323 (86.1)
	2	42 (11.2)
	3	9 (2.4)
	4	1 (0.3)
Index level, n (%)		
	L1-2	4 (1.1)
	L2-3	24 (6.4)
	L3-4	78 (20.8)
	L4-5	173 (46.1)
	L5-S1	96 (25.6)
Side, (%)		
	Left	142 (37.9)
	Right	147 (39.2)
	Bilateral	86 (22.9)
Charlson Comorbidity Index, n (%)		
	0	278 (74.1)
	1	64 (17.1)
	2	21 (5.6)
	3	9 (2.4)
	4	3 (0.8)
ASA Score, n (%)		
	1	63 (16.8)
	2	267 (71.2)
	3	45 (12.0)

Continuous variables are presented as mean ± SD and categorical variables as frequency (percentage).
BMI, body mass index; ASA, American Society of Anesthesiologists; BMRC, British medical research council.

for potential confounders.[3,11,27] The assumptions of the generalized linear models were evaluated, and the model fit was quantified by R^2 values. All analyses were carried out in R version 3.5.1 (The R Foundation for Statistical Computing, Vienna, Austria).[28] A $p \leq 0.05$ on 2-tailed tests was considered statistically significant. The statistical code (Supplementary Material 2) is attached. The statistical analysis was cross-checked with an external biostatistician.

Results

Patient Population

A total of 375 patients were included. There was no missing data. Detailed baseline patient characteristics are provided in Table 1. On average, included patients were 58.9 ± 15.7 years old, with 162 (43.2%) being female. The majority of patients had index pathologies on a single spinal level (86.1%), most commonly at L4-L5 (46.1%), and most frequently presenting with LDH requiring discectomy (50.4%). In terms of medical comorbidities, 278 patients (74.1%) presented without comorbidity according to the CCI, and 63 patients (16.8%) presented with ASA Grade I, signifying absence of systemic comorbidities.

Association of CCI With TUG/OFI

Univariable analysis. Detailed results are provided in Tables 2 and 3. Raw TUG test times were unevenly distributed among the various CCI classes ($p = 0.004$), increasing inconsistently from 10.62 ± 5.94 seconds for CCI = 0 to 13.27 ± 6.39 seconds for CCI = 4. In particular, CCI = 1 demonstrated markedly increased TUG test times with 15.15 ± 15.65 seconds (Figure 1). However, there was no significant association among TUG t-scores and CCI ($p = 0.336$). In univariable regression analysis, compared to CCI = 0, only patients with CCI = 1 demonstrated significantly different TUG test times (regression coefficient [RC]: 4.54, 95% confidence interval [CI]: 2.25 to 6.82, $p < 0.001$), and there was no influence of CCI on TUG t-scores.

Multivariable analysis. Table 3 details the results of the multivariate regression analysis. Corroborating the univariable analysis, only patients with mild systemic comorbidity (CCI = 1) exhibited higher TUG test times (RC: 13.11, 95% CI: 1.73 to 24.49, $p = 0.030$) after correcting for potential confounders. The same effect was now replicated in terms of TUG t-scores (RC: 105.07, 95% CI: 11.66 to 198.48, $p = 0.034$).

Association of ASA Score With TUG/OFI

Univariable analysis. Detailed results are provided in Tables 2 and 3. Patients with ASA = 3 demonstrated a significantly increased TUG test times (15.53 ± 18.10 seconds, $p = 0.003$) compared to ASA = 1 (11.25 ± 8.68 seconds) and ASA = 2 (10.82 ± 5.22 seconds). While ASA grading was weakly associated with TUG t-scores overall ($p = 0.015$), no clear and consistent pattern was distinguishable, with ASA = 2 demonstrating markedly lower t-scores. In univariable regression analysis, these patterns were replicated: Concerning TUG test time, patients with ASA = 3 demonstrated increased test times

Table 2. Baseline Measures of Objective Functional Impairment and Subjective Patient-Reported Questionnaires Stratified by the Presence and Degree of Comorbidities.

Charlson Comorbidity Index	0	1	2	3	4	P Value
TUG test time [s]	10.62 ± 5.94	15.15 ± 15.65	10.75 ± 4.58	12.22 ± 6.86	13.27 ± 6.39	0.004*
TUG t-score	128.08 ± 40.37	143.89 ± 125.91	117.51 ± 17.57	119.67 ± 20.75	118.14 ± 20.37	0.336
RMDQ	11.58 ± 5.25	12.55 ± 5.26	10.67 ± 4.59	11.78 ± 7.33	7.33 ± 5.51	0.328
ODI	48.44 ± 17.80	51.79 ± 16.96	54.00 ± 18.52	51.44 ± 24.81	58.67 ± 12.06	0.374
VAS back pain	3.88 ± 2.78	3.47 ± 2.51	3.86 ± 2.86	5.33 ± 3.20	4.33 ± 4.04	0.412
VAS leg pain	5.09 ± 2.81	4.77 ± 2.90	4.55 ± 2.93	3.61 ± 2.81	5.17 ± 1.89	0.496
EQ5D Index	0.51 ± 0.22	0.46 ± 0.24	0.64 ± 0.20	0.55 ± 0.20	0.43 ± 0.05	0.037*
EQ5D VAS	52.19 ± 20.44	51.17 ± 20.66	51.52 ± 20.17	52.78 ± 21.08	65.00 ± 8.66	0.851
SF12 PCS	31.31 ± 8.16	29.48 ± 7.11	29.10 ± 8.79	32.33 ± 10.79	21.63 ± 4.83	0.097
ASA Score	**1**	**2**	**3**			**P Value**
TUG	11.25 ± 8.68	10.82 ± 5.22	15.53 ± 18.10			0.003*
TUG t-score	143.05 ± 66.16	123.96 ± 27.23	146.73 ± 149.02			0.015*
RMDQ	12.19 ± 5.31	11.28 ± 5.22	13.20 ± 5.33			0.054
ODI	48.00 ± 18.47	48.73 ± 18.18	55.98 ± 13.53			0.032*
VAS back pain	3.04 ± 2.47	3.99 ± 2.81	4.16 ± 2.66			0.035*
VAS leg pain	4.93 ± 2.44	5.01 ± 2.93	4.77 ± 2.75			0.858
EQ5D Index	0.52 ± 0.22	0.52 ± 0.22	0.42 ± 0.21			0.029*
EQ5D VAS	49.05 ± 21.87	52.56 ± 19.90	53.60 ± 20.93			0.408
SF12 PCS	31.78 ± 8.13	30.97 ± 8.41	28.57 ± 5.78			0.108

Continuous variables are presented as mean ± SD and categorical variables as frequency (percentage).
TUG, timed up and go; VAS, visual analogue scale; RMDQ, Roland-Morris Disability Questionnaire; ODI, Oswestry Disability Index; SF12, short form 12 questionnaire; PCS, physical component summary; ASA, American Society of Anesthesiologists.
* $p \leq 0.05$.

Table 3. Uni- and Multivariable Linear Regression Models Describing the Relationship Between Comorbidities and TUG Performance.

	Univariate analysis			Multivariate analysis		
Variable	**RC**	**95% CI**	**P value**	**RC**	**95% CI**	**P value**
Charlson Comorbidity Index						
TUG test time						
0	Reference	-	-	Reference	-	-
1	4.54	2.25 to 6.82	< 0.001*	13.11	1.73 to 24.49	0.030*
2	0.14	−3.59 to 3.86	0.943	−6.18	−27.20 to 14.84	0.568
3	1.61	−3.97 to 7.18	0.573	−7.21	−28.11 to 13.69	0.504
4	2.65	−6.90 to 12.20	0.587	9.82	−21.03 to 40.67	0.537
TUG t-score						
0	Reference	-	-	Reference	-	-
1	15.81	−1.26 to 32.89	0.070	105.07	11.66 to 198.48	0.034*
2	−10.57	−38.44 to 17.30	0.458	−82.37	−254.93 to 90.18	0.356
3	−8.40	−50.11 to 33.31	0.693	−68.78	−240.32 to 102.77	0.437
4	−9.93	−81.42 to 61.55	0.786	73.06	−180.17 to 326.30	0.575
ASA Score						
TUG test time						
1	Reference	-	-	Reference	-	-
2	−0.43	−2.74 to 1.88	0.714	−5.47	−30.84 to 19.90	0.675
3	4.28	1.06 to 7.50	0.010*	3.83	−23.66 to 31.32	0.786
TUG t-score						
1	Reference	-	-	Reference	-	-
2	−19.09	−36.20 to −1.98	0.029*	−78.34	−287.56 to 130.89	0.468
3	3.67	−20.17 to 27.52	0.763	−4.55	−231.28 to 222.18	0.969

Regression coefficients (RCs) are presented for each degree of comorbidity, compared to no comorbidity. Multivariate analysis is adjusted for age, sex, body mass index, paresis, procedure, and index level.
TUG, timed up and go test; RC, regression coefficient; CI, confidence interval; ASA, American Society of Anesthesiologists; * $p \leq 0.05$.

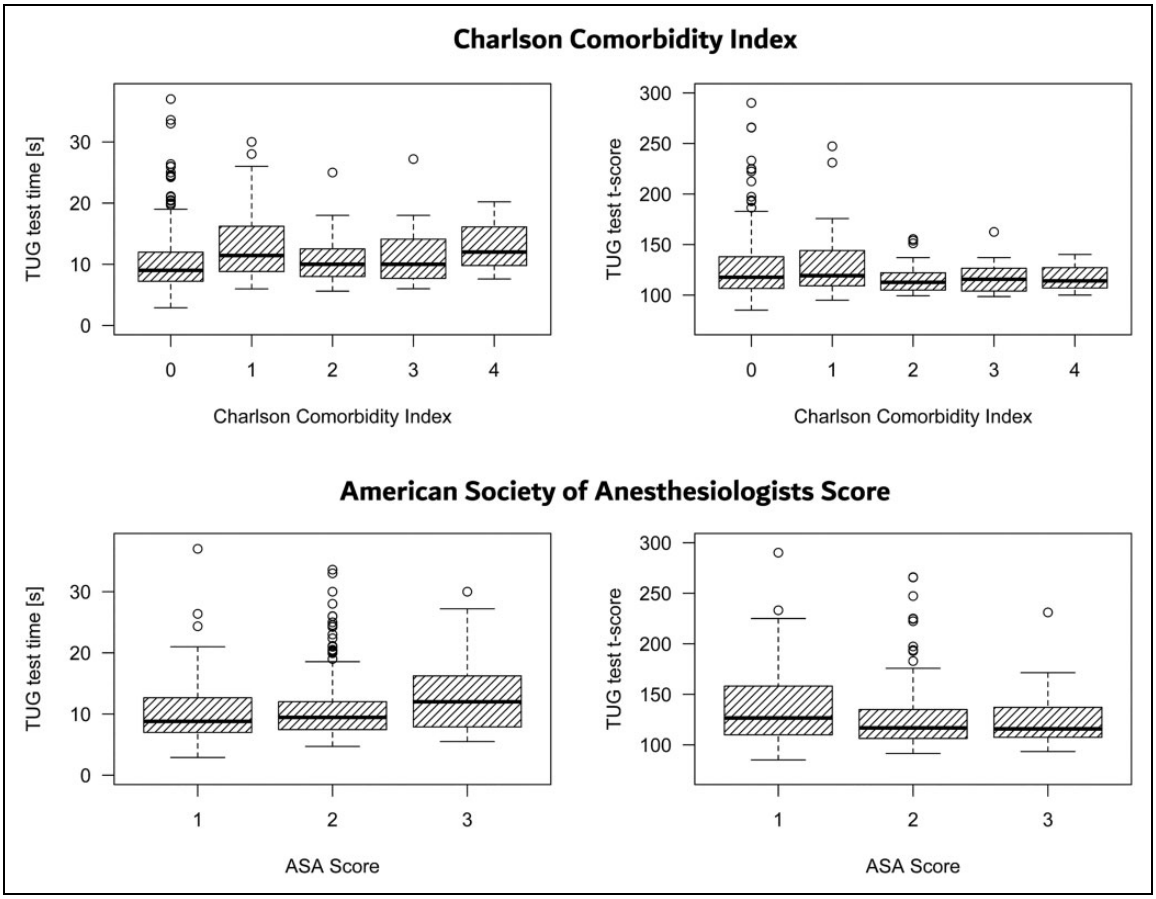

Figure 1. Boxplots demonstrating baseline Timed-Up-and-Go (TUG) performance stratified by medical comorbidities. Both raw TUG test times (top panel) as well as TUG t-scores (bottom panel) are represented. Shown are median values (horizontal line), interquartile ranges (boxes), range (whiskers) and extreme outliers (circles).

(RC: 4.28, 95% CI: 1.06 to 7.50, p = 0.010) compared to ASA = 1. Concerning TUG t-scores, patients with ASA = 2 demonstrated markedly lower t-scores (RC: −19.09, 95% CI: −36.20 to −1.98, p = 0.029).

Multivariable analysis. After correction for potential confounders, an effect of medical comorbidities on both TUG test times as well as on TUG t-scores was not discernable.

Association of Comorbidity With PROMs

Table 2 displays univariable analysis of the association among CCI or ASA grading and various PROMs of pain, disability and HRQOL. In terms of CCI, only the EQ5D index exhibited a weak association (p = 0.037) that was, however, inconsistent. All other PROMs were not correlated to CCI grading. In terms of ASA score, ODI (p = 0.032), VAS back pain (p = 0.035), and EQ5D index (p = 0.029) showed weak but statistically significant and directionally consistent changes among ASA grades.

Discussion

The current investigation identified some weak and inconsistent associations between medical comorbidities (graded according to the CCI or ASA scores) and OFI (as defined by age- and sex-adjusted TUG test results). Patients with lower CCI scores (see Supplemental Material 1) demonstrated significantly higher levels of OFI. This was true even after adjustment for confounders. Our data imply that the extent of medical comorbidities is weakly and inconsistently associated with TUG test performance in patients scheduled for degenerative lumbar spine surgery, especially after controlling for potential confounders. This would in turn suggest that—in this specific spinal patient population—TUG performance is for the greatest part explained by disease severity rather than by comorbidities alone. Thus, TUG testing may be valid even in patients with relatively severe comorbidities able to complete the test.

To the best of our knowledge, this is the first study investigating association of medical comorbidities with objective functional testing in patients suffering from lumbar DDD. In a previous publication from the same cohort, we found that mental comorbidities such as depression do not influence TUG test performance.[29] In addition, the TUG test appears to be relatively inert concerning age,[30] gender,[31] smoking status,[32] and body mass index.[33] Similarly, it has been established that 5R-STS test performance is only marginally influenced by these variables in a consistent and predictable way.[3,9]

Consequently, test performance can be adjusted for common variables such as age and gender, for example by generating t-scores normalized to a normative population as has been done with the TUG test for age and gender.[2]

A reliable and valid test to grade disease severity objectively should be inert to common confounders, or at least easily adjustable for those confounders assuming they affect test performance. In degenerative spine surgery, a test for OFI can only be a reliable outcome measure if the influence of degenerative spinal disease on TUG performance is far greater than that of medical comorbidities. With the ever-increasing age of the world's population, and especially of the population undergoing degenerative spine surgery, the incidence of medical comorbidities has been rising and will inevitably continue to do so in the foreseeable future.[12,34]

While there are currently no studies investigating medical comorbidities in patients with spine disease, Kear et al.[22] analyzed a normative population of 200 participants aged from 20 to 59 years, and found that medical comorbidities were associated with slower TUG times. In 432 older adults, Nevill et al.[23] even found that the TUG test was the only variable able to identify individuals at risk of developing medical comorbidities in the future. Based on this evidence, there is at least some association among medical comorbidities and TUG test performance in normative populations.

The present study identified a weak association among ASA grade 3 and TUG performance (univariate), which consistently disappeared in the multivariable analysis. The most likely explanation is that patients with ASA grade 3 were significantly older, which was the case in our cohort. By controlling for age and other potential confounders, we were thus able to show that there is no apparent direct influence of comorbidity as graded by ASA on TUG performance.

Interestingly, concerning comorbidities as described by the CCI, we found that patients with minor comorbidities that add up to 1 point in the CCI performed slightly worse than those patients without comorbidities or those with severe comorbidities. This effect persisted in the multivariable analysis and is thus evidently not explained by one of the potential confounders controlled for. While not analyzed in this paper, the most likely potential explanation for this phenomenon is that some subsets of the comorbidities that add only 1 point to the CCI (e.g. history of a cerebrovascular ischemia, chronic cognitive deficits, COPD, congestive heart failure, dementia) may influence TUG test performance to a greater extent than those that commonly provide 2 or more points (e.g. complicated diabetes mellitus, chronic kidney disease, chronic leukemia, acquired immune deficiency syndrome [AIDS]). This would correspond to prior evidence that the TUG may be a somewhat sensitive marker of some of the abovementioned comorbidities such as cerebrovascular ischemia,[35] COPD,[36] and dementia.[37] It must be acknowledged that our cohort did not include many patients with such comorbidities and that these were not specifically analyzed, and that the association observed among lower-grade medical comorbidities according to the CCI and TUG test performance was weak in the multivariable analysis.

It could easily be hypothesized that paper-based questionnaires such as PROMs may be much less prone to bias due to medical comorbidities than functional tests. However, our data indicate that even questionnaires are at least influenced to a minor extent by medical comorbidities. We found that ODI, VAS back pain, and EQ5D index were all weakly but statistically significantly and directionally consistently increasing with each ASA grade. As this article focused on the relatively new objective functional evaluation by the TUG test, we did not conduct multivariate analyses for each of the PROMs and hence there is a possibility that the observed relationship between medical comorbidities and PROM results may also be biased by patient- or disease-specific variables including age, sex, body mass index, or disease type and site.

Strengths & Limitations

Strengths of this analysis include the prospective collection of a fairly large dataset with the source data originating from 2 major Swiss hospitals with catchment areas that span across different cultural & linguistic regions, which increases the generalizability of the findings. Besides the application of a relatively novel "objective outcome measure" (TUG test), the dataset contained various well-established PROM questionnaires without any missing data.

Some limitations apply and should be mentioned. Due to inclusion of various spinal pathologies, our results cannot be applied specific to any of the studied disease but should rather be regarded as a description of effects in the general population of patients suffering from lumbar DDD. As the majority of patients presented with LDH, the results are closest to "disease-specific" for LDH patients. Ideally, further disease-specific analyses should be conducted to validate and confirm the present findings. The same can be said for particular medical comorbidities. To preserve statistical power and to objectively and reproducibly collect data on comorbidities, we used the ASA classification as well as the CCI, which summarize the impact of comorbidities roughly. However, this precludes any conclusions on the influence of specific comorbidities such as e.g. congestive heart failure or COPD on TUG test performance, as these were not analyzed. Here, this information was not collected and the sample size available for such subgroup analyses would not be sufficient. Additionally, the apparently high statistical power for this study requires a word of caution, as some of the revealed statistically significant relationships may not be of clinical relevance. For this reason, the confidence intervals of the regression coefficients should be regarded as more informative than the respective p values. Similarly, statistical power for the higher CCI scores was comparatively low as the majority of patients presented with CCI = 0 or CCI = 1. Lastly, our results may be biased by the fact that the majority of patients consumed analgesic medications on the daily at baseline assessment. The exact influence of analgesic medication on OFI currently remains unknown.[4] It should also be noted that not all confounders may have been accounted for, for

example psychological factors such as depression, anxiety, and motivation.

Despite these limitations, our data allow a cautious first glance at the interplay among medical comorbidities and objective functional test performance, and suggest that their effect magnitude on TUG test performance is rather weak when compared to the influence of other variables, especially after controlling for potential confounding variables. TUG testing may be valid even in patients with comorbidities, provided patients are able to complete the test safely.

Conclusions

The extent of medical comorbidities appears to be only weakly and inconsistently associated with OFI (as assessed by the TUG test) in patients scheduled for degenerative lumbar spine surgery, especially after controlling for potential confounders. Thus, results of the TUG test may be valid to estimate functional impairment, even in patients with mild, moderate, or severe comorbidities. Analysis of external cohorts is warranted to further study the influence of specific medical comorbidities on OFI in general and in more defined patient populations.

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Declaration of Conflicting Interests

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Supplemental Material

Supplemental material for this article is available online.

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