Health-related quality of life after total hip replacement: a Taiwan study

Hon-Yi Shi · Mahmud Khan · Richard Culbertson ·
Je-Ken Chang · Jun-Wen Wang · Heng-Chia Chiu

Received: 17 September 2008 / Revised: 29 September 2008 / Accepted: 30 September 2008 / Published online: 31 October 2008
© Springer-Verlag 2008

Abstract This study applied the generalised estimating equations (GEE) in a large-scale prospective cohort study of predictors of health-related quality of life (HRQoL) in a Taiwan population. The study population included all patients who had undergone primary total hip replacement (THR) performed between March 1998 and December 2002 by either of two orthopaedic surgeons in two hospitals. The SF-36 was used in pre- and postoperative assessments of 335 patients. Young age, male gender, minimal comorbidity, use of epidural anaesthesia, lack of readmission within the previous 30 days, and higher preoperative functional status were positively associated with HRQoL ($P < 0.05$). Patients should be advised that their postoperative HRQoL may depend not only on their postoperative health care but also on their preoperative functional status. These analytical results should be applicable to other Taiwan hospitals and to other countries with similar social and cultural practices.

Résumé Cette étude a pour but d'estimer la qualité de vie (HRQoL) de la population Taïwanaise après PTH. Méthode: la population étudiée a inclus tous les patients ayant bénéficié d'une prothèse totale de hanche primaire (THR) réalisée entre mars 1998 et décembre 2002 par deux chirurgiens orthopédistes dans deux établissements hospitaliers différents. Le questionnaire SF-36 a été utilisé en pré et postopératoire sur 335 patients. Résultats: jeune âge, sexe masculin, comorbidités minimales, utilisation de l'anesthésie épidurale et absence de réhospitalisation dans les 30 jours sont corrélés de façon positive avec le score HRQoL ($P < 0.05$). Conclusion: les patients sont avertis que le score HRQoL postopératoire dépend non seulement de leur état de santé postopératoire mais également de leur statut fonctionnel préopératoire. Cette analyse peut être généralisée à d'autres établissements hospitaliers Taïwanais et à d'autres pays présentant des similitudes sur le plan social et culturel.

H.-Y. Shi · H.-C. Chiu (✉)
Graduate Institute of Healthcare Administration,
Kaohsiung Medical University,
100 Shih-Chun 1st Road,
Kaohsiung 807, Taiwan, Republic of China
e-mail: chiu@kmu.edu.tw

M. Khan · R. Culbertson
Department of Health Systems Management, Tulane University,
New Orleans, LA, USA

J.-K. Chang
Department of Orthopaedics,
Kaohsiung Medical University Hospital,
Kaohsiung, Taiwan

J.-W. Wang
Department of Orthopaedics,
Kaohsiung Chang-Gung Memorial Hospital,
Kaohsiung, Taiwan

Introduction

Elective primary total hip replacement (THR) is a common and effective orthopaedic intervention. Health-related quality of life (HRQoL) is a recognised indicator of health care outcome [1, 2]. However, published reports of HRQoL outcomes vary considerably between individual orthopaedic surgeons, even between practitioners in the same facility.

When evaluating THR outcomes, numerous factors other than outcome of the surgery itself should be considered [3–5]. Fortin et al. [6] assessed THR patients six months after discharge to identify predictors of pain and physical function. They reported that poor preoperative pain and function was associated with poor postoperative outcomes.

After two years of follow-up, they demonstrated that preoperative subscale scores were the best predictor of THR outcome. Nilsdotter et al. [7], in a prospective case control study comparing HRQoL after THR, found that older age and increased postoperative pain were predictive of poor THR outcome. Ethgen et al. [3], in a literature review of HRQoL in THR patients, proposed that age is unassociated with surgical outcome and that males benefit from the intervention more than females do.

Despite the growing understanding of the health effects of THR, previous studies have exhibited serious shortcomings. Firstly, few used longitudinal data with more than two time points, and few examined predictors of HRQoL over periods exceeding two years. Second, most studies have analysed populations in the US or in OECD countries, which may substantially differ from those in less developed geographic areas. Third, when analysing longitudinal data, such studies rarely apply the appropriate statistical methodology to control for censoring and intercorrelations arising from repeated measures obtained from the same patient pool.

This study examined the longitudinal changes in each SF-36 subscale and explored their relationships to effective predictors in primary THR patients. This study is, to our knowledge, the first to apply generalised estimating equations (GEE) in a large-scale prospective cohort study of HRQoL changes and predictors in a Taiwan population of THR patients.

Methods

Study design and sample

The study population included all patients who had undergone primary THR (ICD-9-CM procedure code of 8151) performed between March 1998 and December 2002 by either of two orthopaedic surgeons in two different southern Taiwan hospitals. All THR procedures performed to treat injuries sustained in traffic accidents and those performed on patients with cognitive or communicative impairments were excluded. In patients who had undergone repeated bilateral THR procedures, the most recent procedure was selected for analysis.

All involved institutions approved this study of human subjects before initiating the survey. During the sample selection period, 335 subjects were eligible for participation and were interviewed pre- and postoperatively. Thirteen subjects died during the five-year follow-up, and several subjects were excluded from analysis due to loss of contact (change of address or refusal to participate). In total, 131 subjects participated in the preoperative and (five) postoperative assessments in this study.

Instruments and measurements

Each subscale of the Chinese version of SF-36 (SF-36) was used to measure HRQoL, and each was analysed as a dependent variable in this study. The SF-36 is widely used for profiling generic HRQoL and enables comparison of patients with different diseases and across different countries [2]. The SF-36 includes 36 items measuring physical function (PF), role limitations due to physical function (RP), bodily pain (BP), general health perceptions (GH), vitality (energy/fatigue) (VT), social function (SF), role limitations due to emotional functioning (RE), and general mental health perceptions (MH). The assessment results of each SF-36 subscale are converted to values on a 0–100 scale with a higher score indicating better HRQoL [8].

To compare the overall physical and mental function of the study population with the general Taiwan population, physical component summary scores (PCS) and mental component summary scores (MCS) were calculated by norm-based scoring methods [9] and used as dependent variables. Based on a previous study [10], the PCS and MCS were computed in comparison with the general population of Taiwan. Values below 50 indicated that the examined PCS or MCS were below the average values for the general Taiwan population, and vice versa.

Information related to THR outcomes derived from medical records and questionnaire interviews included age, gender, marital status, educational level, number of comorbidities, duration of hip symptoms, previous arthroplasty, principal diagnosis, pain and physical function components (44 and 46 points, respectively) of the modified Harris hip score (HHS) obtained by the physician immediately before surgery, specific orthopaedic surgeons, operation time, implant fixation, type of prosthesis and anaesthesia, readmission within 30 days postsurgery, average length of hospital stay, and complications. These covariates (collected from the chart review and questionnaire interview) were selected and tested as independent variables.

Statistical analysis

The unit of analysis in this study was the individual THR patient. First, descriptive statistics were tabulated to depict the THR patient demographics. Longitudinal data were characterised by repeated observations of the same subjects with a high variability between subjects but low variability within subjects [11]. High correlation within subjects meant that longitudinal relationships could not be analysed by ordinary regression methods, which assume independence of observations. The GEE approach was developed to correct for repeated outcomes within the same subject [11].

By using data from more than two time points, the autoregressive GEE analysis was employed for longitudinal associations.

For model building, multiple regression was first used to explore the best predictors of HRQoL at different time points when using the preoperative measures as the baseline. The application modelled dependent variables (mean value of each SF-36 subscale) as a function of time and effect predictors. These significant independent variables were further included in the longitudinal analysis. Restated, these effective predictive variables were included in the GEE approach as covariates because they were statistically significant in the multi-variable models and are also considered consistent predictors of HRQoL in much of the literature [11, 12]. The GEE procedure under XT gee in Stata, version 8.0 (StataCorp, College Station, Texas USA), was employed for statistical analyses in this study.

Results

Descriptive statistics

Subjects who remained in the study throughout the five-year period and those who were lost to follow-up between the second and fifth years after discharge did not statistically differ in age, gender, previous arthroplasty experience, number of comorbidities, operating time, implant fixation, type of anaesthesia, readmission within 30 days, or in any of the aforementioned preoperative HRQoL parameters (data not shown). Table 1 shows the characteristics of the study sample.

Longitudinal changes in HRQoL

Table 2 shows the mean value, standard error, and *p* value of each SF-36 subscale for the THR patients at each time point after adjusting for age and gender. Other than general health, vitality, and mental health, the subjects significantly improved in all SF-36 subscales between the preoperative period and the sixth month after discharge ($P<0.01$) and then remained stable for the rest of the five-year period. When using the sixth month after discharge as the baseline, the scores for physical function, physical role, bodily pain, vitality, and social function at the first year after discharge improved significantly ($P<0.05$), and all subscales continued to improve throughout the follow-up period.

The PCS improved significantly from the preoperative period until the fifth year after discharge. The MCS improved remarkably from the preoperative period until the sixth month after discharge; however, when setting the

Table 1 Baseline patient characteristics in study sample ($N=335$)

Variables	<i>n</i>	%
Patient attributes		
Age ^a (y)	59.82±14.71	
Gender	Male	190 56.72
	Female	145 43.28
Marital status	Married	304 90.75
	Other	31 9.25
Education level	Below elementary	123 36.72
	Elementary	117 34.92
	High school or above	95 28.36
Number of comorbidities ^a	0.61±0.46	
Duration ^a (mo)	40.31±30.48	
Previous arthroplasty	No	262 78.20
	Yes	73 21.80
Principal diagnosis	Avascular necrosis	126 37.61
	Osteoarthritis	175 52.24
	Other	34 10.15
Harris hip score: postoperative pain ^a	18.15±8.55	
Harris hip score: preoperative physical function ^a	22.31±9.15	
Hospital attributes		
Physician	Surgeon A	192 57.31
	Surgeon B	143 42.69
Operating time ^a (minutes)	140.48±30.70	
Cement type	Cementless	320 95.52
	Cemented	15 4.48
Prosthesis brand	Zimmer	97 28.95
	Corin	167 49.85
	Other	71 21.20
Anaesthesia type	General	178 53.13
	Spinal/epidural	157 46.87
Quality of care		
Readmission within 30 days	No	329 98.21
	Yes	6 1.79
Average length of stay ^a (days)	7.89±2.29	

^a Mean ± standard deviation

sixth month after discharge as the baseline, the MCS at the first year after discharge did not differ significantly (sixth month versus first year = 55.37 and versus baseline = 55.04, $P=0.76$). The PCS performed worse than the norm after THR. The gap in the PCS between the study sample and the general population narrowed from the third month to the fifth year after discharge.

Results of GEE analysis

Table 3 shows the results of multivariate analysis of the effective predictors of HRQoL in THR patients. Each time point was significantly related to the SF-36 subscales

Table 2 Mean value, standard error, and *P* value for each SF-36 subscale measured at varying time points^a

SF-36	Time (mean ± standard error)					
Subscale	Preoperative (n=335)	Third month (n=309)	Sixth month (n=301)	First year (n=266)	Second year (n=206)	Fifth year (n=182)
PF	39.81±3.94	60.41±1.98**	69.61±1.87**	78.72±1.97**	80.89±2.27	87.85±1.78**
RP	12.17±5.91	39.32±2.87**	48.35±3.06**	64.45±3.18**	78.04±3.24**	90.28±2.47**
BP	42.28±1.29	47.85±0.78**	48.42±0.72*	49.25±0.82*	49.54±0.71	49.84±0.63
GH	52.05±3.17	61.71±1.60**	64.01±1.69	66.79±1.70	69.43±1.81	79.85±1.57**
VT	56.21±3.26	66.88±1.43**	67.68±1.52	70.76±1.49*	71.43±1.83	82.94±1.71**
SF	60.88±3.75	66.61±1.60**	74.89±1.59**	81.51±1.67**	88.70±1.91**	94.99±1.66**
RE	43.64±6.11	77.42±3.29**	85.73±3.40**	88.29±3.32	89.95±3.51	95.10±3.21*
MH	61.95±2.67	71.48±1.21**	72.64±1.24	72.85±1.26	74.44±1.59	83.13±1.62**
PCS	25.76±1.51	30.42±0.75**	33.64±0.75**	37.69±0.77**	39.89±0.84**	43.29±0.63**
MCS	47.71±1.53	54.02±0.76**	55.04±0.79*	55.37±0.77	55.99±0.87	59.93±0.87**

PF physical function, RP role physical, RE role emotional, SF social function, BP bodily pain, VT vitality, MH mental health, GH general health, PCS physical component summary score, MCS mental component summary score

P*<0.05; *P*<0.01

^a *P* value denotes significant differences between each time point and baseline

throughout the five years (*P*<0.01). After controlling for related variables, older age revealed associations with interference with normal activity due to pain and loss of physical and social functions during the five years after discharge. Additionally, males scored higher than females

in physical function, physical role, vitality, mental health, general health, and PCS. Increased numbers of comorbidities were associated with poorer performance in social function, bodily pain, and general health. Subjects with higher preoperative scores in both pain and physical

Table 3 Multivariable analysis of effective predictors of HRQoL in total hip replacement patients over a five-year period^a

Variables ^b	PF	RP	RE	SF	BP	VT	MH	GH	PCS	MCS
Intercept	32.97**	15.00**	26.01**	59.32**	42.62**	34.39**	49.28**	37.66**	18.82**	42.44**
Time										
Third month	20.59**	28.84**	38.85**	16.78**	3.51**	10.29**	8.49**	11.62**	7.25**	6.85**
Sixth month	29.81**	37.89**	47.20**	25.07**	4.10**	11.14**	9.67**	13.96**	10.49**	7.87**
First year	38.89**	53.97**	49.83**	31.64**	4.91**	14.26**	9.91**	16.75**	14.52**	7.89**
Second year	40.80**	67.37**	51.63**	38.39**	5.25**	15.13**	11.62**	19.31**	16.62**	8.90**
Fifth year	48.51**	79.41**	56.70**	44.38**	5.58**	26.73**	20.33**	29.65**	19.93**	12.84**
Patient attributes										
Age	-0.15**	-0.01	-0.06	-0.14**	-0.04*	0.01	0.02	-0.01	-0.03	-0.01
Gender	3.49**	4.23	1.98	-0.20	0.51	2.75**	3.58**	2.92*	1.41**	0.44
Comorbidity	-0.06	-1.01	-1.09	-1.29*	-0.93**	-0.75	-0.88	-1.78**	-0.03	-0.68
Preop pain score	0.01	0.15	0.35**	0.02	0.07**	0.11	0.06	0.11*	0.02	0.07*
Preop physical function score	0.43**	0.48**	0.09	0.27**	0.06**	0.11	0.04	0.14**	0.16**	0.01
Hospital attributes										
Surgeon	-0.52	2.37	3.42	-6.81**	0.17	7.65**	4.72**	2.00	-0.26	1.68**
Anaesthesia	5.03**	5.52*	1.35	2.37	0.59	3.99**	2.72**	3.49**	1.85**	0.94
Quality of care										
Rehosp_30	-23.35**	-10.23	-23.52	-16.58**	-3.70**	-5.32**	-4.26	-9.55	-7.15	-3.18

PF physical function, RP role physical, RE role emotional, SF social function, BP bodily pain, VT vitality, MH mental health, GH general health, PCS physical component summary score, MCS mental component summary score, Comorbidity number of comorbidities, Pre-op pain score preoperative pain element of Harris hip score, Pre-op physical function score preoperative physical function element of Harris hip score, Rehosp_30 Readmission within 30 days

^a *P* value denotes the significance of differences between each time point and baseline

^b Gender: 0=female, 1=male; Physician: 1 = surgeon A, 2 = surgeon B; Type of anaesthesia: 1 = general anaesthesia, 2 = spinal or epidural anaesthesia; Readmission within 30 days: 0 = no, 1 = yes

P*<0.05; *P*<0.01

function of HHS scored higher in most SF-36 subscales, PCS, and MCS throughout the five years.

Further, patients treated by surgeon B scored higher in vitality, mental health, and MCS than those treated by surgeon A. However, patients treated by surgeon A scored higher in social functioning than those treated by surgeon B. Regarding type of anaesthesia, subjects who had received epidural or spinal anaesthesia scored higher in physical and social function, vitality, mental health, general health, and PCS than those who had received general anaesthesia. Additionally, subjects who had been readmitted within 30 days scored lower in bodily pain, vitality, mental health, and MCS throughout the five-year period of the study.

Discussion

This study demonstrated that, for each HRQoL dimension, the agreement between a continuous time model and a categorical time model was very similar to that observed using the GEE approach. That is, the results would be similar when predicting changes in HRQoL by using either continuous time variables or categorical time variables in the GEE model.

To elucidate trends in HRQoL over time, survey information was analysed by using the categorical time variable adjusted for age and gender. The regression models indicated that performance in the SF-36, PCS, and MCS subscales improved significantly during the first three months after discharge ($P < 0.01$) and continued improving for the following five years. These statistical results revealed varying trends in the performance of each SF-36 subscale according to the complexity and the involvement of the lower extremities.

This study illustrates that age is independently predictive of THR health outcomes, which is consistent with reports that older patients exhibit less improvement than younger patients in bodily pain and physical and social function [3, 7]. Although such studies also indicate that older patients tend to have more comorbidities and less social support, the number of comorbidities is a controlled variable in the GEE models. Rather, the observed improvement in health outcomes may reflect selection bias in that referring physicians may apply selection criteria more stringently based on patient characteristics associated with increased likelihood of improvement. Alternatively, because pain and physical functions are the main goals of hip replacement surgery, optimal health outcomes are emphasised in younger patients. Further study is needed to address these questions.

This study also confirmed the previously identified gender difference in preoperative HRQoL [3]. Although females had significantly poorer physical function, more role limitations due to physical problems, and poorer

vitality, mental health, and general health than did males, no gender differences were noted in role limitations due to emotional problems, social functioning, or bodily pain after THR. Females tended to be more averse to surgery and more concerned about burdening their families [13]. However, studies performed elsewhere report no evidence of gender-associated risk aversion and have cited referral bias as a potential barrier to access [14]. The Taiwan population examined in our study, however, revealed a gender difference in self-reported HRQoL as measured by the SF-36 [10]. Males scored higher in each SF-36 subscale than did females. However, it is unclear whether this difference reflects gender bias in subject response or truly poorer HRQoL due to increased prevalence of osteoarthritis or other medical conditions in the sampled females. Nevertheless, the gender differences noted here were considerably larger than the potential bias in gender response in the Taiwan population.

Notably, increased incidence of comorbidities was associated with lower HRQoL with respect to pain function and general health, which is consistent with previous reports that increased number of comorbidities is strongly associated with poor functional status after THR [3, 15].

Further, the analytical results suggest that patients who had received spinal or epidural anaesthesia had better outcomes than those who had received general anaesthesia. Generally, the duration of surgery in patients who had received spinal and epidural anaesthesia was shorter than that in patients who had received general anaesthesia, which is consistent with a previous report [16]. Additionally, patients readmitted within 30 days after surgery exhibited poorer performance in pain function, vitality, and mental health than their counterparts.

A final interesting finding is that, over the five-year period of the study, the single best predictor in each SF-36 subscale was preoperative health status, which is consistent with reports that the best predictors of postoperative HRQoL are preoperative pain and physical functions scores [3]. As this issue has been addressed elsewhere [6], data from a randomised trial comparing early and delayed THR surgery would be of great value to clinicians when selecting the optimal timing of surgery. Table 3 summarises the baseline significance of predictive factors identified in this study and their subsequent associations with HRQoL.

Although all research questions were adequately and satisfactorily addressed, several limitations are noted. First, this study collected data from primary THR patients under the supervision of two surgeons in two different medical centres, each of whom performed the highest volume of THR procedures in their respective hospitals. Such a sample selection procedure ensures that the limited experience of surgeons does not significantly influence patient outcomes [17, 18]. By focussing the analysis on these two

orthopaedic surgeons, the results of this study are more representative of all THR patients than one analysing a single surgeon. However, a notable limitation is that, in the prospective patient cohort, the first patient was enrolled in 1998. Therefore, depending on their inclusion date, some surveyed patients had a longer follow-up than others, which may have caused selection bias. Nonetheless, in most SF-36 subscales, subjects who continuously participated in the study throughout the five years did not statistically differ from those who died or dropped out during the observation period of the study (data not shown).

In conclusion, when evaluating HRQoL after THR, several factors other than the surgery itself should be considered. All predictors analysed in this study could be addressed in preoperative consultations and during postoperative health care and can help educate THR candidates awaiting surgery as to the expected course of recovery and functional outcomes. Additionally, patients should be advised that their postoperative HRQoL might depend not only on the success of their hip operations but also on their preoperative health status. The analytical results should be applicable to other Taiwan hospitals as well as other countries with similar social and cultural practices.

References

1. Glazebrook M, Daniels T, Younger A, Foote CJ, Penner M, Wing K, Lau J, Leighton R, Dunbar M (2008) Comparison of health-related quality of life between patients with end-stage ankle and hip arthrosis. *J Bone Joint Surg Am* 90:499–505
2. Shi HY, Chiu HC, Chang JK, Wang JW, Culbertson R, Khan MM (2008) Evaluation and prediction of health-related quality of life for total hip replacement among Chinese in Taiwan. *Int Orthop* 32(1):27–32
3. Ethgen O, Bruyère O, Richy F, Dardennes C, Reginster JY (2004) Health-related quality of life in total hip and total knee arthroplasty. A qualitative and systematic review of the literature. *J Bone Joint Surg Am* 86(5):963–974
4. Kennedy DM, Hanna SE, Stratford PW, Wessel J, Gollish JD (2006) Preoperative function and gender predict pattern of functional recovery after hip and knee arthroplasty. *J Arthroplasty* 21(4):559–566
5. Tien WC, Kao HY, Tu YK, Chiu HC, Lee KT, Shi HY (2008) A population-based study of prevalence and hospital charges in total hip and knee replacement. *Int Orthop*. [Epub ahead of print]
6. Fortin PR, Penrod JR, Clarke AE, St-Pierre Y, Joseph L, Bélisle P, Liang MH, Ferland D, Phillips CB, Mahomed N, Tanzer M, Sledge C, Fossel AH, Katz JN (2002) Timing of total joint replacement affects clinical outcomes among patients with osteoarthritis of the hip or knee. *Arthritis Rheum* 46:3327–3330
7. Nilsdotter AK, Lohmander LS (2002) Age and waiting time as predictors of outcome after total hip replacement for osteoarthritis. *Rheumatology* 41:1261–1267
8. Ware JE (1993) SF-36 health survey: manual and interpretation guide. The Health Institute, New England Medical Center, Boston
9. Ware JE, Kosinski MK, Keller SD (1994) SF-36 physical and mental health summary scales: a user's manual. The Health Institute, New England Medical Center, Boston
10. Huang IC, Wu AW, Frangakis C (2006) Do the SF-36 and WHOQOL-BREF measure the same constructs? Evidence from the Taiwan population. *Qual Life Res* 15(1):15–24
11. Hardin JW, Hilbe JM (2003) Generalized estimating equations, 2nd edn. Chapman & Hall/CRC, Boca Raton, FL, USA
12. Welsing PM, Landewé RB, van Riel PL, Boers M, van Gestel AM, van der Linden S, Swinkels HL, van der Heijde DM (2004) The relationship between disease activity and radiologic progression in patients with rheumatoid arthritis. *Arthritis Rheum* 50(7):2082–2093
13. Karlson EW, Daltroy LH, Liang MH, Eaton HE, Katz JN (1997) Gender differences in patient preferences may underlie differential utilization of elective surgery. *Am J Med* 102(6):524–530
14. Hawker GA, Wright JG, Coyte PC, Williams JI, Harvey B, Glazier R, Badley EM (2000) Differences between men and women in the rate of use of hip and knee arthroplasty. *New Engl J Med* 342(14):1016–1022
15. Bischoff-Ferrari HA, Lingard EA, Losina E, Baron JA, Roos EM, Phillips CB, Mahomed NN, Barrett J, Katz JN (2004) Psychosocial and geriatric correlates of functional status after total hip replacement. *Arthritis Rheum* 51(5):829–835
16. Småbrekke A, Espehaug B, Havelin LI, Furnes O (2004) Operating time and survival of primary total hip replacements. *Acta Orthop Scand* 75(5):524–532
17. Katz JN, Phillips CB, Baron JA, Fossel AH, Mahomed NN, Barrett J, Lingard EA, Harris WH, Poss R, Lew RA, Guadagnoli E, Wright EA, Losina E (2003) Association of hospital and surgeon volume of total hip replacement with functional status and satisfaction three years following surgery. *Arthritis Rheum* 48(2):560–568
18. Solomon DH, Losina E, Baron JA, Fossel AH, Guadagnoli E, Lingard EA, Miner A, Phillips CB, Katz JN (2002) Contribution of hospital characteristics to the volume-outcome relationship. *Arthritis Rheum* 46(9):2436–2444