BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-017455
Article Type:	Research
Date Submitted by the Author:	23-Apr-2017
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Primary Subject Heading:	Mental health
Secondary Subject Heading:	Global health
Keywords:	liver transplantation, posttraumatic growth, quality of life, patients, caregivers

Posttraumatic growth and quality of life up to more than nine years after liver transplantation: a cross-sectional study

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Word count (excluding title page, abstract, references, figures and tables): 3062

Abstract

Objective: Little is known concerning posttraumatic growth after liver transplantation. Against this backdrop the current study compared the degree of posttraumatic growth (PTG) between liver transplant recipients and their caregivers, and analysed the influence of PTG and time since transplantation on quality of life.

Design: Cross-sectional case control study.

Setting: University Hospital in Spain.

Participants: 240 adult liver transplant recipients, having undergone only one transplantation, without severe mental disease. In 216 of these recipients the most important caregiver was also investigated. Moreover results were compared to a previously recruited general population sample.

Outcome measures: All participants completed the Posttraumatic Growth Inventory, additionally recipients filled in the 12-Item Short-Form Health Survey and relevant socio-demographic and clinical parameters were assessed.

Results: Liver transplant recipients compared to their caregivers showed a higher degree of total PTG ($p<0.001$) and higher scores on the subscales relating to others ($p<0.001$), new possibilities ($p<0.001$), and appreciation of life ($p<0.001$). Furthermore, longer duration since transplantation (>9 years) was associated with more pain symptoms ($p=0.026$). Regardless of duration recipients showed lower scores on most quality of life dimensions compared to the general population. However, a high degree of PTG was associated with higher scores on all quality of life dimensions even though this difference was largely non-significant except for the dimension vitality ($p=0.021$). In recipients with high posttraumatic growth specific quality of life dimensions such as bodily pain ($p=0.307$), vitality ($p=0.890$), and mental health ($p=0.353$) even equaled scores in the general population, whereas scores on general health surpassed them ($p=0.006$).

Conclusions: Our findings highlight the protective role of PTG in long-term outcome of liver transplant recipients. Future studies should analyse and develop psychosocial interventions to strengthen posttraumatic growth in transplant recipients and their caregivers.

Strengths and limitations of this study

- First study on posttraumatic growth in liver transplant recipients and their caregivers.

- Investigation of a large sample of 240 organ recipients up to 9 years after transplantation.

- Assessment of medical complications in the immediate post-transplant period.

- Assessment of the impact of posttraumatic growth on quality of life in liver transplant recipients.

- Unilateral cross-sectional study at a University Hospital in Spain.

INTRODUCTION

Terminal liver disease is associated with severe physical and psychological decline.[1] The best medical option is a liver transplantation which provides longer survival and better quality of life.[2-4] However, even after liver transplantation quality of life often remains below levels found in the general population,[5] because acute and chronic graft rejection, recurrence of liver disease or secondary effects of immunosuppressants, are very stressful complications for patients and their families,[6-8] which may lead to the development of psychological disorders.[9-11]

Under these circumstances posttraumatic growth can be regarded as a protective factor,[12,13] which enables patients to reframe threats into challenges thereby strengthening their psychological wellbeing.[14,15] Previous studies found high levels of posttraumatic growth after lung transplantation,[6] which were even higher than those observed in patients suffering from chronic heart disease, cancer or HIV. High levels of posttraumatic growth have also been found after hematopoietic stem cell transplantation (HSCT).[16] To the best of our knowledge there are only two previous studies dealing with posttraumatic growth in liver transplant recipients.[14,15] These studies aimed at investigating implications of posttraumatic growth for affective regulation. Posttraumatic growth is also highly relevant for close relatives, particularly caregivers, of the liver transplant recipient, who is life-long depending on medical care and intensive social support. In this situation the caregiver is confronted with the deep impact of liver transplantation on his or her personal life and its challenging implications.[11,17]

Even though posttraumatic growth is thought to contribute to wellbeing and quality of life after transplantation, not all previous studies found a significant positive association between both variables (e.g. Fox et al.).[6] Against this backdrop we intended to clarify this association in liver transplant recipients. Given the importance of this subject in clinical practice, we decided to compare posttraumatic growth of liver transplant recipients and their caregivers, and, analyse the relationship between different levels of posttraumatic growth and quality of life. First, we hypothesized that as shown in previous studies regardless of the time elapsed since transplantation,

posttraumatic growth is significantly higher in recipients compared to their caregivers.[18-20] Secondly we hypothesized that recipients' quality of life is significantly influenced by the time-span since transplantation as well as the level of posttraumatic growth in the sense that longer duration since transplantation and lower levels of posttraumatic growth are associated with lower quality of life.

METHODS

Participants

A group of 240 liver transplant recipients was selected consisting of 185 men and 55 women with a mean age of 60.21±9.30 years. 61.7%, 22.5% and 15.8% had a low, intermediate and high formal education, respectively. 79.2% of participants were in a partnership. The mean number of immediate post-transplant complications as measured by several medical and laboratory parameters was 4.47±2.06. From the group of 240 recipients a subsample (Figure 1) of 216 recipients and 216 family members (the main caregiver of respective patient) could be recruited. The group of caregivers consisted of 48 men and 168 women with a mean age of 53.19±12.56 years. 88.9% were in a partnership and 54.6%, 22.7% and 22.7% had low, intermediate and high formal education, respectively. The type of family relationship with the recipient was as follows: partner (71.3%), child (19.4%), sibling (4.2%), parent (3.7%) and other (1.4%).

In addition, quality of life of liver transplant patients was compared with a general population sample recruited in a previous study.[21]

Measurements

Medical and laboratory parameters

The medical and laboratory parameters refer to the 16 complications described in Table 1. Most of the measurements were done in the immunology laboratory and all of them refer to the immediate post-transplant period. The score on each of these parameters was summed up to provide

an objective measure of the patients' state of health after transplantation. The total score varied from 0 to 16.

Table 1. Medical and laboratory parameters of liver transplant patients in immediate post-transplant period.

	Presence	Absence	Data unavailable
1. Post-surgery hemorrhaging	24	213	3
2. Cytomegalovirus	211	24	5
3. Epstein Barr virus	198	29	13
4. Bacterial infections	87	151	2
5. Viral infections	17	220	3
6. Fungal infections	7	230	3
7. Acute graft rejection	47	190	3
8. Vascular complications	7	230	3
9. Biliary complications	27	211	2
10. Respiratory complications	49	187	4
11. Refractory ascites	43	195	2
12. Neurological complications	43	194	3
13. Hemodynamic complications	47	189	4
14. Renal complications	119	119	2
15. Hematologic complications	85	149	6
16. Re-operations	29	209	2

Posttraumatic Growth

The Posttraumatic Growth Inventory (PTGI) [12] consists of 21 items answered on a Likert-scale ranging from 0 ("no change") to 5 ("very great degree of change") thereby evaluating the perception of personal benefits in survivors of traumatic events. Test interpretation provides a total score of posttraumatic growth and the following five subdimensions: relating to others, new possibilities, personal strength, spiritual change, and appreciation of life. We used the Spanish version provided by Weiss and Berger.[22] For patients in this study, the Cronbach's alpha was 0.94 for the sum scale and ranged from 0.73 to 0.88 for the subscales. For caregivers, the Cronbach's alpha was 0.95 for the total scale and ranged from 0.77 to 0.90 for the different subscales.

Quality of life

The 12-Item Short Form Health Survey (SF-12v.2) [23,24] consists of 12 items with either 3 or 5-point Likert-scales. It evaluates the following eight dimensions of health-related quality of life: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. The score on each dimension varies from 0 (worst state of health) to 100 (best state of health). The reliability of the eight scales varies from 0.67 to 0.93.[23]

Procedure

After receiving Institutional Review Board approval, we recruited patients and family members from a clinical population of 1053 adult patients who had received a liver transplant at the Virgen del Rocío University Hospital in Seville from 1990 to 2014 (Figure 1). At the beginning all 569 patients still alive as well as their main caregivers were informed about the possibility of study participation by the Association of Liver Transplant Recipients and the Hepatic-Biliary-Pancreatic Surgery and Liver Transplant Unit. Inclusion criteria for both groups were: a) over 18 years of age, b) informed consent, c) no difficulties in understanding the evaluation instruments, d) no severe or disabling psychopathological condition, and e) reception of only one transplant. Thus, 240 recipients could be included in the study of whom 216 participated together with their caregiver. All

patients and their caregivers were evaluated with the PTGI.[12,22] Patient quality of life was evaluated with the SF-12v.2,[23,24] and other target parameters (medical and laboratory) were also collected to assess state of health in the immediate post-transplant period.

Statistical analysis

The data were analyzed with the SPSS 22 statistics program. A Pearson's chi-squared test was used to compare qualitative variables (gender, marital status and education) in the various patient subgroups, and for quantitative variables (age and post-transplant complications), a one-way ANOVA with the Tukey HSD test for post-hoc comparisons was calculated. A 2x3 mixed factorial ANOVA was performed to evaluate the influence of group factors (liver transplant recipients and caregivers) and time elapsed since transplantation (less, medium, more) on posttraumatic growth. And a 3x3 factorial ANOVA was calculated to analyze the influence of time since transplantation (less, medium, more) and posttraumatic growth level (low, medium, high) on quality of life. Cohen's *d* (for quantitative variables) and Cohen's *w* (for qualitative variables) were computed for effect size.

RESULTS

Posttraumatic growth

The sample of 216 liver transplant recipients, who could be investigated together with their caregiver, was divided on the basis of time elapsed since transplantation in three subgroups of equal size: 73 patients ≤3.5 years (33.8%), 71 patients from >3.5 to ≤9 years (32.9%), and 72 patients with >9 years (33.3%). There were no significant differences between these subgroups concerning gender (p=0.128, w=0.14), marital status (p=0.753, w=0.05), education (p=0.683, w=0.10), or medical complications in the immediate post-transplant period (p=0.164). There were significant differences with regard to age (56.37±9.18 vs. 60.44±7.65 vs. 64.35±9.37; p<0.001).

There was no significant effect of group and time since transplantation on posttraumatic growth (F=0.196, p=0.822; Table 2, Figure 2). Concerning main effects, time elapsed since

transplantation did not influence posttraumatic growth. However, patients showed significantly higher scores than their caregivers on total posttraumatic growth (p<0.001) as well as on the subdimensions relating to others (p<0.001), new possibilities (p<0.001), and appreciation of life (p<0.001).

Table 2. Posttraumatic growth: differences between liver transplant recipients (G1) and their caregivers (G2) by time since transplantation.

	Main effects		Interaction effects	Comparisons G1-G2 *p* (Cohen's *d*)			Comparisons time since transplantation *p* (Cohen's *d*)					
	Group	Time		Time since transplantation				G1 (n=216)			G2 (n=216)	
	$F_{(1,213)}$ (*p*)	$F_{(2,213)}$ (*p*)	$F_{(2,213)}$ (*p*)	Less a	Medium b	More c	a-b	a-c	b-c	a-b	a-c	b-c
Relating to others	23.081 (<0.001)	1.464 (0.234)	0.236 (0.790)	0.008 (0.32) S	0.020 (0.30) S	0.001 (0.46) S	1.000 (-0.02) N	0.270 (-0.29) S	0.369 (-0.27) S	1.000 (-0.05) N	0.908 (-0.17) N	1.000 (-0.12) N
New possibilities	33.157 (<0.001)	0.640 (0.528)	0.003 (0.997)	0.001 (0.36) S	0.001 (0.42) S	0.001 (0.45) S	1.000 (-0.03) N	0.987 (-0.16) N	1.000 (-0.14) N	1.000 (-0.02) N	1.000 (-0.14) N	1.000 (-0.12) N
Personal strength	0.001 (0.976)	0.424 (0.655)	0.744 (0.476)	0.425 (-0.10)	0.868 (-0.02)	0.365 (0.13)	1.000 (-0.10)	0.438 (-0.24)	1.000 (-0.14)	1.000 (-0.02)	1.000 (-0.01)	1.000 (0.01)

				N	N	N	N	S	N	S	N	N
Spiritual change	0.001	2.192	0.349	0.898	0.537	0.584	1.000	0.227	0.143	1.000	0.529	0.960
	(0.975)	(0.114)	(0.706)	(0.02)	(-0.08)	(0.07)	(0.04)	(-0.29)	(-0.37)	(-0.06)	(-0.22)	(-0.17)
				N	N	N	N	S	S	N	S	N
Appreciation of life	18.490	0.109	0.067	0.006	0.028	0.014	1.000	1.000	1.000	1.000	1.000	1.000
	(<0.001)	(0.897)	(0.935)	(0.37)	(0.33)	(0.35)	(-0.02)	(-0.02)	(0.00)	(-0.09)	(-0.06)	(0.03)
				S	S	S	N	N	N	N	N	N
Total posttraumatic growth	17.109	0.983	0.196	0.028	0.041	0.004	1.000	0.417	0.674	1.000	1.000	1.000
	(<0.001)	(0.376)	(0.822)	(0.25)	(0.26)	(0.38)	(-0.04)	(-0.24)	(-0.21)	(-0.05)	(-0.14)	(-0.09)
				S	S	S	N	S	S	N	N	N

G1=Liver transplant recipients, G2=Caregivers, N=Null effect size, S=Small effect size.

Quality of life

In a second step of analysis focusing on quality of life the total sample of 240 patients was divided on the basis of time elapsed since transplantation in above mentioned categories: 78 patients ≤3.5 years (32.5%), 82 patients from >3.5 to ≤9 years (34.2%) and 80 patients >9 years (33.3%). There were no differences between subgroups concerning gender (p=0.150, w=0.13), marital status (p=0.744, w=0.05), education (p=0.450, w=0.12) or immediate post-transplant complications (p=0.377). There were significant differences with regard to age (56.46±8.98 vs. 59.94±8.39 vs. 64.14±9.03; p<0.001).

In a further step of analysis, the sample of 240 patients was divided into three equally-sized subgroups on the basis of posttraumatic growth total score: 80 patients with a low level of posttraumatic growth (33.3%; 0 to 59 points), 80 patients with a medium level (33.3%; 60 to 77 points), and 80 patients with a high level (33.3%; 78 to 105 points). There were no significant differences between subgroups concerning age (p=0.506), gender (p=0.639, w=0.06), marital status (p=0.720, w=0.05), education (p=0.187, w=0.16) or post-transplant complications (p=0.443).

We found no significant effect of time since transplantation as well as posttraumatic growth level on quality of life (Table 3, Figures 3 and 4). Regarding main effects, time since transplantation showed a significant effect on the bodily pain dimension (p=0.017) in the sense that recipients after more than 9 years since transplantation showed more pain than after a medium duration of time (>3.5 and ≤9 years) (p=0.026, d=0.41). Furthermore, regarding recipients posttraumatic growth significantly influenced the dimension vitality, with high compared to medium posttraumatic growth being associated with significantly more vitality (p=0.021, d=-0.43) as well as a statistical trend towards higher scores on general health (p=0.067, d=-0.36), social functioning (p=0.085, d=-0.35), and role-emotional (p=0.093, d=-0.34) with small effect sizes.

Table 3. Quality of life: differences between liver transplant recipients by time since transplantation and patient posttraumatic growth levels.

	Main effects		Interaction effects
	Time	Posttraumatic growth	
	$F_{(2,231)}$ (p)	$F_{(2,231)}$ (p)	$F_{(4,231)}$ (p)
Physical functioning	1.199 (0.303)	0.694 (0.501)	1.438 (0.222)
Role-physical	0.866 (0.422)	1.273 (0.282)	0.848 (0.496)
Bodily pain	4.138 (0.017)	0.808 (0.447)	0.760 (0.552)
General health	1.669 (0.191)	3.706 (0.026)	0.564 (0.689)
Vitality	0.076 (0.927)	4.031 (0.019)	0.254 (0.907)
Social functioning	0.103 (0.902)	2.440 (0.089)	0.852 (0.494)
Role-emotional	0.538 (0.585)	2.370 (0.096)	1.395 (0.237)
Mental health	1.062 (0.348)	1.543 (0.216)	1.129 (0.344)

In addition, liver transplant patients showed lower quality of life compared to the Spanish general population regardless of the duration since transplantation even though a longer time-span increased the difference on most dimensions (Figure 3).

Taking posttraumatic growth into account liver transplant patients with lower levels of posttraumatic growth showed in general lower quality of life compared to the Spanish general population. However, a high level of posttraumatic growth was associated with smaller differences rendering the difference on the dimensions vitality (p=0.890, d=-0.02), mental health (p=0.353, d=-0.11), and bodily pain (p=0.307, d=-0.12) non-significant, even though the latter dimension showed a different pattern as it also showed a non-significant difference in the subgroup with low posttraumatic growth (p=0.142, d=-0.17). On the dimension general health, which already showed no significant differences with the general population in the subgroups with low (p=0.827, d=-0.03) or medium (p=0.926, d=-0.01) posttraumatic growth, it was even associated with significantly higher scores (p=0.006, d=0.33) (Figure 4).

DICCUSSION

To the best of our knowledge our study is the first to investigate the relationship between posttraumatic growth and quality of life in liver transplant recipients. In this context we were not only interested in the patient himself but also in the family support system as represented by the caregiver. We found that, regardless of time elapsed since transplantation recipients showed more posttraumatic growth than their caregivers. This result confirms our first hypothesis and is in keeping with findings in HSCT-recipients [18] and other cancer patients.[19,20] One might argue that the patients themselves have been directly exposed to traumatic events such as liver disease, transplant surgery, and side effects of immunosuppressants, which increases the activation of intrapersonal resources thereby leading to higher levels of posttraumatic growth. Furthermore, the liver transplantation symbolizes the beginning of a new life for the patient often after a long period of physical suffering and fear of death. This may be associated with a sense of gratitude towards the

deceased donor and the medical team and a feeling of personal responsibility to justify all these efforts, which in turn may mobilize a large amount of energy.[6,25]

Regarding specific aspects of posttraumatic growth as captured by subscales mainly the scales relating to others, new possibilities and appreciation of life proved to be relevant, which has also been found in previous studies.[16,25,26] Posttraumatic growth did not alter significantly in the course of time, a phenomenon also observed in breast cancer [27] and colorectal cancer patients.[28] This can be partially explained by the psychological construct of posttraumatic growth itself, which is defined by Tedeschi and Calhoun as follows: *"The phenomenon is complex, and cannot easily be reduced to simply a coping mechanism, a cognitive distortion, psychological adjustment or well-being, or a host of apparently similar constructs. The outcomes of posttraumatic growth might be best considered as iterative, and it will take longitudinal work to trace the varied trajectories of the posttraumatic growth process. This process is likely to involve a powerful combination of demand for emotional relief and cognitive clarity, that is achieved through construction of higher order schemas that allow for appreciation of paradox"* (p.15).[13] Thus, the process of posttraumatic growth is thought to be iterative thereby gradually constructing higher order schemas, which implicates rather small and slow alterations and relative stability over time. This is also reflected in the construction of the posttraumatic growth inventory, which asks to indicate for each of the statements the degree, to which this change occurred in life as a result of the crisis/disaster. The concrete formulation of a change in life in response to a specific disaster rather suggests a stable cognitive-behavioural pattern than a state sensitive to fluctuations.

Our hypotheses with respect to quality of life were partially confirmed, since neither time nor posttraumatic growth significantly influenced all dimensions of quality of life. Moreover, recipients compared to the general population showed significantly lower scores on most quality of life dimensions. One might argue in accordance with the above mentioned definition that posttraumatic growth does not immediately lead to higher quality of life as it mirrors the inner struggle to form a convincing narrative from existential paradoxes associated with life-threatening disease. We found

that merely the bodily pain dimension in the SF-12 was significantly influenced by the time since transplantation. This finding may be explained by the increase of imunosuppressants' side effects over time such as arthralgia and muskuloskeletal pain.[29,30] In addition our findings displayed particularly low levels of quality of life compared to the general population [5] after a post-transplantation time-span of over 9 years. In the long run the combination of medication side effects and restrictions from medical treatment such as diet and ongoing medical supervision may negatively affect recipients' quality of life.

A high level compared to a medium level of posttraumatic growth in recipients was associated with significantly greater scores on vitality, and a statistical trend towards greater scores on general health, social functioning and role-emotional. In recipients with high posttraumatic growth vitality scores even equaled scores in the general population. In general a high level of posttraumatic growth was associated with smaller differences between quality of life scores in recipients and the general population rendering the differences on bodily pain, vitality and mental health non significant and revealing even higher scores on general health. These findings highlight the potentially protective role of posttraumatic growth in liver transplant patients and they are in keeping with other studies which showed a positive association between posttraumatic growth and quality of life.[16,27] In line with the protective role of posttraumatic growth personality traits such as extraversion, optimism, and openness to experience have been positively associated with this psychological construct.[31]

From a clinical perspective the posttraumatic growth inventory could be used to identify those patients after liver transplantation, who are in special need of psychological support. Mindfulness-based stress reduction [32] and positive psychotherapy [33] have demonstrated their efficacy in augmenting posttraumatic growth in patients.

Our study shows several limitations. First, we did not analyse the influence of further clinical variables such as the etiology of liver disease [8] and personality variables such as specific coping strategies on posttraumatic growth.[34] Second, we did not assess long-term transplant-related

health parameters such as occurrence of infections, rehospitalizations and other complications. Third, recruitment of patients took place at a single site which may limit external validity of findings.

Nevertheless, the large sample size and the analysis of recipients and caregivers can be seen as a major strength of this study.

CONCLUSIONS

In summary, our study demonstrated that regardless of the time elapsed since liver transplantation, recipients showed more posttraumatic growth than their caregivers. A high level of posttraumatic growth had a positive impact on specific aspects of quality of life such as vitality, whereas a longer time span since transplantation had a negative impact on aspects such as pain. Compared to the general population, recipients showed in general a lower quality of life except for the fact that in patients with high levels of posttraumatic growth specific dimensions of quality of life such as bodily pain, vitality, mental health and general health equaled or even surpassed scores in the general population. Facilitation of posttraumatic growth after liver transplantation may be crucial to ensure long-term quality of life in recipients.

ACKNOWLEDGMENTS

The authors would like to thank all the participants (liver transplant patients and their family members).

CONTRIBUTORS

MÁPSG and AMR: Study concept and design, data analysis and interpretation, drafting of manuscript, manuscript revisions, and drafting figures. MBM and MLAN: Study concept and design, critical revision of article. JPB: Institutional support, data collection, critical revision of

article. RC and MÁGB: Data analysis and interpretation, drafting of manuscript, critical revision of article. All authors gave final approval to the version submitted for publication.

FUNDING

This study was funded by the Spanish Ministry of Economy and Competitiveness (Project PSI2014-51950-P).

COMPETING INTERESTS

None declared.

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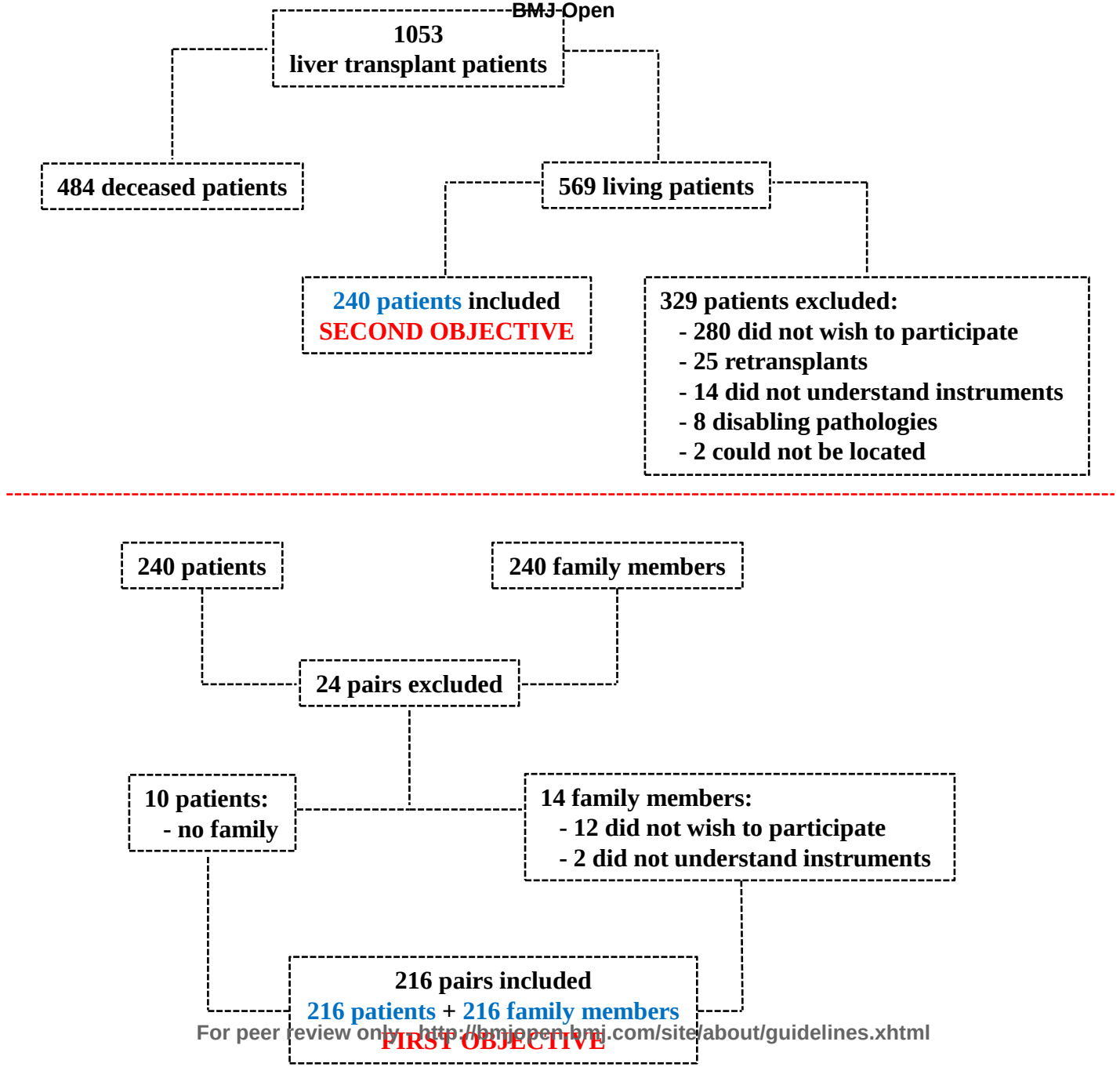
FIGURES

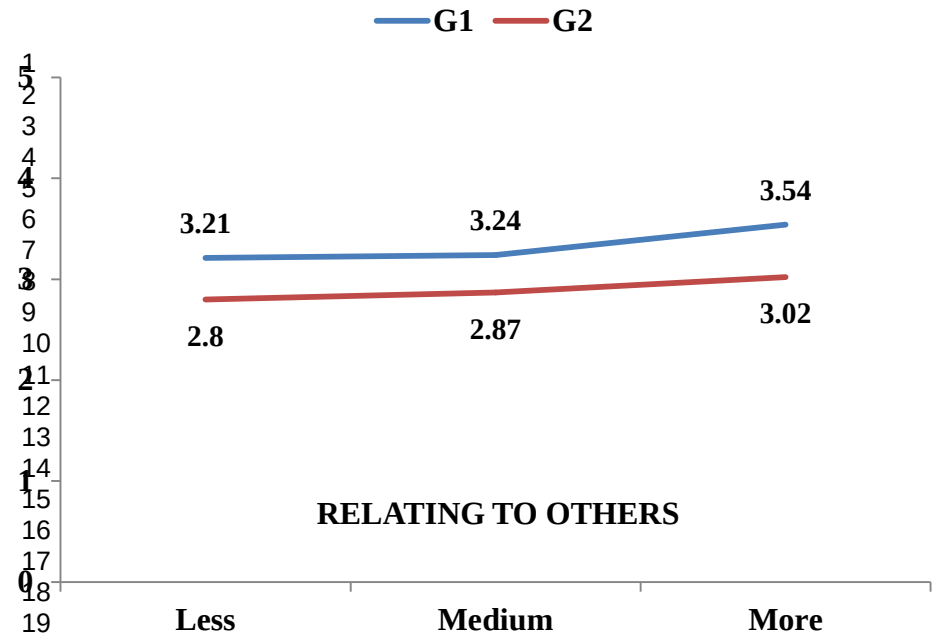
Figure 1. Participant selection process for the study's two objectives.

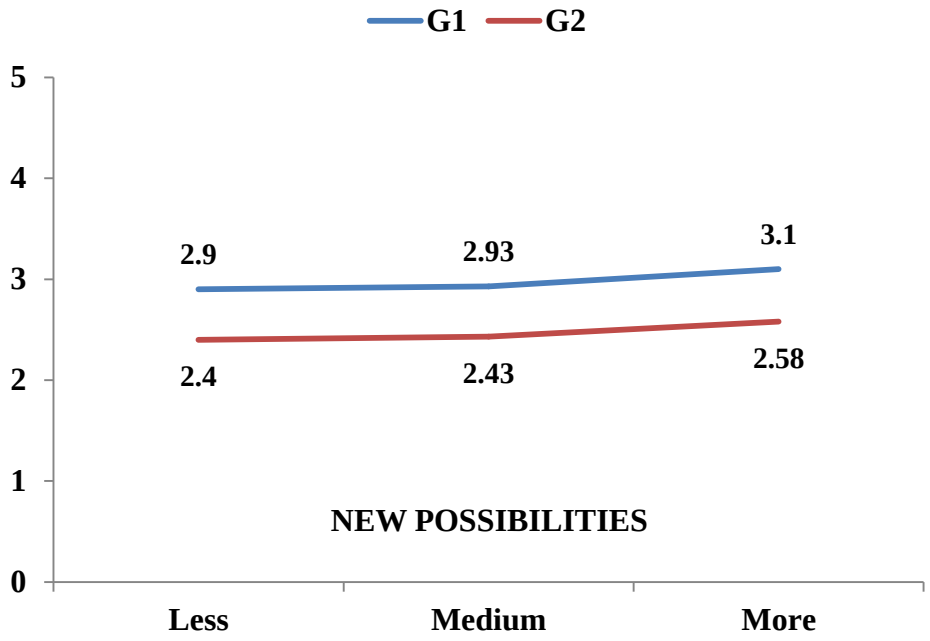
Figure 2. Posttraumatic growth: mean scores on variables with statistically significant differences between the two groups. Higher scores show more growth. G1=Liver transplant recipients, G2=Caregivers.

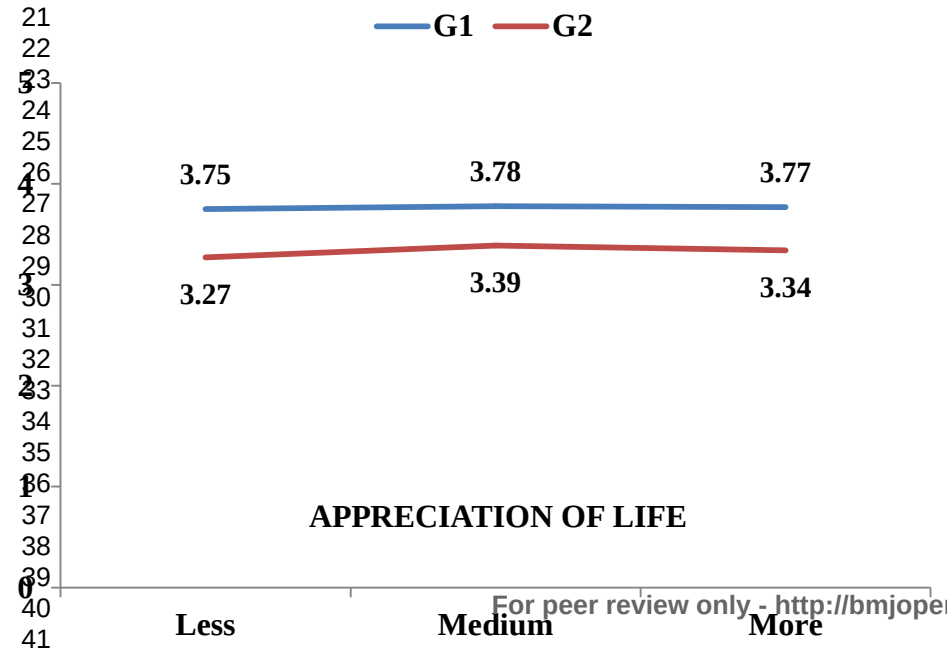
Figure 3. Influence of time since transplantation on patient quality of life. Comparison with General Spanish population. Lower mean scores show worse quality of life. N=Null effect size, S=Small effect size, M=Medium effect size, L=Large effect size, GSP=General Spanish population.

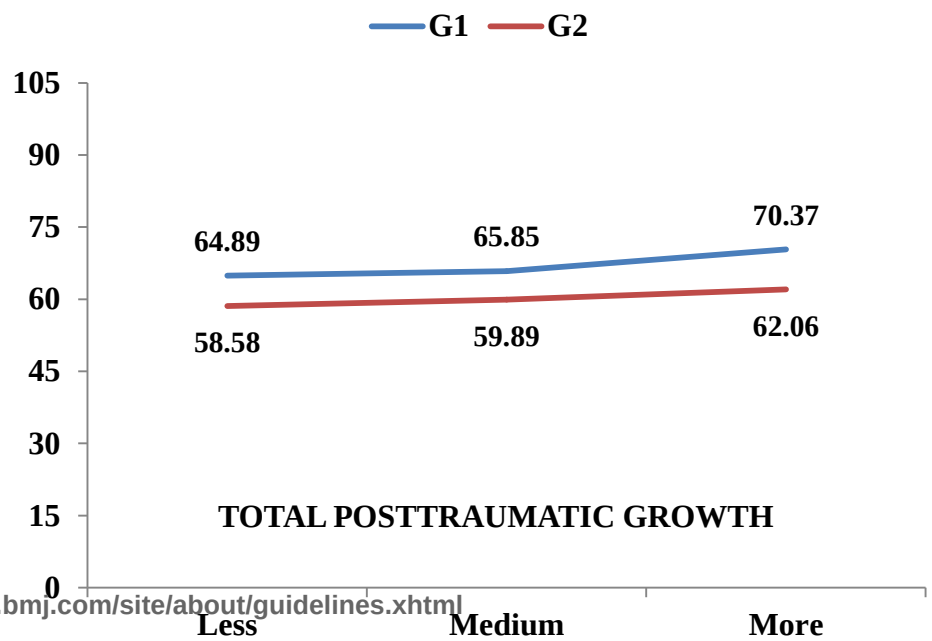
Figure 4. Influence of posttraumatic growth level on patient quality of life. Comparison with General Spanish population. Lower mean scores show worse quality of life. N=Null effect size, S=Small effect size, M=Medium effect size, L=Large effect size, GSP=General Spanish population.

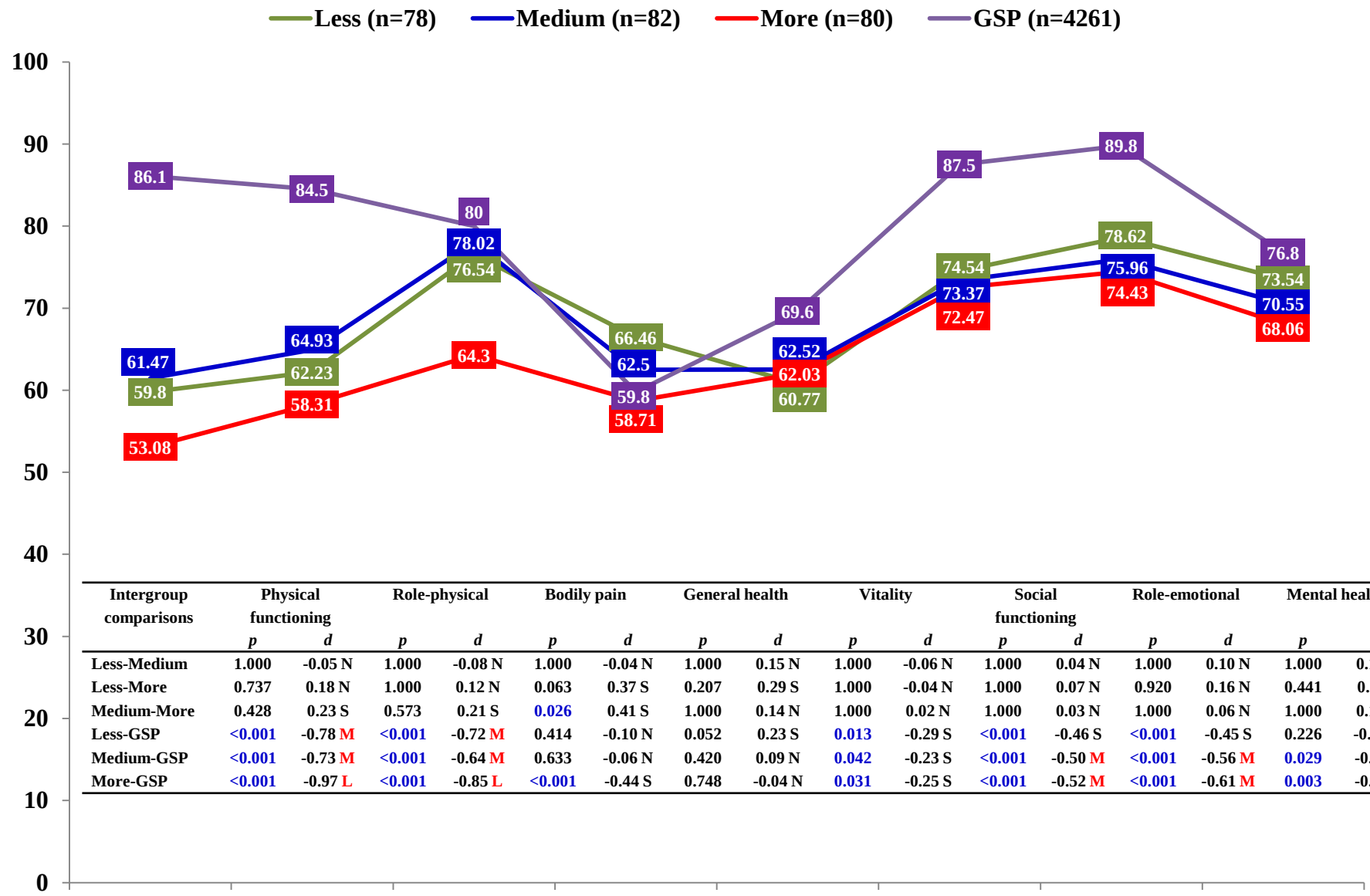




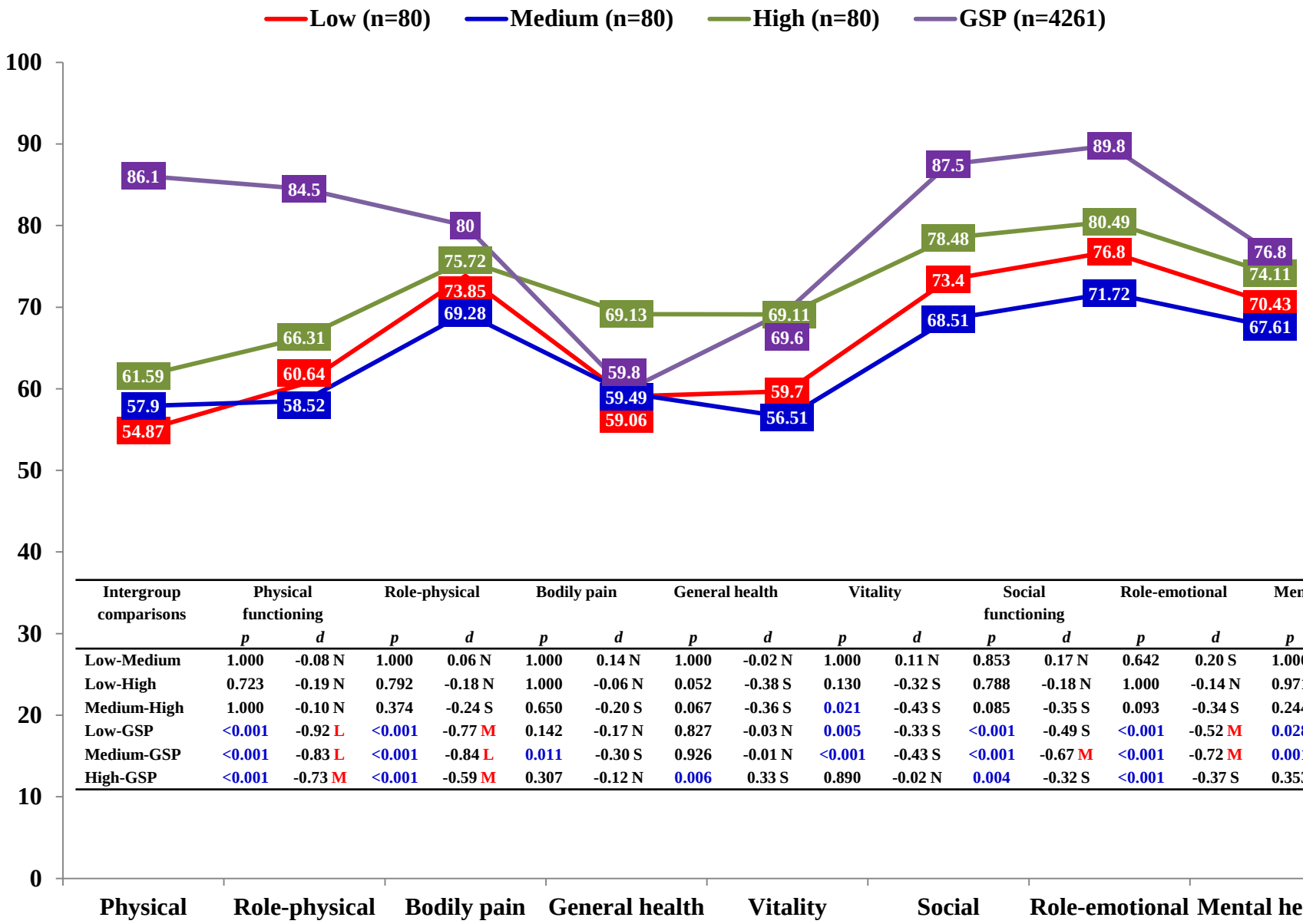








Intergroup comparisons	Physical functioning		Role-physical		Bodily pain		General health		Vitality		Social functioning		Role-emotional		Mental health	
	p	*d*	*p*	*d*	*p*	*d*	*p*	*d*	*p*	*d*	*p*	*d*	*p*	*d*	*p*	*d*
Less-Medium	1.000	-0.05 N	1.000	-0.08 N	1.000	-0.04 N	1.000	0.15 N	1.000	-0.06 N	1.000	0.04 N	1.000	0.10 N	1.000	0.13 N
Less-More	0.737	0.18 N	1.000	0.12 N	0.063	0.37 S	0.207	0.29 S	1.000	-0.04 N	1.000	0.07 N	0.920	0.16 N	0.441	0.23 S
Medium-More	0.428	0.23 S	0.573	0.21 S	0.026	0.41 S	1.000	0.14 N	1.000	0.02 N	1.000	0.03 N	1.000	0.06 N	1.000	0.10 N
Less-GSP	<0.001	-0.78 M	<0.001	-0.72 M	0.414	-0.10 N	0.052	0.23 S	0.013	-0.29 S	<0.001	-0.46 S	<0.001	-0.45 S	0.226	-0.13 N
Medium-GSP	<0.001	-0.73 M	<0.001	-0.64 M	0.633	-0.06 N	0.420	0.09 N	0.042	-0.23 S	<0.001	-0.50 M	<0.001	-0.56 M	0.029	-0.25 S
More-GSP	<0.001	-0.97 L	<0.001	-0.85 L	<0.001	-0.44 S	0.748	-0.04 N	0.031	-0.25 S	<0.001	-0.52 M	<0.001	-0.61 M	0.003	-0.35 S



Intergroup comparisons	Physical functioning		Role-physical		Bodily pain		General health		Vitality		Social functioning		Role-emotional		Mental health	
	p	*d*	*p*	*d*	*p*	*d*	*p*	*d*	*p*	*d*	*p*	*d*	*p*	*d*	*p*	*d*
Low-Medium	1.000	-0.08 N	1.000	0.06 N	1.000	0.14 N	1.000	-0.02 N	1.000	0.11 N	0.853	0.17 N	0.642	0.20 S	1.000	0.12 N
Low-High	0.723	-0.19 N	0.792	-0.18 N	1.000	-0.06 N	0.052	-0.38 S	0.130	-0.32 S	0.788	-0.18 N	1.000	-0.14 N	0.971	-0.16 N
Medium-High	1.000	-0.10 N	0.374	-0.24 S	0.650	-0.20 S	0.067	-0.36 S	0.021	-0.43 S	0.085	-0.35 S	0.093	-0.34 S	0.244	-0.28 S
Low-GSP	<0.001	-0.92 L	<0.001	-0.77 M	0.142	-0.17 N	0.827	-0.03 N	0.005	-0.33 S	<0.001	-0.49 S	<0.001	-0.52 M	0.028	-0.26 S
Medium-GSP	<0.001	-0.83 L	<0.001	-0.84 L	0.011	-0.30 S	0.926	-0.01 N	<0.001	-0.43 S	<0.001	-0.67 M	<0.001	-0.72 M	0.001	-0.37 S
High-GSP	<0.001	-0.73 M	<0.001	-0.59 M	0.307	-0.12 N	0.006	0.33 S	0.890	-0.02 N	0.004	-0.32 S	<0.001	-0.37 S	0.353	-0.11 N

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4, 5
Methods			
Study design	4	Present key elements of study design early in the paper	8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7, 8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	7, Figure 1
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5 to 8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5 to 8
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	7, 8, Figure 1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	Not applicable
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	Not applicable
		(*e*) Describe any sensitivity analyses	Not applicable
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5, Figure 1
		(b) Give reasons for non-participation at each stage	7, 8, Figure 1
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5
		(b) Indicate number of participants with missing data for each variable of interest	Not applicable
Outcome data	15*	Report numbers of outcome events or summary measures	8 to 14, Tables 2 and 3, Figures 2 to 4
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8, 12
		(*b*) Report category boundaries when continuous variables were categorized	8, 12
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8, 9, 12, 14, Tables 2 and 3, Figures 2 to 4
Discussion			
Key results	18	Summarise key results with reference to study objectives	17
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16, 17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14 to 17
Generalisability	21	Discuss the generalisability (external validity) of the study results	16, 17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Posttraumatic growth and its relationship to quality of life up to nine years after liver transplantation: a cross-sectional study in Spain

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-017455.R1
Article Type:	Research
Date Submitted by the Author:	04-Jul-2017
Complete List of Authors:	Pérez-San-Gregorio, María Ángeles; University of Seville, Department of Personality, Assessment, and Psychological Treatment Martín-Rodríguez, Agustín; University of Seville, Department of Personality, Assessment, and Psychological Treatment Borda-Mas, Mercedes; University of Seville, Department of Personality, Assessment, and Psychological Treatment Avargues-Navarro, María Luisa; University of Seville, Department of Personality, Assessment, and Psychological Treatment Pérez-Bernal, José; University Hospital Virgen del Rocío of Seville, Critical Care and Urgencies Conrad, Rupert; University of Bonn, Department of Psychosomatic Medicine and Psychotherapy Gómez-Bravo, Miguel Ángel; University Hospital Virgen del Rocío of Seville, Hepatic-Biliary-Pancreatic Surgery and Liver Transplant Unit
Primary Subject Heading:	Mental health
Secondary Subject Heading:	Global health
Keywords:	liver transplantation, posttraumatic growth, quality of life, patients, caregivers

Posttraumatic growth and its relationship to quality of life up to nine years after liver transplantation: a cross-sectional study in Spain

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Word count (excluding title page, abstract, references, figures and tables): 3536

Abstract

Objective: Little is known concerning posttraumatic growth after liver transplantation. Against this backdrop the current study analyzed the relationship between PTG and time since transplantation on quality of life. Furthermore, it compared the degree of posttraumatic growth (PTG) between liver transplant recipients and their caregivers.

Design: Cross-sectional case control study.

Setting: University Hospital in Spain.

Participants: 240 adult liver transplant recipients, who had undergone only one transplantation, with no severe mental disease. Specific additional analyses were conducted on the subset of 216 participants for whom caregiver data was available. Moreover, results were compared to a previously recruited general population sample.

Outcome measures: All participants completed the Posttraumatic Growth Inventory, and recipients also filled in the 12-Item Short-Form Health Survey. Relevant socio-demographic and clinical parameters were also assessed.

Results: In the sample of 240 recipients, longer duration since transplantation (>9 years) was associated with more pain symptoms (p=0.026). Regardless of duration, recipients showed lower scores on most quality of life dimensions than the general population. However, high PTG was associated with a significantly higher score on the vitality quality of life dimension (p=0.021). In recipients with high posttraumatic growth, specific quality of life dimensions, such as bodily pain (p=0.307), vitality (p=0.890), and mental health (p=0.353), even equaled scores in the general population, whereas scores on general health surpassed them (p=0.006). Furthermore, liver transplant recipients (n=216) compared to their caregivers showed higher total PTG (p<0.001) and higher scores on the subscales relating to others (p<0.001), new possibilities (p<0.001), and appreciation of life (p<0.001).

Conclusions: Our findings highlight the protective role of PTG in the long-term outcome of liver transplant recipients. Future studies should analyze and develop psychosocial interventions to strengthen posttraumatic growth in transplant recipients and their caregivers.

Strengths and limitations of this study

- The first study on posttraumatic growth in liver transplant recipients and their caregivers.
- Study of a large sample of 240 organ recipients up to nine years after transplantation.
- Assessment of medical complications in the immediate post-transplant period.
- Assessment of the association between posttraumatic growth and quality of life.
- Unilateral cross-sectional study at a University Hospital in Spain.

INTRODUCTION

Terminal liver disease is associated with severe physical and psychological decline.[1] The best medical option is liver transplantation which provides longer survival and better quality of life.[2-4] However, even after liver transplantation, quality of life often remains below levels found in the general population,[5] because acute and chronic graft rejection, recurrence of liver disease or secondary effects of immunosuppressants, are very stressful complications for patients and their families,[6-8] and may lead to the development of psychological disorders.[9-11]

Under these circumstances, the concept of posttraumatic growth, which is the idea that stressful life events may create the opportunity to activate one's resources, leading to a higher level of functioning than before, is highly relevant. This concept, developed by Tedeschi and Calhoun, is associated with the positive psychology movement.[12] Basically posttraumatic growth can be regarded as a protective factor,[12,13] which enables patients to reframe threats into challenges, thereby strengthening their psychological wellbeing.[14,15] Previous studies have found high levels of posttraumatic growth after lung transplantation,[6] which were even higher than those observed in patients suffering from chronic heart disease, cancer or HIV. High levels of posttraumatic growth have also been found after hematopoietic stem cell transplantation (HSCT).[16] However, lung transplantation and HSCT have markedly lower survival rates than liver transplantation,[17] which may have important implications regarding traumatization as well as posttraumatic growth. To the best of our knowledge, there are only two previous studies dealing with posttraumatic growth in liver transplant recipients.[14,15] In a longitudinal study, Scrignaro et al. [14] used a sample of 100 liver transplant patients from the outpatient population. Participants filled in the posttraumatic growth inventory and group identification scales at two different times 24 months apart. Results showed that PTG positively predicted identification with the family group and the transplantee group over time. The second study by Zieba et al. [15] examined 48 liver transplant recipients about 10 weeks after surgery. Recipients told two stories about freely chosen important events in their lives. The measurement of posttraumatic growth 10–12 months later showed that the affective tone

of the narratives was associated with the level of posttraumatic growth, and that positive affective tone was related to greater posttraumatic growth. Both studies unveiled potentially important mechanisms by which posttraumatic growth may positively affect well-being. However, the association of posttraumatic growth and quality of life, which is of central importance in the present study, was not dealt with in those papers.

Posttraumatic growth is also highly relevant for close relatives, particularly caregivers of the liver transplant recipient, who is dependent life-long on medical care and intensive social support. In this situation, the caregiver is confronted with the profound impact of liver transplantation on his or her personal life and its challenging implications.[11,18] There is growing evidence regarding the great amount of stress in caregivers before and after liver transplantation, which may even result in symptoms of posttraumatic stress.[19,20] The close mutual relationship between transplant recipient and caregiver makes it understandable that caregiver stress may also negatively affect the patient's quality of life and compliance.

Even though posttraumatic growth is thought to contribute to wellbeing and quality of life after transplantation, not all previous studies have found a significant positive association between these two variables. For example, Fox et al.,[6] found in a sample of 64 lung transplant recipients a minimal association between PTG and physical functional quality of life. This result could illustrate that posttraumatic growth is not related per se to higher quality of life, but rather increases the likelihood of a flexible adaptation to a new situation, which in the long run is thought to be beneficial to personal wellbeing.

Against this backdrop, we wanted to clarify this association in liver transplant recipients. Given the importance of this subject in clinical practice, we decided to analyze the relationship between different levels of posttraumatic growth and quality of life and to compare posttraumatic growth of liver transplant recipients and their caregivers. First, we hypothesized that the recipients' quality of life will be significantly associated with the time elapsed since transplantation as well as the level of posttraumatic growth, in the sense that longer duration since transplantation and lower

levels of posttraumatic growth are associated with lower quality of life. Second, we hypothesized that as shown in previous studies, regardless of the time elapsed since transplantation, posttraumatic growth will be significantly higher in recipients than in their caregivers.[21-23]

METHODS

Participants

The group of 240 liver transplant recipients selected had undergone transplantation surgery at the Virgen del Rocio University Hospital in Seville from 1990 to 2014. The sample consisted of 185 men and 55 women with a mean age of 60.21, SD=9.30 years. 61.7%, 22.5% and 15.8% had a low (did not complete high school), intermediate (high school education) and higher formal education (A level), respectively. 79.2% of participants had a stable relationship. The mean number of immediate post-transplant complications, as measured by several medical and laboratory parameters, was 4.47, SD=2.06. A subsample (Figure 1) of 216 recipients and 216 family members (the main caregiver of the respective patient) could be recruited from the total group of 240 recipients. The group of caregivers consisted of 48 men and 168 women with a mean age of 53.19, SD=12.56 years. 88.9% had a stable relationship and 54.6%, 22.7% and 22.7% had a low, intermediate and higher formal education, respectively. Their family relationships to the recipients were as follows: partner (71.3%), child (19.4%), sibling (4.2%), parent (3.7%) and other (1.4%).

In addition, quality of life of the liver transplant patients was compared to a general population sample recruited in a previous study. [24] The sample consisted of 4261 individuals (2133 women) with the following age distribution: 18-24 (11.6%), 25-34 (21.1%), 35-44 (20.1%), 45-54 (15.5%), 55-64 (13.7%), 65-74 (10.1%), ≥75 years (7.8%). 57.8% were married.[24]

Measurements

Medical and laboratory parameters

The medical and laboratory parameters refer to the 16 complications described in Table 1. Most of the measurements were done in the immunology laboratory and all of them refer to the

immediate post-transplant period. The score on the medical parameters was found by scoring participants one point for each complication they had, leading to a value that could range from 0 to 16. Higher values show poorer health.

Table 1. Medical and laboratory parameters of liver transplant patients in immediate post-transplant period.

	Presence	Absence	Data unavailable
1. Post-surgery hemorrhaging	24	213	3
2. Cytomegalovirus	211	24	5
3. Epstein Barr virus	198	29	13
4. Bacterial infections	87	151	2
5. Viral infections	17	220	3
6. Fungal infections	7	230	3
7. Acute graft rejection	47	190	3
8. Vascular complications	7	230	3
9. Biliary complications	27	211	2
10. Respiratory complications	49	187	4
11. Refractory ascites	43	195	2
12. Neurological complications	43	194	3
13. Hemodynamic complications	47	189	4
14. Renal complications	119	119	2
15. Hematologic complications	85	149	6
16. Re-operations	29	209	2

Posttraumatic Growth

Recipients and caregivers filled in the Posttraumatic Growth Inventory (PTGI) [13]. This consists of 21 items answered on a Likert scale ranging from 0 ("no change") to 5 ("very great degree of change") thereby evaluating the perception of personal benefits in survivors of traumatic events. Test interpretation provides a total score of posttraumatic growth and the following five sub-dimensions: relating to others, new possibilities, personal strength, spiritual change, and appreciation of life. We used the Spanish version provided by Weiss and Berger.[25] For patients in this study, the Cronbach's alpha was 0.94 for the sum scale and ranged from 0.73 to 0.88 for the subscales. For caregivers, the Cronbach's alpha was 0.95 for the total scale and ranged from 0.77 to 0.90 for the various subscales.

Quality of life

The 12-Item Short Form Health Survey (SF-12v.2) [26,27] consists of 12 items with either 3 or 5-point Likert scales. It evaluates the following eight dimensions of health-related quality of life: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. The score on each dimension varies from 0 (worst state of health) to 100 (best state of health). The reliability of the eight scales varied in our sample from 0.72 to 0.89. In our study, this questionnaire was filled in only by recipients.

Procedure

After receiving Institutional Review Board approval, we recruited patients and family members from a clinical population of 1053 adult transplant recipients (Figure 1). At the beginning, all 569 patients still alive and their main caregivers were informed of the possibility of participation in the study by the Association of Liver Transplant Recipients and the Hepatic-Biliary-Pancreatic Surgery and Liver Transplant Unit. Inclusion criteria for both groups were: a) over 18 years of age, b) informed consent, c) no difficulties in understanding the evaluation instruments, d) no severe or disabling psychopathological condition, and e) reception of only one transplant. Thus, 240 recipients could be included in the study of whom 216 participated along with their caregiver.

Statistical analysis

Statistical analysis of the sample of 240 transplant recipients was performed using the SPSS 22 statistics program. Specific additional analyses were conducted on the subset of 216 participants for whom caregiver data was available. A Pearson's chi-squared test was used to compare qualitative variables (gender, marital status and education) in the various patient subgroups, and for quantitative variables (age and post-transplant complications), a one-way ANOVA with the Tukey HSD test for post-hoc comparisons was calculated. A 2x3 mixed factorial ANOVA was performed to evaluate the relationship between group factors (liver transplant recipients and caregivers) and time elapsed since transplantation (less, medium, more) on posttraumatic growth. A 3x3 factorial ANOVA was calculated to analyze the association of time since transplantation (less, medium, more) and posttraumatic growth level (low, medium, high) on quality of life. Cohen's *d* (for quantitative variables) and Cohen's *w* (for qualitative variables) were computed for effect size.

RESULTS

Quality of life and time since transplantation in transplant recipients (n=240)

The association between quality of life and time since transplantation as well as posttraumatic growth was studied. In the first part of the analysis, the total sample of 240 patients was divided into three almost equal groups on the basis of time elapsed since transplantation: 78 patients ≤3.5 years (32.5%), 82 patients from >3.5 to ≤9 years (34.2%) and 80 patients >9 years (33.3%). There were no differences among subgroups in gender (p=0.150, w=0.13), marital status (p=0.744, w=0.05), education (p=0.450, w=0.12) or immediate post-transplant complications (p=0.377), although there were significant differences in age (56.46±8.98 vs. 59.94±8.39 vs. 64.14±9.03; p<0.001). We found no significant interaction effect between time since transplantation and posttraumatic growth on quality of life (Table 2, Figure 2). The main effect time since transplantation showed a significant effect on the bodily pain dimension (p=0.017) in that after more than nine years since transplantation recipients showed more pain than after a medium

duration of time (>3.5 and ≤9 years) (p=0.026, d=0.41) (Table 3). In comparison to the Spanish general population liver transplant recipients showed lower quality of life on almost all dimensions except for General Health regardless of the duration since transplantation (Table 3, Figure 2).

Table 2. Quality of life: differences between liver transplant recipients by time since transplantation and patient posttraumatic growth levels (3 x 3 factorial ANOVA).

	Main effects		Interaction effects
	Time	Posttraumatic growth	
	$F_{(2,231)}$ (p)	$F_{(2,231)}$ (p)	$F_{(4,231)}$ (p)
Physical functioning	1.199 (0.303)	0.694 (0.501)	1.438 (0.222)
Role-physical	0.866 (0.422)	1.273 (0.282)	0.848 (0.496)
Bodily pain	4.138 (0.017)	0.808 (0.447)	0.760 (0.552)
General health	1.669 (0.191)	3.706 (0.026)	0.564 (0.689)
Vitality	0.076 (0.927)	4.031 (0.019)	0.254 (0.907)
Social functioning	0.103 (0.902)	2.440 (0.089)	0.852 (0.494)

Role-emotional	0.538	2.370	1.395
	(0.585)	(0.096)	(0.237)
Mental health	1.062	1.543	1.129
	(0.348)	(0.216)	(0.344)

Table 3. Quality of life in relation to time since transplantation in transplant recipients (factorial ANOVA and Bonferroni post-hoc test, Cohen's *d*) and compared to a Spanish population sample (unpaired *t* test, Cohen's *d*).

Intergroup Comparisons	Physical functioning *p* (*d*)	Role-physical *p* (*d*)	Bodily pain *p* (*d*)	General health *p* (*d*)	Vitality *p* (*d*)	Social functioning *p* (*d*)	Role-emotional *p* (*d*)	Mental health *p* (*d*)
Less-Medium	1.000 (-0.05 N)	1.000 (-0.08 N)	1.000 (-0.04 N)	1.000 (0.15 N)	1.000 (-0.06 N)	1.000 (0.04 N)	1.000 (0.10 N)	1.000 (0.13 N)
Less-More	0.737 (0.18 N)	1.000 (0.12 N)	0.063 (0.37 S)	0.207 (0.29 S)	1.000 (-0.04 N)	1.000 (0.07 N)	0.920 (0.16 N)	0.441 (0.23 S)
Medium-More	0.428 (0.23 S)	0.573 (0.21 S)	0.026 (0.41 S)	1.000 (0.14 N)	1.000 (0.02 N)	1.000 (0.03 N)	1.000 (0.06 N)	1.000 (0.10 N)
Less-GSP	<0.001 (-0.78 M)	<0.001 (-0.72 M)	0.414 (-0.10 N)	0.052 (0.23 S)	0.013 (-0.29 S)	<0.001 (-0.46 S)	<0.001 (-0.45 S)	0.226 (-0.13 N)
Medium-GSP	<0.001 (-0.73 M)	<0.001 (-0.64 M)	0.633 (-0.06 N)	0.420 (0.09 N)	0.042 (-0.23 S)	<0.001 (-0.50 M)	<0.001 (-0.56 M)	0.029 (-0.25 S)

More-GSP	<0.001	<0.001	<0.001	0.748	0.031	<0.001	<0.001	0.003
	(-0.97 L)	(-0.85 L)	(-0.44 S)	(-0.04 N)	(-0.25 S)	(-0.52 M)	(-0.61 M)	(-0.35 S)

GSP=General Spanish population, N=Null effect size, S=Small effect size, M=Medium effect size, L=Large effect size.

Quality of life and posttraumatic growth in transplant recipients (n=240)

In the second part of the analysis, the sample of 240 patients was divided into three equally-sized subgroups on the basis of total posttraumatic growth score: 80 patients with a low level of posttraumatic growth (33.3%; 0 to 59 points), 80 patients with a medium level (33.3%; 60 to 77 points), and 80 patients with a high level (33.3%; 78 to 105 points). There were no significant differences between subgroups concerning age (p=0.506), gender (p=0.639, w=0.06), marital status (p=0.720, w=0.05), education (p=0.187, w=0.16) or post-transplant complications (p=0.443).

There was no significant correlation between posttraumatic growth and time since transplantation (r=0.119; p=0.065). Neither did we find any significant interaction effect between time since transplantation and posttraumatic growth on quality of life (Table 2, Figure 3). Furthermore, recipients' posttraumatic growth was significantly related to the vitality dimension, with high compared to medium posttraumatic growth being associated with significantly more vitality (p=0.021, d=-0.43), as well as a statistical trend towards higher scores on general health (p=0.067, d=-0.36), social functioning (p=0.085, d=-0.35), and role-emotional (p=0.093, d=-0.34) with small effect sizes (Table 4). Compared to the general Spanish population, liver transplant recipients with lower levels of posttraumatic growth showed a generally lower quality of life. However, a high level of posttraumatic growth was associated with smaller differences, rendering the differences in the vitality (p=0.890, d=-0.02), mental health (p=0.353, d=-0.11), and bodily pain (p=0.307, d=-0.12) dimensions non-significant, even though the latter's dimension pattern differed, as it also showed a non-significant difference in the subgroup with low posttraumatic growth (p=0.142, d=-0.17). In the general health dimension, which showed no significant differences in the general population in the subgroups with low (p=0.827, d=-0.03) or medium (p=0.926, d=-0.01) posttraumatic growth, it was associated with significantly higher scores (p=0.006, d=0.33) (Table 4, Figure 3).

Table 4. Quality of life in relation to posttraumatic growth (factorial ANOVA and Bonferroni post-hoc test, Cohen's *d*) and compared to a Spanish population sample (unpaired *t* test, Cohen's *d*).

Intergroup Comparisons	Physical functioning *p* (*d*)	Role-physical *p* (*d*)	Bodily pain *p* (*d*)	General health *p* (*d*)	Vitality *p* (*d*)	Social functioning *p* (*d*)	Role-emotional *p* (*d*)	Mental health *p* (*d*)
Low-Medium	1.000 (-0.08 N)	1.000 (0.06 N)	1.000 (0.14 N)	1.000 (-0.02 N)	1.000 (0.11 N)	0.853 (0.17 N)	0.642 (0.20 S)	1.000 (0.12 N)
Low-High	0.723 (-0.19 N)	0.792 (-0.18 N)	1.000 (-0.06 N)	0.052 (-0.38 S)	0.130 (-0.32 S)	0.788 (-0.18 N)	1.000 (-0.14 N)	0.971 (-0.16 N)
Medium-High	1.000 (-0.10 N)	0.374 (-0.24 S)	0.650 (-0.20 S)	0.067 (-0.36 S)	0.021 (-0.43 S)	0.085 (-0.35 S)	0.093 (-0.34 S)	0.244 (-0.28 S)
Low-GSP	<0.001 (-0.92 L)	<0.001 (-0.77 M)	0.142 (-0.17 N)	0.827 (-0.03 N)	0.005 (-0.33 S)	<0.001 (-0.49 S)	<0.001 (-0.52 M)	0.028 (-0.26 S)
Medium-GSP	<0.001 (-0.83 L)	<0.001 (-0.84 L)	0.011 (-0.30 S)	0.926 (-0.01 N)	<0.001 (-0.43 S)	<0.001 (-0.67 M)	<0.001 (-0.72 M)	0.001 (-0.37 S)

High-GSP	<0.001	<0.001	0.307	0.006	0.890	0.004	<0.001	0.353
	(-0.73 M)	(-0.59 M)	(-0.12 N)	(0.33 S)	(-0.02 N)	(-0.32 S)	(-0.37 S)	(-0.11 N)

GSP=General Spanish population, N=Null effect size, S=Small effect size, M=Medium effect size, L=Large effect size.

Posttraumatic growth related to time since transplantation in transplant recipients (n=216) compared to their caregivers (n=216)

The sample of 216 liver transplant recipients who could be examined with their caregivers was divided on the basis of time elapsed since transplantation in three subgroups of equal size: 73 patients ≤3.5 years (33.8%), 71 patients from >3.5 to ≤9 years (32.9%), and 72 patients with >9 years (33.3%). There were no significant differences in gender (p=0.128, w=0.14), marital status (p=0.753, w=0.05), education (p=0.683, w=0.10), or medical complications in the immediate post-transplant period (p=0.164) among these subgroups, however, there were significant differences with regard to age (56.37±9.18 vs. 60.44±7.65 vs. 64.35±9.37; p<0.001).

There was no significant effect of between-group interaction and time since transplantation on posttraumatic growth (F=0.196, p=0.822; Table 5, Figure 4). The main effect time elapsed since transplantation was not associated with posttraumatic growth. However, patients showed significantly higher scores than their caregivers on total posttraumatic growth (p<0.001), as well as on the subdimensions relating to others (p<0.001), new possibilities (p<0.001), and appreciation of life (p<0.001).

Table 5. Posttraumatic growth: differences between liver transplant recipients (G1) and their caregivers (G2) by time since transplantation (2 x 3 mixed factorial ANOVA).

	Main effects		Interaction effects	Comparisons G1-G2 *p* (Cohen's *d*)			Comparisons time since transplantation *p* (Cohen's *d*)					
	Group	Time		Time since transplantation				G1 (n=216)			G2 (n=216)	
	$F_{(1,213)}$ (*p*)	$F_{(2,213)}$ (*p*)	$F_{(2,213)}$ (*p*)	Less a	Medium b	More c	a-b	a-c	b-c	a-b	a-c	b-c
Relating to others	23.081 (<0.001)	1.464 (0.234)	0.236 (0.790)	0.008 (0.32) S	0.020 (0.30) S	0.001 (0.46) S	1.000 (-0.02) N	0.270 (-0.29) S	0.369 (-0.27) S	1.000 (-0.05) N	0.908 (-0.17) N	1.000 (-0.12) N
New possibilities	33.157 (<0.001)	0.640 (0.528)	0.003 (0.997)	0.001 (0.36) S	0.001 (0.42) S	0.001 (0.45) S	1.000 (-0.03) N	0.987 (-0.16) N	1.000 (-0.14) N	1.000 (-0.02) N	1.000 (-0.14) N	1.000 (-0.12) N

Personal strength	0.001	0.424	0.744	0.425	0.868	0.365	1.000	0.438	1.000	1.000	1.000	1.000
	(0.976)	(0.655)	(0.476)	(-0.10)	(-0.02)	(0.13)	(-0.10)	(-0.24)	(-0.14)	(-0.02)	(-0.01)	(0.01)
				N	N	N	N	S	N	S	N	N
Spiritual change	0.001	2.192	0.349	0.898	0.537	0.584	1.000	0.227	0.143	1.000	0.529	0.960
	(0.975)	(0.114)	(0.706)	(0.02)	(-0.08)	(0.07)	(0.04)	(-0.29)	(-0.37)	(-0.06)	(-0.22)	(-0.17)
				N	N	N	N	S	S	N	S	N
Appreciation of life	18.490	0.109	0.067	0.006	0.028	0.014	1.000	1.000	1.000	1.000	1.000	1.000
	(<0.001)	(0.897)	(0.935)	(0.37)	(0.33)	(0.35)	(-0.02)	(-0.02)	(0.00)	(-0.09)	(-0.06)	(0.03)
				S	S	S	N	N	N	N	N	N
Total posttraumatic growth	17.109	0.983	0.196	0.028	0.041	0.004	1.000	0.417	0.674	1.000	1.000	1.000
	(<0.001)	(0.376)	(0.822)	(0.25)	(0.26)	(0.38)	(-0.04)	(-0.24)	(-0.21)	(-0.05)	(-0.14)	(-0.09)
				S	S	S	N	S	S	N	N	N

G1=Liver transplant recipients, G2=Caregivers, N=Null effect size, S=Small effect size.

DICCUSSION

To the best of our knowledge, our study is the first on the relationship between posttraumatic growth and quality of life in liver transplant recipients. In this context we were not only interested in the patient, but also in the family support system as represented by the caregiver. We found that, regardless of time elapsed since transplantation, recipients showed more posttraumatic growth than their caregivers. This result confirms our hypothesis and is in keeping with findings in HSCT-recipients [21] and other cancer patients.[22,23] It might be argued that the patients themselves have been directly exposed to traumatic events such as liver disease, transplant surgery, and the side effects of immunosuppressants, which increases the activation of intrapersonal resources, thereby leading to higher levels of posttraumatic growth. Furthermore, liver transplantation symbolizes the beginning of a new life for the patient, often after a long period of physical suffering and fear of death. This may be associated with a sense of gratitude towards the deceased donor and the medical team, and a feeling of personal responsibility for justifying all their efforts, which may in turn mobilize a large amount of energy.[6,28]

The specific aspects of posttraumatic growth, as captured mainly by the relating to others, new possibilities and appreciation of life subscales, proved to be relevant, as also found in previous studies.[16,28,29] Posttraumatic growth did not alter significantly over the course of time, a phenomenon also observed in breast cancer [30] and colorectal cancer patients.[31] This may be partially explained by the psychological construct of posttraumatic growth itself, which is defined by Tedeschi and Calhoun as: *"The phenomenon is complex, and cannot easily be reduced to simply a coping mechanism, a cognitive distortion, psychological adjustment or well-being, or a host of apparently similar constructs. The outcomes of posttraumatic growth might be best considered as iterative, and it will take longitudinal work to trace the varied trajectories of the posttraumatic growth process. This process is likely to involve a powerful combination of demand for emotional relief and cognitive clarity, that is achieved through construction of higher order schemas that allow for appreciation of paradox"* (p.15).[12] Thus the process of posttraumatic growth is thought

to be iterative, thereby gradually constructing higher order schemas, which involve rather small slow alterations, relatively stable over time. This is also reflected in the construction of the posttraumatic growth inventory, which asks participants to indicate for each statement the degree to which this change occurred during their life as a result of the crisis/disaster. This concrete formulation of a change in life in response to a specific disaster would suggest a stable cognitive-behavioral pattern rather than a state sensitive to fluctuation.

Our hypotheses with respect to quality of life were partially confirmed, since neither time nor posttraumatic growth was significantly associated with all the dimensions of quality of life. Moreover, on most quality of life dimensions, recipients showed significantly lower scores than the general population. In accordance with the above mentioned definition, one might argue that posttraumatic growth does not immediately lead to higher quality of life, as it mirrors the inner struggle to form a convincing narrative from existential paradoxes associated with life-threatening disease. We found that only the SF-12 bodily pain dimension was significantly related to time since transplantation. This finding may be explained by the increase in imunosuppressant side effects, such as arthralgia and muskuloskeletal pain, over time.[32,33] In addition our findings displayed particularly low levels of quality of life compared to the general population [5] after a post-transplantation time-span of over nine years. In the long run, the combination of the side effects of medication and the restrictions of medical treatment, such as diet and ongoing medical supervision, may negatively affect recipients' quality of life.

A high level of posttraumatic growth in recipients compared to a medium level was associated with significantly higher scores on vitality, and a statistical trend towards higher scores on general health, social functioning and role-emotional. Recipients with high posttraumatic growth vitality scores even equaled scores in the general population. In general, a high level of posttraumatic growth was associated with smaller differences between quality of life scores in recipients and the general population, rendering the differences on bodily pain, vitality and mental health non-significant and revealing even higher scores on general health. These findings highlight the

potentially protective role of posttraumatic growth in liver transplant patients and are in keeping with other studies which showed a positive association between posttraumatic growth and quality of life, even though to date the clinical relevance of these findings is not clear.[16,30,34] In line with the protective role of posttraumatic growth, personality traits such as extraversion, optimism, and openness to experience have been positively associated with this psychological construct.[35]

From a clinical perspective, the posttraumatic growth inventory could be used after liver transplantation to identify those patients who are in special need of psychological support. Mindfulness-based stress reduction [36] and positive psychotherapy [37] have demonstrated their efficacy in augmenting posttraumatic growth in patients.

Our study had several limitations. First, we did not analyze the relevance of further clinical variables, such as the etiology of the liver disease [8], or personality variables, such as specific coping strategies, on posttraumatic growth.[38] Second, we did not assess long-term transplant-related health parameters, such as infections, rehospitalization or other complications. Third, recruitment of patients took place at a single site which may limit external validity of findings. Finally, the study design was not longitudinal, so it was not possible to explore individuals' change in PTG and quality of life over time, which would allow for the investigation of causal relationships.

Nevertheless, the large sample size and the analysis of recipients and caregivers can be seen as a major strength of this study.

CONCLUSIONS

To summarize, our study demonstrated that regardless of the time elapsed since liver transplantation, recipients showed more posttraumatic growth than their caregivers. A high level of posttraumatic growth was associated with high levels of specific aspects of quality of life such as vitality, whereas a longer time span since transplantation was related to more pain. Compared to the general population, recipients generally showed lower quality of life, except in patients with high

levels of posttraumatic growth, in whom specific dimensions of quality of life, such as bodily pain, vitality, mental health and general health, equaled or even surpassed scores in the general population. Facilitation of posttraumatic growth after liver transplantation may be crucial to ensure long-term quality of life in recipients.

ACKNOWLEDGMENTS

The authors would like to thank all the participants (liver transplant patients and their family members).

CONTRIBUTORS

MÁPSG and AMR: Study concept and design, data analysis and interpretation, drafting of manuscript, manuscript revisions, and drafting figures. MBM and MLAN: Study concept and design, critical revision of article. JPB: Institutional support, data collection, critical revision of article. RC and MÁGB: Data analysis and interpretation, drafting of manuscript, critical revision of article. All authors gave final approval to the version submitted for publication.

FUNDING

This study was funded by the Spanish Ministry of Economy and Competitiveness (Project PSI2014-51950-P).

COMPETING INTERESTS

None declared.

DATA SHARING STATEMENT

Data may compromise the privacy of study participants and may not be shared publicly. The public availability of the data is restricted by the Ethics Committee of the Virgen del Rocío

University Hospital of Seville (Spain). Data are available upon request to the authors. Contact person: Dra. M.A. Pérez-San-Gregorio (anperez@us.es).

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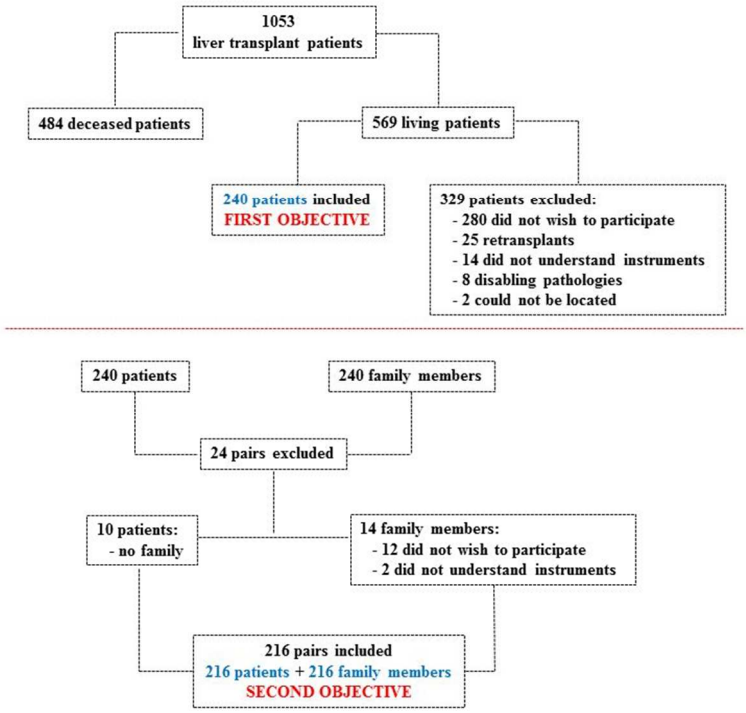
FIGURES

Figure 1. Participant selection for the study's two objectives.

Figure 2. Relationship between time since transplantation and quality of life. Comparison with General Spanish population. Lower mean scores show poorer quality of life. GSP=General Spanish population.

Figure 3. Relationship between posttraumatic growth level and quality of life. Comparison with General Spanish population. Lower mean scores show poorer quality of life. GSP=General Spanish population. Less (≤3.5 years), medium (>3.5 to ≤9 years), more (>9 years).

Figure 4. Posttraumatic growth: mean scores on variables with statistically significant differences between the two groups. Higher scores show more growth. G1=Liver transplant recipients (n=216), G2=Caregivers (n=216).



Participant selection for the study's two objectives.

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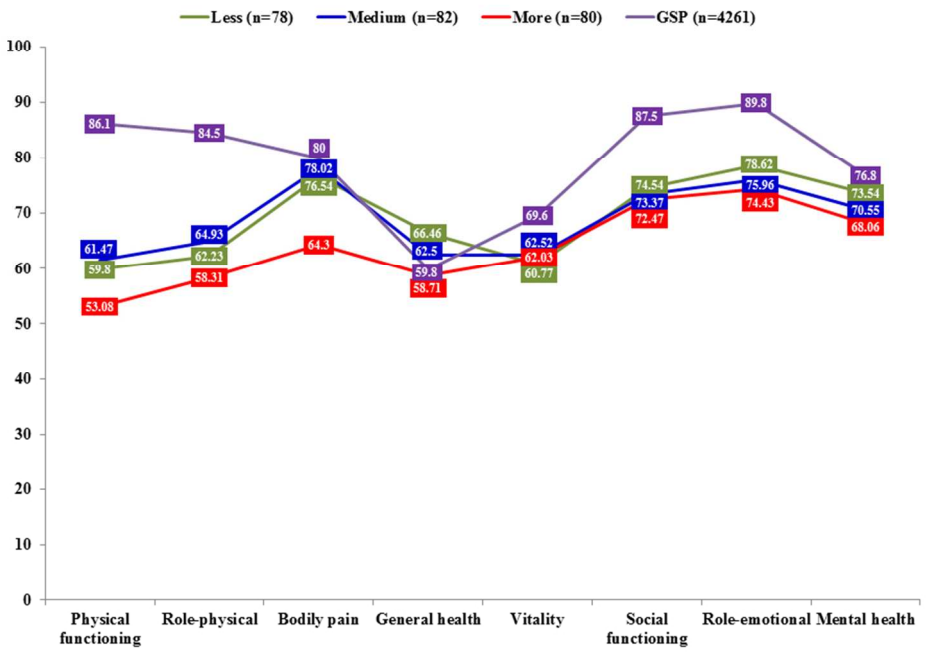

Relationship between time since transplantation and quality of life. Comparison with General Spanish population. Lower mean scores show poorer quality of life. GSP=General Spanish population.Less (≤3.5 years), medium (>3.5 to ≤9 years), more (>9 years).

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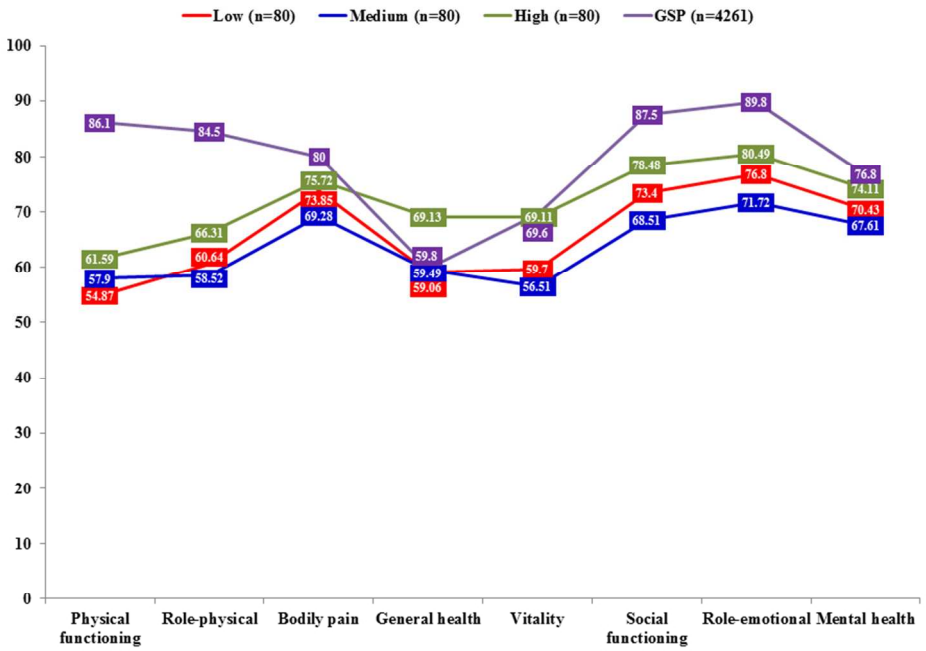

Relationship between posttraumatic growth level and quality of life. Comparison with General Spanish population. Lower mean scores show poorer quality of life. GSP=General Spanish population.

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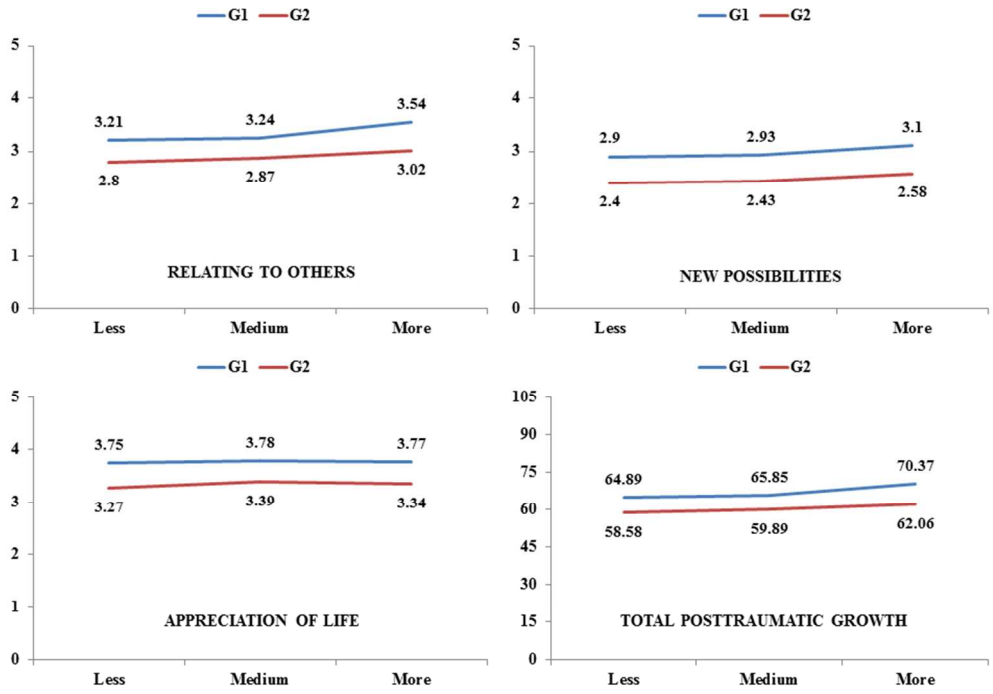

Posttraumatic growth: mean scores on variables with statistically significant differences between the two groups. Higher scores show more growth. G1=Liver transplant recipients (n=216), G2=Caregivers (n=216).

81x60mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2, 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4, 5
Objectives	3	State specific objectives, including any prespecified hypotheses	5, 6
Methods			
Study design	4	Present key elements of study design early in the paper	9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6, 7, 8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	8, Figure 1
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6 to 9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6 to 9
Bias	9	Describe any efforts to address potential sources of bias	9
Study size	10	Explain how the study size was arrived at	8, Figure 1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	9
		(*c*) Explain how missing data were addressed	Not applicable
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	Not applicable
		(*e*) Describe any sensitivity analyses	Not applicable
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6, Figure 1
		(b) Give reasons for non-participation at each stage	8, Figure 1
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	Not applicable
Outcome data	15*	Report numbers of outcome events or summary measures	9 to 19, Tables 2 to 5, Figures 2 to 4
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9, 10, 14, 17
		(*b*) Report category boundaries when continuous variables were categorized	9, 10, 14, 17
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9 to 19, Tables 2 to 5, Figures 2 to 4
Discussion			
Key results	18	Summarise key results with reference to study objectives	22, 23
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	22
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	20 to 23
Generalisability	21	Discuss the generalisability (external validity) of the study results	22
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	23

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Posttraumatic growth and its relationship to quality of life up to nine years after liver transplantation: a cross-sectional study in Spain

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-017455.R2
Article Type:	Research
Date Submitted by the Author:	17-Jul-2017
Complete List of Authors:	Pérez-San-Gregorio, María Ángeles; University of Seville, Department of Personality, Assessment, and Psychological Treatment Martín-Rodríguez, Agustín; University of Seville, Department of Personality, Assessment, and Psychological Treatment Borda-Mas, Mercedes; University of Seville, Department of Personality, Assessment, and Psychological Treatment Avargues-Navarro, María Luisa; University of Seville, Department of Personality, Assessment, and Psychological Treatment Pérez-Bernal, José; University Hospital Virgen del Rocío of Seville, Critical Care and Urgencies Conrad, Rupert; University of Bonn, Department of Psychosomatic Medicine and Psychotherapy Gómez-Bravo, Miguel Ángel; University Hospital Virgen del Rocío of Seville, Hepatic-Biliary-Pancreatic Surgery and Liver Transplant Unit
Primary Subject Heading:	Mental health
Secondary Subject Heading:	Global health
Keywords:	liver transplantation, posttraumatic growth, quality of life, patients, caregivers

Posttraumatic growth and its relationship to quality of life up to nine years after liver transplantation: a cross-sectional study in Spain

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Word count (excluding title page, abstract, references, figures and tables): 3611

Abstract

Objective: Little is known concerning posttraumatic growth after liver transplantation. Against this backdrop the current study analyzed the relationship between PTG and time since transplantation on quality of life. Furthermore, it compared the degree of posttraumatic growth (PTG) between liver transplant recipients and their caregivers.

Design: Cross-sectional case control study.

Setting: University Hospital in Spain.

Participants: 240 adult liver transplant recipients, who had undergone only one transplantation, with no severe mental disease. Specific additional analyses were conducted on the subset of 216 participants for whom caregiver data was available. Moreover, results were compared to a previously recruited general population sample.

Outcome measures: All participants completed the Posttraumatic Growth Inventory, and recipients also filled in the 12-Item Short-Form Health Survey. Relevant socio-demographic and clinical parameters were also assessed.

Results: In the sample of 240 recipients, longer time since transplantation (>9 years) was associated with more pain symptoms (p=0.026). Regardless of duration, recipients showed lower scores on most quality of life dimensions than the general population. However, high PTG was associated with a significantly higher score on the vitality quality of life dimension (p=0.021). In recipients with high posttraumatic growth, specific quality of life dimensions, such as bodily pain (p=0.307), vitality (p=0.890), and mental health (p=0.353), even equaled scores in the general population, whereas scores on general health surpassed them (p=0.006). Furthermore, liver transplant recipients (n=216) compared to their caregivers showed higher total PTG (p<0.001) and higher scores on the subscales relating to others (p<0.001), new possibilities (p<0.001), and appreciation of life (p<0.001).

Conclusions: Our findings highlight the protective role of PTG in the long-term outcome of liver transplant recipients. Future studies should analyze and develop psychosocial interventions to strengthen posttraumatic growth in transplant recipients and their caregivers.

Strengths and limitations of this study

- The first study on posttraumatic growth in liver transplant recipients and their caregivers.
- The study investigates a large sample of 240 liver organ recipients up to nine years after transplantation.
- The study only assesses short-term medical complications in the immediate post-transplant period.
- The cross-sectional study design does not allow for the investigation of causal relationships.
- The recruitment of patients at a single site may limit external validity of findings.

INTRODUCTION

Terminal liver disease is associated with severe physical and psychological decline.[1] The best medical option is liver transplantation which provides longer survival and better quality of life.[2-4] However, even after liver transplantation, quality of life often remains below levels found in the general population,[5] because acute and chronic graft rejection, recurrence of liver disease or secondary effects of immunosuppressants, are very stressful complications for patients and their families,[6-8] and may lead to the development of psychological disorders.[9-11]

Under these circumstances, the concept of posttraumatic growth, which is the idea that stressful life events may create the opportunity to activate one's resources, leading to a higher level of functioning than before, is highly relevant. This concept, developed by Tedeschi and Calhoun, is associated with the positive psychology movement.[12] Basically posttraumatic growth can be regarded as a protective factor,[12,13] which enables patients to reframe threats into challenges, thereby strengthening their psychological wellbeing.[14,15] Previous studies have found high levels of posttraumatic growth after lung transplantation,[6] which were even higher than those observed in patients suffering from chronic heart disease, cancer or HIV. High levels of posttraumatic growth have also been found after hematopoietic stem cell transplantation (HSCT).[16] However, lung transplantation and HSCT have markedly lower survival rates than liver transplantation,[17] which may have important implications regarding traumatization as well as posttraumatic growth. To the best of our knowledge, there are only two previous studies dealing with posttraumatic growth in liver transplant recipients.[14,15] In a longitudinal study, Scrignaro et al. [14] used a sample of 100 liver transplant patients from the outpatient population. Participants filled in the posttraumatic growth inventory and group identification scales at two different times 24 months apart. Results showed that PTG positively predicted identification with the family group and the transplantee group over time. The second study by Zieba et al. [15] examined 48 liver transplant recipients about 10 weeks after surgery. Recipients told two stories about freely chosen important events in their lives. The measurement of posttraumatic growth 10–12 months later showed that the affective tone

of the narratives was associated with the level of posttraumatic growth, and that positive affective tone was related to greater posttraumatic growth. Both studies unveiled potentially important mechanisms by which posttraumatic growth may positively affect well-being. However, the association of posttraumatic growth and quality of life, which is of central importance in the present study, was not dealt with in those papers.

Posttraumatic growth is also highly relevant for close relatives, particularly caregivers of the liver transplant recipient, who is dependent life-long on medical care and intensive social support. In this situation, the caregiver is confronted with the profound impact of liver transplantation on his or her personal life and its challenging implications.[11,18] There is growing evidence regarding the great amount of stress in caregivers before and after liver transplantation, which may even result in symptoms of posttraumatic stress.[19,20] The close mutual relationship between transplant recipient and caregiver makes it understandable that caregiver stress may also negatively affect the patient's quality of life and therapy adherence.

Even though posttraumatic growth is thought to contribute to wellbeing and quality of life after transplantation, not all previous studies have found a significant positive association between these two variables. For example, Fox et al.,[6] found in a sample of 64 lung transplant recipients a minimal association between PTG and physical functional quality of life. This result illustrates that posttraumatic growth is not related per se to higher quality of life. The relationship between both constructs could be interpreted in the sense that posttraumatic growth increases the likelihood of a flexible adaptation to a new situation, which in the long run is thought to be beneficial to personal wellbeing.

Against this backdrop, we wanted to clarify this association in liver transplant recipients. Given the importance of this subject in clinical practice, we decided to analyze the relationship between different levels of posttraumatic growth and quality of life and to compare posttraumatic growth of liver transplant recipients and their caregivers. First, we hypothesized that the recipients' quality of life will be significantly associated with the time elapsed since transplantation as well as

the level of posttraumatic growth, in the sense that longer time since transplantation and lower levels of posttraumatic growth are associated with lower quality of life. The negative association between time since transplantation and quality of life is based on the assumption that recipients may increasingly suffer from adverse side effects of immunosuppressants such as pain. Furthermore, in the course of time they may develop serious comorbidities.

Second, we hypothesized that as shown in previous studies, regardless of the time elapsed since transplantation, posttraumatic growth will be significantly higher in recipients than in their caregivers.[21-23]

METHODS

Participants

The group of 240 liver transplant recipients selected had undergone transplantation surgery at the Virgen del Rocio University Hospital in Seville from 1990 to 2014. The sample consisted of 185 men and 55 women with a mean age of 60.21, SD=9.30 years. 61.7%, 22.5% and 15.8% had a low (did not complete high school), intermediate (high school education) and higher formal education (A level), respectively. 79.2% of participants had a stable relationship. The mean number of immediate post-transplant complications, as measured by several medical and laboratory parameters, was 4.47, SD=2.06. A subsample (Figure 1) of 216 recipients and 216 family members (the main caregiver of the respective patient) could be recruited from the total group of 240 recipients. The group of caregivers consisted of 48 men and 168 women with a mean age of 53.19, SD=12.56 years. 88.9% had a stable relationship and 54.6%, 22.7% and 22.7% had a low, intermediate and higher formal education, respectively. Their family relationships to the recipients were as follows: partner (71.3%), child (19.4%), sibling (4.2%), parent (3.7%) and other (1.4%).

In addition, quality of life of the liver transplant patients was compared to a general population sample recruited in a previous study. [24] The sample consisted of 4261 individuals

(2133 women) with the following age distribution: 18-24 (11.6%), 25-34 (21.1%), 35-44 (20.1%), 45-54 (15.5%), 55-64 (13.7%), 65-74 (10.1%), ≥75 years (7.8%). 57.8% were married.[24]

Measurements

Medical and laboratory parameters

The medical and laboratory parameters refer to the 16 complications described in Table 1. Most of the measurements were done in the immunology laboratory and all of them refer to the immediate post-transplant period. The score on the medical parameters was found by scoring participants one point for each complication they had, leading to a value that could range from 0 to 16. Higher values show poorer health.

Table 1. Medical and laboratory parameters of liver transplant patients in immediate post-transplant period.

	Presence	Absence	Data unavailable
1. Post-surgery hemorrhaging	24	213	3
2. Cytomegalovirus	211	24	5
3. Epstein Barr virus	198	29	13
4. Bacterial infections	87	151	2
5. Viral infections	17	220	3
6. Fungal infections	7	230	3
7. Acute graft rejection	47	190	3
8. Vascular complications	7	230	3
9. Biliary complications	27	211	2
10. Respiratory complications	49	187	4

11. Refractory ascites	43	195	2
12. Neurological complications	43	194	3
13. Hemodynamic complications	47	189	4
14. Renal complications	119	119	2
15. Hematologic complications	85	149	6
16. Re-operations	29	209	2

Posttraumatic Growth

Recipients and caregivers filled in the Posttraumatic Growth Inventory (PTGI) [13]. This consists of 21 items answered on a Likert scale ranging from 0 ("no change") to 5 ("very great degree of change") thereby evaluating the perception of personal benefits in survivors of traumatic events. Test interpretation provides a total score of posttraumatic growth and the following five sub-dimensions: relating to others, new possibilities, personal strength, spiritual change, and appreciation of life. We used the Spanish version provided by Weiss and Berger.[25] For patients in this study, the Cronbach's alpha was 0.94 for the sum scale and ranged from 0.73 to 0.88 for the subscales. For caregivers, the Cronbach's alpha was 0.95 for the total scale and ranged from 0.77 to 0.90 for the various subscales.

Quality of life

The 12-Item Short Form Health Survey (SF-12v.2) [26,27] consists of 12 items with either 3 or 5-point Likert scales. It evaluates the following eight dimensions of health-related quality of life: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. The score on each dimension varies from 0 (worst state of health) to 100 (best state of health). The reliability of the eight scales varied in our sample from 0.72 to 0.89. In our study, this questionnaire was filled in only by recipients.

Procedure

After receiving Institutional Review Board approval, we recruited patients and family members from a clinical population of 1053 adult transplant recipients (Figure 1). At the beginning, all 569 patients still alive and their main caregivers were informed of the possibility of participation in the study by the Association of Liver Transplant Recipients and the Hepatic-Biliary-Pancreatic Surgery and Liver Transplant Unit. Inclusion criteria for both groups were: a) over 18 years of age, b) informed consent, c) no difficulties in understanding the evaluation instruments, d) no severe or disabling psychopathological condition, and e) reception of only one transplant. Thus, 240 recipients could be included in the study of whom 216 participated along with their caregiver.

Statistical analysis

Statistical analysis of the sample of 240 transplant recipients was performed using the SPSS 22 statistics program. Specific additional analyses were conducted on the subset of 216 participants for whom caregiver data was available. A Pearson's chi-squared test was used to compare qualitative variables (gender, marital status and education) in the various patient subgroups, and for quantitative variables (age and post-transplant complications), a one-way ANOVA with the Tukey HSD test for post-hoc comparisons was calculated. A 2x3 mixed factorial ANOVA and Bonferroni post-hoc test was performed to evaluate the impact of group factors (liver transplant recipients and caregivers) and time elapsed since transplantation on posttraumatic growth. Time since transplantation was categorized as follows: less ≤3.5 years; medium >3.5 to ≤9 years; more >9 years. A 3x3 factorial ANOVA and Bonferroni post-hoc test was calculated to analyze the association of time since transplantation (less, medium, more) and posttraumatic growth level (low, medium, high) on quality of life. Cohen's *d* (for quantitative variables) and Cohen's *w* (for qualitative variables) were computed for effect size.

RESULTS

Quality of life and time since transplantation in transplant recipients (n=240)

The association between quality of life and time since transplantation as well as posttraumatic growth was studied. In the first part of the analysis, the total sample of 240 patients was divided into three almost equal groups on the basis of time elapsed since transplantation: 78 patients ≤3.5 years (32.5%), 82 patients from >3.5 to ≤9 years (34.2%) and 80 patients >9 years (33.3%). There were no differences among subgroups in gender (p=0.150, w=0.13), marital status (p=0.744, w=0.05), education (p=0.450, w=0.12) or immediate post-transplant complications (p=0.377), although there were significant differences in age (56.46, SD=8.98 vs. 59.94, SD=8.39 vs. 64.14, SD=9.03; p<0.001). We found no significant interaction effect between time since transplantation and posttraumatic growth on quality of life (Table 2, Figure 2). The main effect time since transplantation showed a significant effect on the bodily pain dimension (p=0.017) in that after more than nine years since transplantation recipients showed more pain than after a medium duration of time (>3.5 and ≤9 years) (p=0.026, d=0.41) (Table 3). In comparison to the Spanish general population liver transplant recipients showed lower quality of life on almost all dimensions except for General Health regardless of the time since transplantation (Table 3, Figure 2).

Table 2. Quality of life: differences between liver transplant recipients by time since transplantation and patient posttraumatic growth levels (3 x 3 factorial ANOVA).

	Main effects		Interaction effects
	Time	Posttraumatic growth	
	$F_{(2,231)}$ (p)	$F_{(2,231)}$ (p)	$F_{(4,231)}$ (p)
Physical functioning	1.199 (0.303)	0.694 (0.501)	1.438 (0.222)
Role-physical	0.866 (0.422)	1.273 (0.282)	0.848 (0.496)
Bodily pain	4.138 (0.017)	0.808 (0.447)	0.760 (0.552)
General health	1.669 (0.191)	3.706 (0.026)	0.564 (0.689)
Vitality	0.076 (0.927)	4.031 (0.019)	0.254 (0.907)
Social functioning	0.103 (0.902)	2.440 (0.089)	0.852 (0.494)
Role-emotional	0.538 (0.585)	2.370 (0.096)	1.395 (0.237)
Mental health	1.062 (0.348)	1.543 (0.216)	1.129 (0.344)

Table 3. Quality of life in relation to time since transplantation in transplant recipients (factorial ANOVA and Bonferroni post-hoc test, Cohen's *d*) and compared to a Spanish population sample (unpaired *t* test, Cohen's *d*).

Comparisons on time since transplantation[1]	Physical functioning *p* (*d*)	Role-physical *p* (*d*)	Bodily pain *p* (*d*)	General health *p* (*d*)	Vitality *p* (*d*)	Social functioning *p* (*d*)	Role-emotional *p* (*d*)	Mental health *p* (*d*)
Less-Medium	1.000 (-0.05 N)	1.000 (-0.08 N)	1.000 (-0.04 N)	1.000 (0.15 N)	1.000 (-0.06 N)	1.000 (0.04 N)	1.000 (0.10 N)	1.000 (0.13 N)
Less-More	0.737 (0.18 N)	1.000 (0.12 N)	0.063 (0.37 S)	0.207 (0.29 S)	1.000 (-0.04 N)	1.000 (0.07 N)	0.920 (0.16 N)	0.441 (0.23 S)
Medium-More	0.428 (0.23 S)	0.573 (0.21 S)	0.026 (0.41 S)	1.000 (0.14 N)	1.000 (0.02 N)	1.000 (0.03 N)	1.000 (0.06 N)	1.000 (0.10 N)
Less-GSP	<0.001 (-0.78 M)	<0.001 (-0.72 M)	0.414 (-0.10 N)	0.052 (0.23 S)	0.013 (-0.29 S)	<0.001 (-0.46 S)	<0.001 (-0.45 S)	0.226 (-0.13 N)
Medium-GSP	<0.001 (-0.73 M)	<0.001 (-0.64 M)	0.633 (-0.06 N)	0.420 (0.09 N)	0.042 (-0.23 S)	<0.001 (-0.50 M)	<0.001 (-0.56 M)	0.029 (-0.25 S)

More-GSP	<0.001	<0.001	<0.001	0.748	0.031	<0.001	<0.001	0.003
	(-0.97 L)	(-0.85 L)	(-0.44 S)	(-0.04 N)	(-0.25 S)	(-0.52 M)	(-0.61 M)	(-0.35 S)

[1]Less (≤3.5 years), medium (>3.5 to ≤9 years), more (>9 years), GSP=General Spanish population, N=Null effect size, S=Small effect size, M=Medium effect size, L=Large effect size.

Quality of life and posttraumatic growth in transplant recipients (n=240)

In the second part of the analysis, the sample of 240 patients was divided into three equally-sized subgroups on the basis of total posttraumatic growth score: 80 patients with a low level of posttraumatic growth (33.3%; 0 to 59 points), 80 patients with a medium level (33.3%; 60 to 77 points), and 80 patients with a high level (33.3%; 78 to 105 points). There were no significant differences between subgroups concerning age (p=0.506), gender (p=0.639, w=0.06), marital status (p=0.720, w=0.05), education (p=0.187, w=0.16) or post-transplant complications (p=0.443).

There was no significant correlation between posttraumatic growth and time since transplantation (r=0.119; p=0.065). Neither did we find any significant interaction effect between time since transplantation and posttraumatic growth on quality of life (Table 2, Figure 3). Furthermore, recipients' posttraumatic growth was significantly related to the vitality dimension, with high compared to medium posttraumatic growth being associated with significantly more vitality (p=0.021, d=-0.43), as well as a statistical trend towards higher scores on general health (p=0.067, d=-0.36), social functioning (p=0.085, d=-0.35), and role-emotional (p=0.093, d=-0.34) with small effect sizes (Table 4). Compared to the general Spanish population, liver transplant recipients with lower levels of posttraumatic growth showed a generally lower quality of life. However, a high level of posttraumatic growth was associated with smaller differences, rendering the differences in the vitality (p=0.890, d=-0.02), mental health (p=0.353, d=-0.11), and bodily pain (p=0.307, d=-0.12) dimensions non-significant, even though the latter's dimension pattern differed, as it also showed a non-significant difference in the subgroup with low posttraumatic growth (p=0.142, d=-0.17). On the general health dimension there were no significant differences between the general population and the recipients' subgroups with low (p=0.827, d=-0.03) or medium (p=0.926, d=-0.01) posttraumatic growth. However, the subgroup with high levels of posttraumatic growth showed significantly higher scores on general health compared to the population sample (p=0.006, d=0.33) (Table 4, Figure 3).

Table 4. Quality of life in relation to posttraumatic growth (factorial ANOVA and Bonferroni post-hoc test, Cohen's *d*) and compared to a Spanish population sample (unpaired *t* test, Cohen's *d*).

Comparisons on posttraumatic growth level	Physical functioning *p* (*d*)	Role-physical *p* (*d*)	Bodily pain *p* (*d*)	General health *p* (*d*)	Vitality *p* (*d*)	Social functioning *p* (*d*)	Role-emotional *p* (*d*)	Mental health *p* (*d*)
Low-Medium	1.000 (-0.08 N)	1.000 (0.06 N)	1.000 (0.14 N)	1.000 (-0.02 N)	1.000 (0.11 N)	0.853 (0.17 N)	0.642 (0.20 S)	1.000 (0.12 N)
Low-High	0.723 (-0.19 N)	0.792 (-0.18 N)	1.000 (-0.06 N)	0.052 (-0.38 S)	0.130 (-0.32 S)	0.788 (-0.18 N)	1.000 (-0.14 N)	0.971 (-0.16 N)
Medium-High	1.000 (-0.10 N)	0.374 (-0.24 S)	0.650 (-0.20 S)	0.067 (-0.36 S)	0.021 (-0.43 S)	0.085 (-0.35 S)	0.093 (-0.34 S)	0.244 (-0.28 S)
Low-GSP	<0.001 (-0.92 L)	<0.001 (-0.77 M)	0.142 (-0.17 N)	0.827 (-0.03 N)	0.005 (-0.33 S)	<0.001 (-0.49 S)	<0.001 (-0.52 M)	0.028 (-0.26 S)
Medium-GSP	<0.001 (-0.83 L)	<0.001 (-0.84 L)	0.011 (-0.30 S)	0.926 (-0.01 N)	<0.001 (-0.43 S)	<0.001 (-0.67 M)	<0.001 (-0.72 M)	0.001 (-0.37 S)

High-GSP	<0.001	<0.001	0.307	0.006	0.890	0.004	<0.001	0.353
	(-0.73 M)	(-0.59 M)	(-0.12 N)	(0.33 S)	(-0.02 N)	(-0.32 S)	(-0.37 S)	(-0.11 N)

GSP=General Spanish population, N=Null effect size, S=Small effect size, M=Medium effect size, L=Large effect size.

Posttraumatic growth related to time since transplantation in transplant recipients (n=216) compared to their caregivers (n=216)

The sample of 216 liver transplant recipients who could be examined with their caregivers was divided on the basis of time elapsed since transplantation in three subgroups of equal size: 73 patients ≤3.5 years (33.8%), 71 patients from >3.5 to ≤9 years (32.9%), and 72 patients with >9 years (33.3%). There were no significant differences in gender (p=0.128, w=0.14), marital status (p=0.753, w=0.05), education (p=0.683, w=0.10), or medical complications in the immediate post-transplant period (p=0.164) among these subgroups, however, there were significant differences with regard to age (56.37, SD=9.18 vs. 60.44, SD=7.65 vs. 64.35, SD=9.37; p<0.001).

There was no significant effect of between-group interaction and time since transplantation on posttraumatic growth (F=0.196, p=0.822; Table 5, Figure 4). The main effect time elapsed since transplantation was not associated with posttraumatic growth. However, patients showed significantly higher scores than their caregivers on total posttraumatic growth (p<0.001), as well as on the subdimensions relating to others (p<0.001), new possibilities (p<0.001), and appreciation of life (p<0.001).

Table 5. Posttraumatic growth: differences between liver transplant recipients (G1) and their caregivers (G2) by time since transplantation (2 x 3 mixed factorial ANOVA and Bonferroni post-hoc test).

	Main effects		Interaction effects	Comparisons G1-G2 *p* (Cohen's *d*)			Comparisons time since transplantation *p* (Cohen's *d*)					
	Group	Time		Time since transplantation				G1 (n=216)			G2 (n=216)	
	$F_{(1,213)}$ (*p*)	$F_{(2,213)}$ (*p*)	$F_{(2,213)}$ (*p*)	Less a	Medium b	More c	a-b	a-c	b-c	a-b	a-c	b-c
Relating to others	23.081 (<0.001)	1.464 (0.234)	0.236 (0.790)	0.008 (0.32) S	0.020 (0.30) S	0.001 (0.46) S	1.000 (-0.02) N	0.270 (-0.29) S	0.369 (-0.27) S	1.000 (-0.05) N	0.908 (-0.17) N	1.000 (-0.12) N
New possibilities	33.157 (<0.001)	0.640 (0.528)	0.003 (0.997)	0.001 (0.36) S	0.001 (0.42) S	0.001 (0.45) S	1.000 (-0.03) N	0.987 (-0.16) N	1.000 (-0.14) N	1.000 (-0.02) N	1.000 (-0.14) N	1.000 (-0.12) N

Personal strength	0.001	0.424	0.744	0.425	0.868	0.365	1.000	0.438	1.000	1.000	1.000	1.000
	(0.976)	(0.655)	(0.476)	(-0.10)	(-0.02)	(0.13)	(-0.10)	(-0.24)	(-0.14)	(-0.02)	(-0.01)	(0.01)
				N	N	N	N	S	N	S	N	N
Spiritual change	0.001	2.192	0.349	0.898	0.537	0.584	1.000	0.227	0.143	1.000	0.529	0.960
	(0.975)	(0.114)	(0.706)	(0.02)	(-0.08)	(0.07)	(0.04)	(-0.29)	(-0.37)	(-0.06)	(-0.22)	(-0.17)
				N	N	N	N	S	S	N	S	N
Appreciation of life	18.490	0.109	0.067	0.006	0.028	0.014	1.000	1.000	1.000	1.000	1.000	1.000
	(<0.001)	(0.897)	(0.935)	(0.37)	(0.33)	(0.35)	(-0.02)	(-0.02)	(0.00)	(-0.09)	(-0.06)	(0.03)
				S	S	S	N	N	N	N	N	N
Total posttraumatic growth	17.109	0.983	0.196	0.028	0.041	0.004	1.000	0.417	0.674	1.000	1.000	1.000
	(<0.001)	(0.376)	(0.822)	(0.25)	(0.26)	(0.38)	(-0.04)	(-0.24)	(-0.21)	(-0.05)	(-0.14)	(-0.09)
				S	S	S	N	S	S	N	N	N

G1=Liver transplant recipients, G2=Caregivers, N=Null effect size, S=Small effect size.

DICCUSSION

To the best of our knowledge, our study is the first on the relationship between posttraumatic growth and quality of life in liver transplant recipients. In this context we were not only interested in the patient, but also in the family support system as represented by the caregiver. We found that, regardless of time elapsed since transplantation, recipients showed more posttraumatic growth than their caregivers. This result confirms our hypothesis and is in keeping with findings in HSCT-recipients [21] and other cancer patients.[22,23] It might be argued that the patients themselves have been directly exposed to traumatic events such as liver disease, transplant surgery, and the side effects of immunosuppressants, which increases the activation of intrapersonal resources, thereby leading to higher levels of posttraumatic growth. Furthermore, liver transplantation symbolizes the beginning of a new life for the patient, often after a long period of physical suffering and fear of death. This may be associated with a sense of gratitude towards the deceased donor and the medical team, and a feeling of personal responsibility for justifying all their efforts, which may in turn mobilize a large amount of energy.[6,28]

The specific aspects of posttraumatic growth, as captured mainly by the relating to others, new possibilities and appreciation of life subscales, proved to be relevant, as also found in previous studies.[16,28,29] Posttraumatic growth did not alter significantly over the course of time, a phenomenon also observed in breast cancer [30] and colorectal cancer patients.[31] This may be partially explained by the psychological construct of posttraumatic growth itself, which is described by Tedeschi and Calhoun as: *"The phenomenon is complex, and cannot easily be reduced to simply a coping mechanism, a cognitive distortion, psychological adjustment or well-being, or a host of apparently similar constructs. The outcomes of posttraumatic growth might be best considered as iterative, and it will take longitudinal work to trace the varied trajectories of the posttraumatic growth process. This process is likely to involve a powerful combination of demand for emotional relief and cognitive clarity, that is achieved through construction of higher order schemas that allow for appreciation of paradox"* (p.15).[12] Thus the process of posttraumatic growth is thought

to be iterative, thereby gradually constructing higher order schemas, which involve rather small slow alterations, relatively stable over time. This is also reflected in the construction of the posttraumatic growth inventory, which asks participants to indicate for each statement the degree to which this change occurred during their life as a result of the crisis/disaster. This concrete formulation of a change in life in response to a specific disaster would suggest a stable cognitive-behavioral pattern rather than a state sensitive to fluctuation.

Our hypotheses with respect to quality of life were partially confirmed, since neither time nor posttraumatic growth was significantly associated with all the dimensions of quality of life. Moreover, on most quality of life dimensions, recipients showed significantly lower scores than the general population. In accordance with the above mentioned definition, one might argue that posttraumatic growth does not immediately lead to higher quality of life, as it mirrors the inner struggle to form a convincing narrative from existential paradoxes associated with life-threatening disease. We found that only the SF-12 bodily pain dimension was significantly related to time since transplantation. This finding may be explained by the increase in imunosuppressant side effects, such as arthralgia and muskuloskeletal pain, over time.[32,33] In addition our findings displayed particularly low levels of quality of life compared to the general population [5] after a post-transplantation time-span of over nine years. In the long run, the combination of the side effects of medication and the restrictions of medical treatment, such as diet and ongoing medical supervision, may negatively affect recipients' quality of life.

A high level of posttraumatic growth in recipients compared to a medium level was associated with significantly higher scores on vitality, and a statistical trend towards higher scores on general health, social functioning and role-emotional. Recipients with high posttraumatic growth vitality scores even equaled scores in the general population. In general, a high level of posttraumatic growth was associated with smaller differences between quality of life scores in recipients and the general population, rendering the differences on bodily pain, vitality and mental health non-significant and revealing even higher scores on general health. These findings highlight the

potentially protective role of posttraumatic growth in liver transplant patients and are in keeping with other studies which showed a positive association between posttraumatic growth and quality of life, even though to date the clinical relevance of these findings is not clear.[16,30,34] In line with the protective role of posttraumatic growth, personality traits such as extraversion, optimism, and openness to experience have been positively associated with this psychological construct.[35]

From a clinical perspective, the posttraumatic growth inventory could be used after liver transplantation to identify those patients who are in special need of psychological support. Mindfulness-based stress reduction [36] and positive psychotherapy [37] have demonstrated their efficacy in augmenting posttraumatic growth in patients.

Our study had several limitations. First, we did not analyze the relevance of further clinical variables, such as the etiology of the liver disease [8], or personality variables, such as specific coping strategies, on posttraumatic growth.[38] Second, we did not assess long-term transplant-related health parameters, such as infections, rehospitalization or other complications. Third, recruitment of patients took place at a single site which may limit external validity of findings. Finally, the study design was not longitudinal, so it was not possible to explore individuals' change in PTG and quality of life over time, which would allow for the investigation of causal relationships.

Nevertheless, the large sample size and the analysis of recipients and caregivers can be seen as a major strength of this study.

CONCLUSIONS

To summarize, our study demonstrated that regardless of the time elapsed since liver transplantation, recipients showed more posttraumatic growth than their caregivers. A high level of posttraumatic growth was associated with high levels of specific aspects of quality of life such as vitality, whereas a longer time span since transplantation was related to more pain. Compared to the general population, recipients generally showed lower quality of life, except in patients with high

levels of posttraumatic growth, in whom specific dimensions of quality of life, such as bodily pain, vitality, mental health and general health, equaled or even surpassed scores in the general population. Facilitation of posttraumatic growth after liver transplantation may be crucial to ensure long-term quality of life in recipients.

ACKNOWLEDGMENTS

The authors would like to thank all the participants (liver transplant patients and their family members).

CONTRIBUTORS

MÁPSG and AMR: Study concept and design, data analysis and interpretation, drafting of manuscript, manuscript revisions, and drafting figures. MBM and MLAN: Study concept and design, critical revision of article. JPB: Institutional support, data collection, critical revision of article. RC and MÁGB: Data analysis and interpretation, drafting of manuscript, critical revision of article. All authors gave final approval to the version submitted for publication.

FUNDING

This study was funded by the Spanish Ministry of Economy and Competitiveness (Project PSI2014-51950-P).

COMPETING INTERESTS

None declared.

DATA SHARING STATEMENT

Data may compromise the privacy of study participants and may not be shared publicly. The public availability of the data is restricted by the Ethics Committee of the Virgen del Rocío

University Hospital of Seville (Spain). Data are available upon request to the authors. Contact person: Dra. M.A. Pérez-San-Gregorio (anperez@us.es).

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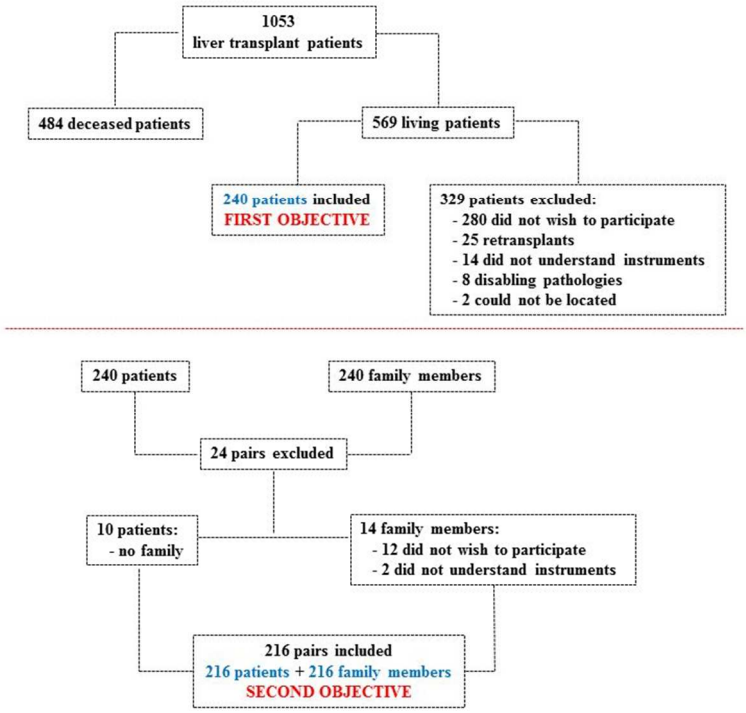
FIGURES

Figure 1. Participant selection for the study's two objectives.

Figure 2. Relationship between time since transplantation and quality of life. Comparison with General Spanish population. Lower mean scores show poorer quality of life. GSP=General Spanish population. Less (≤3.5 years), medium (>3.5 to ≤9 years), more (>9 years).

Figure 3. Relationship between posttraumatic growth level and quality of life. Comparison with General Spanish population. Lower mean scores show poorer quality of life. GSP=General Spanish population.

Figure 4. Posttraumatic growth: mean scores on variables with statistically significant differences between the two groups. Higher scores show more growth. G1=Liver transplant recipients (n=216), G2=Caregivers (n=216).



Participant selection for the study's two objectives.

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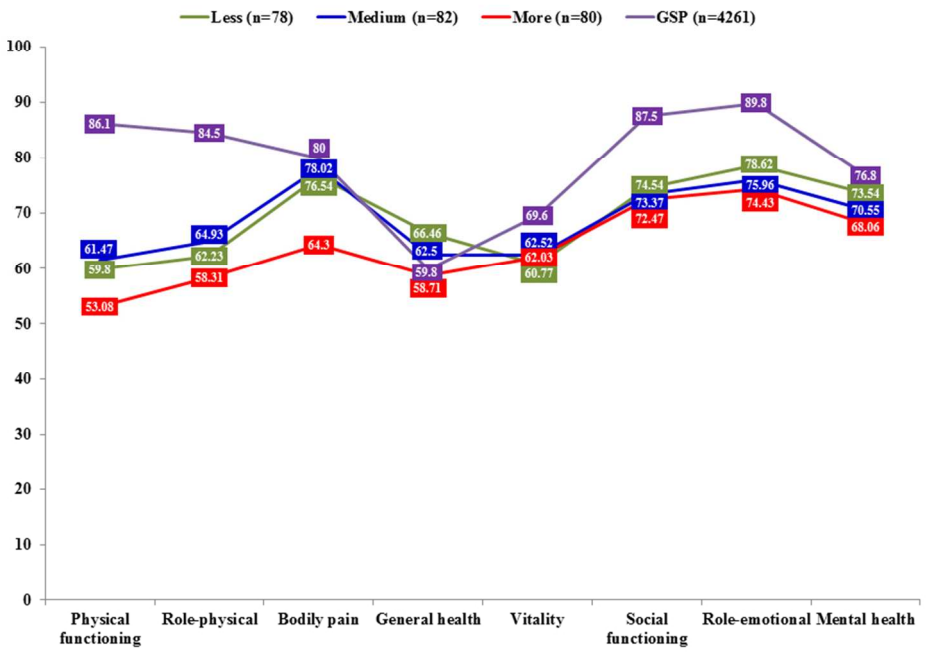

Relationship between time since transplantation and quality of life. Comparison with General Spanish population. Lower mean scores show poorer quality of life. GSP=General Spanish population.Less (≤3.5 years), medium (>3.5 to ≤9 years), more (>9 years).

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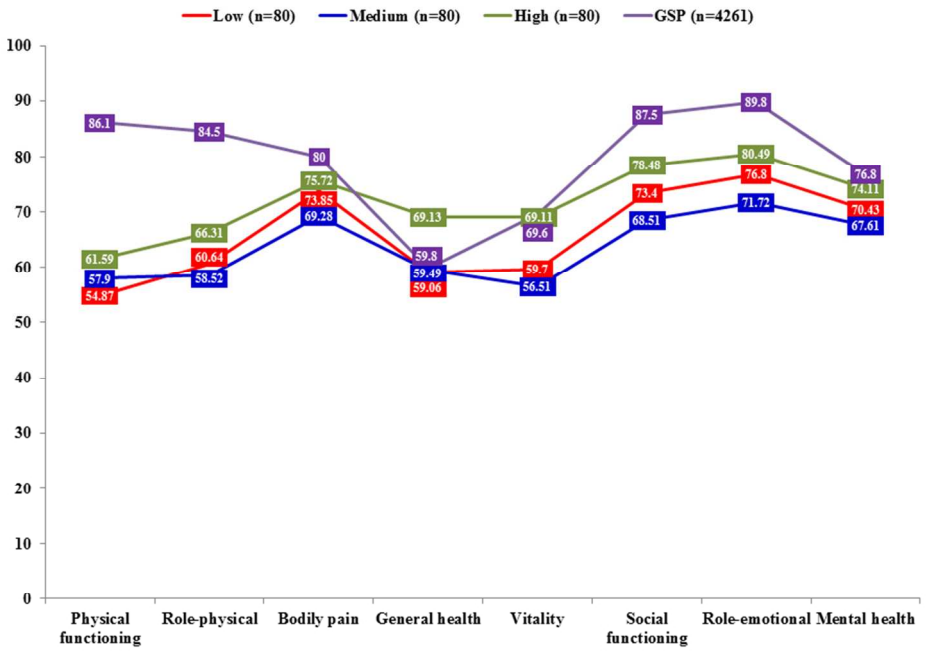

Relationship between posttraumatic growth level and quality of life. Comparison with General Spanish population. Lower mean scores show poorer quality of life. GSP=General Spanish population.

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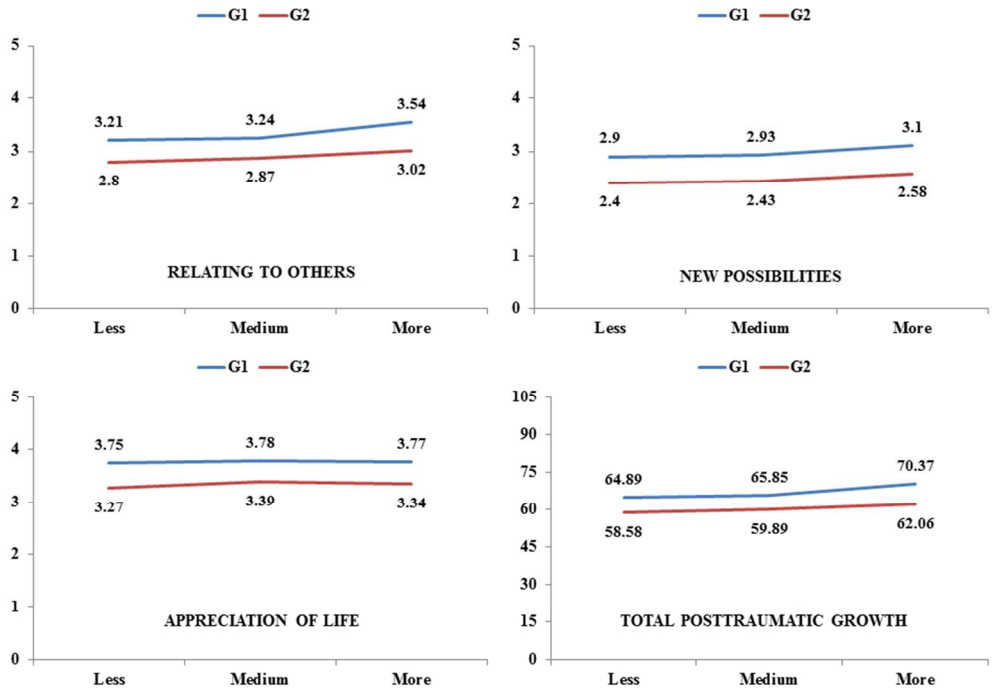

Posttraumatic growth: mean scores on variables with statistically significant differences between the two groups. Higher scores show more growth. G1=Liver transplant recipients (n=216), G2=Caregivers (n=216).

81x60mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2, 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4, 5
Objectives	3	State specific objectives, including any prespecified hypotheses	5, 6
Methods			
Study design	4	Present key elements of study design early in the paper	9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6, 7, 8, 9
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	9, Figure 1
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6 to 9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6 to 9
Bias	9	Describe any efforts to address potential sources of bias	9
Study size	10	Explain how the study size was arrived at	9, Figure 1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	9
		(*c*) Explain how missing data were addressed	Not applicable
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	Not applicable
		(*e*) Describe any sensitivity analyses	Not applicable
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6, 7, Figure 1
		(b) Give reasons for non-participation at each stage	9, Figure 1
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6, 7
		(b) Indicate number of participants with missing data for each variable of interest	Not applicable
Outcome data	15*	Report numbers of outcome events or summary measures	10 to 19, Tables 2 to 5, Figures 2 to 4
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10, 14, 17
		(*b*) Report category boundaries when continuous variables were categorized	10, 14, 17
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10 to 19, Tables 2 to 5, Figures 2 to 4
Discussion			
Key results	18	Summarise key results with reference to study objectives	22, 23
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	22
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	20 to 23
Generalisability	21	Discuss the generalisability (external validity) of the study results	22
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	23

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.