

Psychosocial Predictors of Upper Extremity Transplantation Outcomes: A Review of the International Registry 1998–2016

Sarah E. Kinsley, PA-C*
 Shuang Song, MPH, DVM†
 Palmina Petruzzo, MD‡
 Claudia Sardu, PhD§
 Elena Losina, PhD, MSc†
 Simon G. Talbot, MD*

Background: Upper extremity transplantation (UET) is becoming increasingly common. This article attempts to collate data from cases contributing to the International Registry on Hand and Composite Tissue Transplantation (IRHCTT), define psychosocial themes perceived as predictors of success using statistical methods, and provide an objective measure for optimization and selection of candidates.

Methods: The IRHCTT provided anonymous data on UET recipients. A supplementary psychosocial survey was developed focusing on themes of depression, posttraumatic stress disorder (PTSD), anxiety, interpersonal functioning and dependence, compliance, chronic pain, social support, quality of life, and patient expectations. We determined the risk of transplant loss and psychological factors associated with higher risk of transplant loss.

Results: Sixty-two UET recipients reported to the IRHCTT. Forty-three psychosocial surveys (68%) were received, with 38 (88%) having intact transplants and 5 (12%) being amputated. Among recipients with a diagnosis of anxiety (N = 29, 67%), 5 (17%) reported transplant loss ($P = 0.03$). Among those with depression (N = 14, 33%), 2 recipients (14%) has transplant loss ($P = 0.17$); while 4 recipients (22%) with PTSD (N = 18, 42%) had transplant loss ($P = 0.01$). Of participants active in occupational therapy (N = 28, 65%), 2 (7%) reported transplant loss ($P = 0.09$). Of recipients with realistic functional expectations (N = 34, 79%), 2 (6%) had transplant loss versus 3 (34%) who were felt to not have realistic expectations (N = 9, 21%, $P = 0.05$). Recipients with strong family support (N = 33, 77%) had a lower risk of transplant loss compared with poor or fair family support (N = 10, 23%), but did not reach statistical significance (6% versus 30%, $P = 0.14$).

Conclusion: Anxiety, depression, PTSD, participation in occupational therapy, expectations for posttransplant function, and family support are associated with postsurgical transplant status. (*Plast Reconstr Surg Glob Open* 2020;8:e3133; doi: 10.1097/GOX.0000000000003133; Published online 23 September 2020.)

INTRODUCTION

Upper extremity vascularized composite allotransplantation, commonly referred to as upper extremity transplantation (UET), has moved from an experimental option

From the *Division of Plastic Surgery, Brigham and Women's Hospital, Boston, Mass.; †Department of Orthopedic Surgery, Brigham and Women's Hospital, Boston, Mass.; ‡Department of Surgery, University of Cagliari, Cagliari, Italy; and §Department of Public Health, University of Cagliari, Cagliari, Italy.

Received for publication June 8, 2020; accepted July 31, 2020.

S.E. Kinsley and S. Song contributed equally to this study.

Copyright © 2020 The Authors. Published by Wolters Kluwer Health, Inc. on behalf of The American Society of Plastic Surgeons. This is an open-access article distributed under the terms of the [Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 \(CCBY-NC-ND\)](https://creativecommons.org/licenses/by-nc-nd/4.0/), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

DOI: 10.1097/GOX.0000000000003133

to the most commonly performed type of reconstructive transplantation.¹ This transition has occurred without detailed, comprehensive, and objective analysis of the factors that predict success or failure of these unique transplants. Anecdotal evidence and expert opinion suggest that psychosocial factors are an important contributor to consistent, predictable, and reliable patient outcomes.²

Much of our current research is centered on surgical technique, transplant survival, immunosuppression,^{3–5} and rehabilitation protocols,^{6,7} with limited emphasis

Disclosure: The authors have no financial interest to declare in relation to the content of this article. This work is funded by the NIH award W81XWH-17-1-0400, K24AR057827, and P30AR072577.

Related Digital Media are available in the full-text version of the article on www.PRSGlobalOpen.com.

placed on the importance of patient selection.^{2,8-11} Often, UET candidacy is based on prior experience with more routine surgical procedures or based on biases from small numbers of transplants. To date, psychosocial factors in UET patients have been poorly published, likely related to the difficulty in gathering data in these areas and their seeming intangibility.

This article presents the summary of data from the International Registry on Hand and Composite Tissue Transplantation (IRHCTT)—the primary registry for data from almost all UET centers worldwide—and describes psychosocial themes perceived as predictors of success using statistical methods. These data may offer important insights into defining objective measures for the optimization and selection of UET candidates.

METHODS

The IRHCTT is a global registry dedicated to collecting information on all face and UET. Through collaboration with the IRHCTT, deidentified data were collected in 2016 on 62 UET recipients (36 bilateral and 26 unilateral). This comprised the vast majority of UET recipients at this time. These data included factors pertaining to demographics; anatomy (level of amputation, transplant performed); graft status; medical, immunological (tissue matching, immunosuppression), surgical (ischemia time, vessels/nerves coapted), and rejection status; and social factors for transplant donors and recipients. Psychosocial factors were limited to alcohol, nicotine, and drug use, and an unstandardized perceived level of satisfaction.

Given the limited psychosocial data, a supplementary survey was developed based on an aggregation of solid-organ transplant candidacy assessment instruments: the “Psychosocial Assessment of Candidates for Transplantation,”¹² the “Transplant Evaluation Rating Scale,”¹³ and the “Stanford Integrated Psychosocial Assessment for Transplantation,”¹⁴ which emphasized the importance of psychiatric history, family support, substance dependency history, knowledge of transplantation, and history of compliance.

Our survey focused on themes of depression, post-traumatic stress disorder (PTSD), anxiety, interpersonal functioning and dependence, compliance (including medication compliance, punctuality, and participation in therapy), chronic pain, social support, quality of life, and patient expectations. While several of these diagnoses were based on validated metrics, several were at the discretion of the treating team, accepting that the tradeoff for diagnostic accuracy was a greater sample size. The survey was distributed by email to the leaders at each worldwide UET center contributing to the IRHCTT. Emails were resent 3 times. Centers who did not respond were personally approached at the International Society of Vascularized Composite Allograft Transplantation (ISVCA) conference in 2017. The survey was completed by each center’s lead clinician, psychiatrist, or their designee.

In the analysis, we included the 4 prospectively collected variables from the IRHCTT (alcohol, nicotine, drug use, and level of satisfaction) and 19 psychosocial risk factors

from the supplementary survey focusing on UET recipients’ psychosocial health, including depression, PTSD, anxiety, interpersonal functioning and dependence, medication compliance, punctuality, participation in therapy, chronic pain, social support, quality of life, and patient expectations. Transplanted extremity status at the time of the survey was selected as the indicator of postsurgery outcome, coded as “intact” or “amputated.” Given the limited sample size and sparse expected cell frequency in the contingency table, the Fisher exact test of independence was used to test the association between psychosocial factors and postsurgical transplant status. The analysis was completed in SAS version 9.4 (SAS Institute Inc, Cary, N.C.).

RESULTS

From the 19 worldwide transplant centers registered in the IRHCTT, deidentified data was collected on 62 UET recipients from 1998 to 2016. Of these 62 recipients, 43 psychosocial surveys (69%) were retrospectively completed by the centers. The mean follow up from surgery at the time of survey was 7 years with 6 surveys being completed within 1 year of transplant. Survey responses were scored between 1 and 5, with 1 being the least favorable answer and 5 being the most favorable, suggesting that transplant recipients with a wide range of psychosocial variables have been transplanted (see appendix 1, Supplemental Digital Content 1, which displays psychosocial survey of upper extremity transplant recipients, <http://links.lww.com/PRSGO/B478>).

Of the 43 survey responses, 38 recipients (88%) had intact transplant(s) after receiving UET and 5 (12%) recipients had their transplant(s) amputated. Table 1 and Supplemental Digital Content 2 show the distribution of responses related to psychosocial factors of transplant recipients stratified by transplant status (intact or amputated) at the time of survey completion in 2017. (See appendix 2, Supplemental Digital Content 2, which displays summary statistics of survey result by graft status (intact/amputated), <http://links.lww.com/PRSGO/B479>).

In total, 29 of 43 transplant recipients (67%) were reported to have anxiety. Among those patients with anxiety, 5 underwent transplant removal (17%). No recipients without anxiety (N = 14, 33%) reported transplant loss ($P = 0.03$).

One-third of our UET population were reported as having depression (N = 14, 33%). Of the 14 recipients treated for depression, there was minimally higher risk of transplant removal compared with patients without depression (N = 29, 67%), this difference is well below statistical significance (14% versus 10%; $P = 0.17$).

Among UET recipients with PTSD (N = 18, 42%), 4 recipients (22%) had their transplant(s) removed; among non-PTSD transplant recipients (N = 25, 58%), only 1 subject (4%) underwent transplant removal ($P = 0.02$).

We observed a negative association between participation in occupational therapy (OT) and transplant removal. While the majority of our UET recipients actively engaged in OT and home exercises (N = 28, 65%), recipients who did not “actively participate and perform exercises at home” (N = 15, 35%) had a nearly 3-fold risk of

Table 1. Short Summary of Survey Results Statistics by Graft Status (Intact/Amputated)

	Graft Status		<i>P</i> *
	Intact (N = 38), N (%)	Amputated (N = 5), N (%)	
Anxiety			
Not at all anxious	14 (100.00)		
A little anxious	11 (91.67)	1 (8.33)	
Somewhat anxious	9 (90.00)	1 (10.00)	0.0296
Anxious	4 (57.13)	3 (42.86)	
Depression			
Depressed	8 (100.00)		
Somewhat depressed	4 (66.67)	2 (33.33)	0.1718
Good mood	26 (89.66)	3 (10.34)	
Posttraumatic stress disorder			
No symptoms	24 (96.00)	1 (4.00)	
Some symptoms	6 (60.00)	4 (40.00)	0.01262
Many symptoms	8 (100.00)		
Participation in therapy			
Does not actively participate	2 (10.00)		
Distant in therapy		1 (100.00)	
Somewhat engaged in therapy but does not perform exercises at home	4 (100.00)		0.0872
Engaged in therapy and sometimes performs exercises at home	6 (75.00)	2 (25.00)	
Actively participates and performs exercises at home	26 (92.86)	2 (7.14)	
Were patients' expectations for posttransplant function realistic?			
Yes	32 (94.12)	2 (5.88)	0.0535
No	6 (66.67)	3 (33.33)	
Family/Friend Support System			
Poor (patient is alone and uses most outside services)	2 (66.67)	1 (33.33)	
Fair (support is involved when necessary, but patient relies on outside support)	5 (71.43)	2 (28.57)	
Good (support is involved and often assists with transportation and homecare)	6 (100.00)		0.1387
Very involved (very involved support that assists in transportation and homecare)	25 (92.59)	2 (7.41)	

*More than 20% of cells have expected frequencies <5, Fisher's exact was used to calculate *P* value.

transplant removal compared with recipients who actively participated in therapy. This difference did not reach statistical significance (20% versus 7%; $P = 0.09$). Recipients who were not "always on time" for OT ($N = 19$, 44%) also had double the risk of transplant removal compared with recipients who were "always on time" for OT ($N = 24$, 55%), although again this did not reach statistical significance (16% versus 8%; $P = 0.29$).

Most UET recipients in our study were felt to have realistic expectations toward posttransplant function. Recipients' expectations toward posttransplant function show a strong association with posttransplant status. Among recipients felt to have realistic expectations of postsurgical function ($N = 34$, 79%), 2 recipients (6%) lost their transplants, compared with 3 recipients (33%) who did not have realistic expectations ($N = 9$, 21%; $P = 0.05$).

The majority of UET recipients had good or very involved family/friend support at the time of survey completion ($N = 33$, 77%). Recipients with strong support had a lower chance of transplant removal compared with recipients with poor or fair support ($N = 10$, 23%), but the difference did not reach statistical significance (6% versus 30%; $P = 0.14$).

DISCUSSION

Through review of deidentified data in the IRHCTT, psychosocial data were found to be lacking on transplant recipients. A survey was developed to further evaluate the role of psychosocial factors of each transplant recipient, as perceived by each center's transplant surgeon, psychiatrist, and/or designee. Transplant recipients with anxiety, depression, and symptoms of PTSD were more likely to

have undergone transplant removal at the time of survey completion. Risk of transplant removal was negatively associated with active participation in OT, realistic expectations for posttransplant function, and family support.

Psychosocial evaluation of factors associated with UET success is limited and, to date, this is the largest study of its kind. Other groups have correlated psychosocial variables with disability after extremity injuries and found similar importance of psychosocial variables.¹⁵ On review of our own center's first successful transplant recipient at 3.5 years posttransplant, we discussed the stability in psychosocial outcome scores as demonstrating "well compensated, both functionally and psychologically, functioning quite independently... and with very stable social support."¹⁶ Our quantitative findings mirror and strengthen this assessment of a psychosocially stable candidate with consistent social support and reliable compliance, leading to a low incidence of transplant failure. Transplant recipients with anxiety, depression, and poor compliance, as demonstrated by a lack of therapy participation and medication compliance, have a greater risk of transplant removal. While these findings may seem obvious and/or intuitive, we believe there is value in confirming this formally, and recognize that these are associations rather than either directly causative of transplant removal. Importantly, understanding these important variables allows us both to be cognizant during patient evaluation and also to focus resources in modifying those factors that can be optimized pre- and posttransplantation. These factors are not intended to be contraindications to candidacy.

This study suffers from several important limitations. First, this is a retrospective study. Second, this field is limited by its small patient population, albeit including

almost all transplant recipients to date worldwide. We have attempted to gather the most data possible using all data contained within the IRHCTT and individually surveying each center participating in the IRHCTT. Related to this, there may be a contribution of nonresponse bias. Third, due to the limited statistical power, we cannot draw definitive conclusions nor conduct stratified analysis for certain age groups and sex. Fourth, there is no standardized patient selection method,^{2,8,17} and selection bias prevails in transplant candidacy. Fifth, there is limited global standardization of psychiatric care and psychosocial metric utilization between transplant centers. We chose to be inclusive to ensure international participation even though we realize that there is variability in psychosocial diagnoses. Sixth, since our survey data were collected from surgeons and psychiatrists, whose answers were based on reflection of patients, our results are also prone to recall bias. Seventh, this study is lacking in expert consensus of these psychosocial factors being associated with transplant outcomes and revalidation is needed. We are in the process of qualitative research methodology to better elucidate and confirm these factors. Eighth, we recognize reasons for UET loss or failure are multifactorial. The aim of this study was to examine whether psychosocial factors are associated with limb loss by any cause rather than the mechanism by which that may happen.

Nevertheless, we believe that these data help form the basis for making informed choices and directing resources, and will help encourage further study into the psychosocial aspects of UET.

CONCLUSIONS

Our study suggests that psychosocial factors play a role in determining postoperative outcomes among UET recipients. Anxiety, depression, PTSD, participation in OT, expectations for posttransplant function, and family support are all associated with postsurgical transplant status, among which anxiety, PTSD, and posttransplant expectation reached statistical significance at alpha level 0.05. A deeper understanding of the psychosocial themes associated with UET outcomes is vital to developing standardized guidelines for recipient optimization and candidacy.

Simon G. Talbot, MD

Division of Plastic Surgery
Brigham and Women's Hospital
75 Francis Street
Boston, MA 02115
E-mail: sgtalbot@bwh.harvard.edu

ACKNOWLEDGMENTS

The authors gratefully acknowledge participants of the IRHCTT (Australia, Melbourne; Austria, Innsbruck; Belgium, Brussels; France, Lyon, Paris; India, Kochi, Kerala and

Pondicherry; Italy, Monza; Mexico, Mexico City; Poland, Wroclaw; South Korea, Daegu; Spain, Madrid, Valencia; Taiwan, Kaohsiung; Turkey, Antalya; United Kingdom, Leeds; United States, Atlanta/Durham, Boston, Los Angeles, Louisville, Philadelphia, and San Antonio).

REFERENCES

1. Shores JT, Brandacher G, Lee WP. Hand and upper extremity transplantation: an update of outcomes in the worldwide experience. *Plast Reconstr Surg*. 2015;135:351e–360e.
2. Jowsey-Gregoire SG, Kumnig M, Moreno E, . The Chauvet 2014 meeting report: psychiatric and psychosocial evaluation and outcomes of upper extremity grafted patients. *Transplantation*. 2016;100:1453–1459.
3. Kanitakis J, Jullien D, Petruzzo P, et al. Clinicopathologic features of graft rejection of the first human hand allograft. *Transplantation*. 2003;76:688–693.
4. Foroohar A, Elliott RM, Kim TW, et al. The history and evolution of hand transplantation. *Hand Clin*. 2011;27:405–9, vii.
5. Cavadas PC, Ibáñez J, Thione A, et al. Bilateral trans-humeral arm transplantation: result at 2 years. *Am J Transplant*. 2011;11:1085–1090.
6. Bueno E, Benjamin MJ, Sisk G, et al. Rehabilitation following hand transplantation. *Hand (N Y)*. 2014;9:9–15.
7. Petruzzo P, Lanzetta M, Dubernard JM, et al. The international registry on hand and composite tissue transplantation. *Transplantation*. 2010;90:1590–1594.
8. Shore, JT. Recipient screening and selection: who is the right candidate for hand transplantation. *Hand Clin*. 2011;27:539–543.
9. Kumnig M, Jowsey SG, DiMartini AF. Psychological aspects of hand transplantation. *Curr Opin Organ Transplant*. 2014;19:188–195.
10. Kumnig M, Jowsey SG, Moreno E, et al. An overview of psychosocial assessment procedures in reconstructive hand transplantation. *Transpl Int*. 2014;27:417–427.
11. Kiwanuka H, Aycart MA, Bueno EM, et al. Experience with patient referrals for upper extremity transplantation at a U.S. academic medical center. *J Hand Surg Am*. 2017;42:751.e1–751.e6.
12. Olbrisch ME, Levenson JL, Hamer R. The PACT: a rating scale for the study of clinical decision making in psychosocial screening of organ transplant candidates. *Clin Transplant*. 1989;3:164.
13. Twillman RK, Manetto C, Wellisch DK, et al. The transplant evaluation rating scale. A revision of the psychosocial levels system for evaluating organ transplant candidates. *Psychosomatics*. 1993;34:144–153.
14. Maldonado JR, Dubois HC, David EE, et al. The Stanford Integrated Psychosocial Assessment for Transplantation (SIPAT): a new tool for the psychosocial evaluation of pre-transplant candidates. *Psychosomatics*. 2012;53:123–132.
15. Jayakumar P, Overbeek CL, Lamb S, et al. What factors are associated with disability after upper extremity injuries? A systematic review. *Clin Orthop Relat Res*. 2018;476:2190–2215.
16. Singh M, Oser M, Zinser J, et al. Psychosocial outcomes after bilateral hand transplantation. *Plast Reconstr Surg Glob Open*. 2015;3:e533.
17. Caplan AL, Parent B, Kahn J, et al. Emerging ethical challenges raised by the evolution of vascularized composite allotransplantation. *Transplantation*. 2019;103:1240–1246.