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SEX DIFFERENCES IN DONOR SITE MORBIDITY AFTER MICROVASCULAR FREE TISSUE HEAD AND NECK RECONSTRUCTION

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ABSTRACT

Background: The purpose of this study is to investigate whether sex plays a role in donor site dysfunction after head and neck reconstruction.

Methods: In this retrospective case series, seventy-six patients were assessed for donor site morbidity using the Short Form 36, Short Musculoskeletal Function Assessment, Disabilities of the Arm, Shoulder, and Hand, and Lower Limb Core Scale. Differences by sex were compared using t-tests. Multivariable linear regression analysis was conducted to adjust for potential confounders.

Results: Females observed significantly greater disability for the SF-36 Mental Component (MCS) score with a mean of 45.9 (SD 10.5) compared to males, with a mean of 51.8 (SD 10.2), p= 0.02. Sex is significantly related to SF-36 MCS after controlling for neuropsychiatric disease and tracheostomy status.

Conclusion: Females reported significantly worse mental component scores compared to males undergoing free flap reconstruction of the head and neck.

Keywords: head and neck neoplasm, free tissue flaps, sex differences, sex characteristics, quality of life.

Introduction

Globally, head and neck cancer (HNC) is a common malignancy accounting for more than 650,000 cases and 330,000 deaths annually.[1] In the United States HNC is responsible for 3 per cent of malignancies, with approximately 53,000 new cases annually. HNC accounts for almost 15,000 deaths per year. [2] Males are 2.7 times more likely to develop oral and pharyngeal cancer and 2.8 times more likely to die of this disease when compared to females. Males are 4.5 times more likely to develop larynx cancer and 4.8 times more likely to die of this disease when compared to females. [3] Although these differences alone are insufficient to explain the threefold higher male HNC rates, males are 1.26 times more likely to drink alcohol and 1.48 times more likely to smoke in the U.S. Some hormone protective theories have been suggested to explain sex differences in head and neck cancer, but the evidence is not conclusive. [4] Further studies are needed to elucidate these differences.

Treatment of head and neck cancer affects function and appearance. Surgical treatment of HNC can obviously cause deficits in speech, swallowing, cosmesis and breathing which affect quality of life. [5] The introduction of microvascular free tissue transfer in the 1970s greatly improved the treatment of head and neck cancer by providing better functional and aesthetic results after reconstruction. [6] Free flap utilization has become the standard for reconstruction after HNC resection, proving more versatile for wound closure, appearance, and restoration of function. [6,7] With significant improvements in success rates for free flap reconstruction, attention has turned to donor-site morbidity. [8] Many issues have been also associated with their use

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including systematic, recipient site and donor site complications. [9] Age, sex, alcohol use, tobacco use, pre-operative irradiation, comorbidity grade, cancer stage, operative time and reconstruction characteristics have all been studied to determine if they affect outcomes after microvascular reconstruction. Singh et al. [9] noted that preoperative morbidity and prior radiation are factors associated with the development and complications. Egestad et al. [10] and Peters et al.[11] concluded that age was a predictor of medical complications. Loupatazi et al.[12] found that female sex and alcohol use were associated with severe complications. Sex has been studied as a variable in the quality of life for HNC patients, but most results do not show significant differences. [10,11,13] However, our group recently reported a trend in greater emotional disability among females. [14,15] Although sex differences have been shown in incidence, morbidity and mortality in HNC, few studies have examined the effect of sex as a factor of donor site morbidity.

This study aimed to detect whether differences exist in donor site morbidity between males and females following head and neck free tissue reconstruction.

Methods

A retrospective study was designed to identify all head and neck reconstruction patients who specifically underwent free tissue reconstruction. Patients were excluded if they were unable or failed to complete all questions in the study tool. No sex, racial/ethnic, or educational level exclusion criteria were used. All patients were called by the senior author or members of the research staff to assess their willingness to participate in the survey. Surveys were then mailed to all patients in a single packet. If surveys were not returned, the patients were then called to request the completion and return of the surveys. Surveys were then completed either

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over the telephone or at their next follow-up visit. We used general, site-specific, and disease-specific questionnaires to study post-operative patients. Four validated instruments were used: (general) Short Form 36 Health Survey (SF-36) with its two categories, Physical Component Summary (PCS) and Mental Component Summary (MCS),[16,17] (disease-specific) Short Musculoskeletal Function Assessment Questionnaire (SMFA) which has two indices—the functional index (FI) and the bothersome index (BI), [18,19] and (site-specific) Lower Limb Core Scale (LLCS), [19-21]and Disabilities of the Arm, Shoulder and Hand (DASH).[22]Patients' general well-being was assessed using the SF-36 questionnaire. This questionnaire evaluates eight distinct elements, including bodily pain, physical function, general health, vitality, mental health, social function, and role limitations secondary to physical and emotional problems, but it can be aggregated into two over-arching categories—mental health (MCS) and physical health (PCS). In this questionnaire, lower scores demonstrate poorer quality of life. [16]

SMFA, DASH and LLCS questionnaires examine functional outcomes. The SMFA evaluates general musculoskeletal function [18] while the DASH and LLCS specifically focus on the musculoskeletal function of the upper and lower extremities. [20,22] The SMFA has two general indices—the functional index and the bothersome index, demonstrating the actual physical dysfunction and the extent to which patients are bothered by it respectively. For these questionnaires, higher scores indicate poorer function. [18]

The DASH questionnaire is a generic measure of "disability and symptoms" related to any condition of any joint of the upper extremity. It is a 30-item questionnaire (21 physical function items, six symptom items and three social/role function items) with two optional four items modules to measure the impact of upper extremity disability on work (work module) or playing sports or musical instruments (sports and performing arts module) It is designed so that

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higher scores indicate greater disability. [22] The LLCS questionnaire consists of seven items addressing pain, stiffness, swelling and function, performed at an acceptable level to measure the impact of lower extremity disability. [20] These site-specific questionnaires often differ in their length and time to complete, which can greatly affect their clinical utility. We believe that the combination of these four questionnaires provides reliable results in the evaluation of donor site morbidity.

The study protocol was approved by the Institutional Review Board at the University of Cincinnati College of Medicine (protocol 2013-5488). Between January 2009 and July 2014, 76 patients (21 years and older) were recruited from the University of Cincinnati Medical Centre. One of two microvascular surgeons (author YJP and another surgeon) performed all reconstruction procedures.

Statistical Analysis

All questionnaires and their respective sub-components were scored as previously described in the literature. Distributions of continuous variables were examined and summarized using means with standard deviation (SD) or medians with interquartile range (IQR). Percentages and frequencies were used to summarize categorical variables. Differences in the distributions of clinical characteristics (age, type of insurance, Charlson Comorbidity Index (CCI), length to completion (time in months from surgery to survey), flap location (donor site), flap type, squamous cell carcinoma (SCC), malignancy, cancer stage, adjuvant therapy, diagnosis of chronic pain not related to cancer, neuropsychiatric disease at the time of survey (anxiety,

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depression and/or bipolar)percutaneous endoscopic gastrostomy at the date of surgery and the date of survey (PEG), tracheotomy at date of surgery and date of survey (Trach), and recurrence were examined by sex using chi-square or Fisher exact tests for categorical data and t-test or Wilcoxon rank sum test for continuous data. Differences in mean survey scores by sex were compared using a t-test. We used multivariable linear regression to adjust for potential confounders of the relationship between sex and survey scores. Stepwise backward elimination was used for model parsimony. P-values less than 0.05 were considered statistically significant. Least squares mean with 95% confidence intervals are reported. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina, USA).

Results

Eighty-four consecutive patients underwent head and neck reconstruction with microvascular free tissue transfer. Eight patients who were deceased or unable to be reached were excluded. The remaining 76 completed the study (88%). Donor sites included radial forearm (n=24, 31.6%), latissimus (n=21, 27.6%), fibula (n=19, 25.0%) and scapula (n=12, 15.8%). All patients completed SF-36 and SMFA. Additionally, the site-specific questionnaire, DASH, was used in the radial forearm, scapula, and latissimus free flaps post-operatively while patients with fibula-free flaps completed the LLCS.

The mean patient age was 63 years old; SD 11.0, range; 25-84 (Table 1). Forty-eight (63.2%) males and 28 (36.8%) females were included. All patients in this study were cis-gendered based on self-reporting. Sixteen patients (21%) were being treated for a recurrence at the time of the study. The median time between surgery and completion of the survey was 13 months [Interquartile range (IQR) 6.5, 32.0]. All patients required reconstruction for

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oropharyngeal defects. Seventy-two (94.5%) patients had cancer diagnosis while benign diagnoses included ameloblastoma (1), cocaine-induced oronasal fistula (1), and fractures (2). Three patients had sarcoma, while individual cases had myoepithelial, mucoepidermoid, adenoid cystic, oncocytic, adenocarcinoma and acinic cell carcinomas. All other patients had squamous cell carcinoma. Sixty (82.2%) patients underwent chemoradiation therapy. There were no patients who experienced flap loss. There were no major complications related to the donor site requiring reoperation.

Distributions of all other clinical variables including age, type of insurance, CCI, donor site, length of completion, donor site, flap type, malignancy, cancer stage, adjuvant therapy, chronic pain, neuropsychiatric disease (none vs one or more), SCC, PEG on date of surgery, tracheotomy on date of surgery, PEG on date of survey, tracheotomy on date of survey, and recurrence were similar between females and males (Table 1). Questionnaires' scores were normally distributed. Female patients observed lower scores for the SF-36 MCS score with a mean and standard deviation (SD) score of 45.9 (10.5) compared to males, with a mean and SD of 51.8 (10.2) ($p= 0.02$). SF-36 PCS, disease-specific (SMFA BI and FI), and site-specific (LLCS, and DASH) scores were similar by sex. (Table 2).

In addition to sex differences in SF-36 MCS scores (Female vs Male beta estimate (SE): -6.56 (2.3)), multivariable regression model results showed that patients who had a tracheotomy on the date of the survey and/or one or more neuropsychiatric disease had lower SF36 MCS scores (indicating greater disability). Least square means [95% Confidence Intervals (CI)] for Females were 46.2 [42.4, 50.0] vs Males 51.6 [48.7, 54.5]; having a tracheotomy 39.4 [32.4, 46.4] vs no tracheotomy on the date of survey 49.8 [47.5, 52.2]; and one or more neuropsychiatric diagnoses 42.4 [38.2, 46.5] vs none 46.9 [42.3, 51.5]. Sex is significantly

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related to SF-36 MCS after controlling for neuropsychiatric disease and trach status, such that males have higher SF-36 MCS scores.

Figure 1 illustrates the observed SF-36 MCS scores, and the regression lines predicted by sex, tracheotomy status and neuropsychiatric diagnoses. Males without a tracheotomy or neuropsychiatric diagnosis had higher SF-36 MCS scores, followed by males without a tracheotomy with one or more neuropsychiatric diagnoses and females without a tracheotomy or neuropsychiatric diagnosis.

Discussion

The main objective of this study was to evaluate sex-based differences in donor site morbidity after microvascular tissue transfer for head and neck reconstruction. We utilized four clinically validated questionnaires including general, disease-specific, and site-specific surveys: SF-36, SMFA, and DASH / LLCS respectively. [16,18,20,22] Understanding factors that affect donor site dysfunction or its perception will aid pre-operative counselling, flap selection, and post-operative care.

Sex has been studied as a factor in prognosis, morbidity and as a predictor of complications after surgery in oesophageal, urological, colon and other types of cancer. While females have a better prognosis than males after esophagectomy,[23] they have a higher rate of complications after cystectomy.[24] In HNC, Loupatatzi et al. [12] found that females seem to affect the presence and/or severity of complications after microvascular free flap reconstruction. This finding suggests that sex differences exist after head and neck reconstructive surgery, however more studies are needed to examine these differences.

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Sex and its effect on Quality of Life (QOL) have been examined in multiple studies. While some studies reported a slightly lower score for women in many dimensions of QOL, the literature on sex difference has shown inconsistent results. [25] Studies performed in developing countries have shown low female scores; and this could be more related to the level of education, social or marital status rather than gender itself. [13] Some reports have found other factors that affect health-related quality of life more than sex, such as smoking, [10] age, [11] or disease-related variables like site, stage, treatment, and comorbidity. Site and stage have the biggest impact on QOL for HNC. [25] Although health surveys in the general population show higher rates of symptoms, physical illness and depression in women, studies in cancer concerning health related to QOL, do not show a consistent difference between men and women.[25] There is a paucity of data regarding how sex as a factor could influence head and neck reconstruction. The role of sex as a factor affecting morbidity after free tissue transfer reconstruction of head and neck patients remains unknown.

In this study, we evaluated the degree of deficit in upper or lower extremity donor sites following free tissue transfer reconstruction using these four validated instruments and showed that sex is associated with the SF-36 MCS. In previous reports, the senior author has shown that there is a higher subjective dysfunction related to the donor site (upper and lower extremities) and these patients were significantly more bothered by this dysfunction than normal populations after free-flap reconstruction [14, 15]

In this sample, we performed a comparison of scores of all domains between females and males and we only found that they significantly differ in SF-36 MCS. There are only a few studies that evaluated the sex differences in head and neck morbidity after FTT [12]. We did not

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find a sex difference in physical well-being (PC), subjective dysfunction of the donor site area (LLC, DASH) or in being bothered (BI) by this dysfunction. In addition, we have considered other variables that could influence these results as such age, type of insurance, Charlson Comorbidity Index (CCI), length to completion (time in months from surgery to survey), flap location (donor site), flap type, squamous cell carcinoma (SCC), malignancy, cancer stage, adjuvant therapy, diagnosis of chronic pain not related to cancer, neuropsychiatric disease at the time of survey (anxiety, depression and/or bipolar), percutaneous endoscopic gastrostomy at the date of surgery and date of survey (PEG), tracheotomy at date of surgery and date of survey (Trach), and recurrence. After controlling for these characteristics, sex is significantly related to SF-36 MCS. This result agrees with previous reports which found that females tend to have more difficulty handling stress, pain and report decreased quality of life during cancer treatment. [26,27]

SF-36 MCS is a measure of mental health status which includes four domains: vitality, emotional role functioning, social functioning, and mental health. Studies suggest that the perception of pain in head and neck cancer patients is heightened in women [28]. Pain is a domain that is evaluated in the SF-36 PCS which were similar in our population. Also, we have evaluated chronic pain as a pre-existing diagnosis and did not find differences between females and males. We postulate that one or multiple domains in the SF-36 MCS are differentially affected by cancer surgery and treatment. Further studies are required to determine exactly which domains are affected.

In this study we demonstrate that females can be an independent predictor factor for worse mental health in patients after reconstruction with free flaps. We cannot conclude they are

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bothered by donor site dysfunction or that female patients' discontent is related to their donor site morbidity. Additional studies are needed.

To our knowledge, this is the first study designed to compare sex differences in donor site morbidity after tissue transfer for HNC reconstruction. It is important to identify factors that are predictors of poor physical and psychological outcomes after HNC reconstructive surgery. For future studies, sex should be considered as an additional feature and should be evaluated with validated questionnaires that examine the quality of life in HNC patients.

Limitations

This study included some limitations. Survey administration was completed at variable intervals after surgery. This limitation is inherent in survey studies.

The skin graft size was not evaluated. All patients with FFF or RFFF underwent skin grafting at the donor site, but the surface area was not recorded. The administration of multiple questionnaires made successful, timely completion challenging. These results may be limited by small sample sizes as well.

Conclusion

Female patients reported worsened subjective mental assessment compared to male patients undergoing free flap reconstruction of the head and neck. Sex may be a factor to consider when counselling patients on options for head and neck reconstruction. This is the first

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study designed to compare the sex differences in donor site morbidity after tissue transfer for head and neck reconstruction.

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None.

Conflict of Interest

None declared.

Financial Disclosure

None of the authors has a financial interest in this manuscript.

Summary

- Free flap utilization has become the standard for reconstruction after HN resection. Attention has turned to donor site morbidity.
- There is a paucity regarding how sex could influence HN reconstruction.
- We demonstrated significant greater disability for female SF-36 Mental Component after controlling for cofounders.

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Table 1.- Demographics and Clinical characteristics by sex.

Characteristics, N=76	Total	Female (n=28)	Male (n=48)	P-value
Age, Mean (SD)	63.0 (11.0)	64.25 (8.1)	62.25 (12.4)	0.40
Insurance				0.64
Public/None	27 (35.5)	9 (32.1)	18 (37.5)	
Private	49 (64.5)	19 (67.9)	30 (62.5)	
Charlson Comorbidity index (CCI)	5.2 (2.1)	4.79 (1.4)	5.48 (2.4)	0.12
Length Completion (m), Median [IQR]	13 [6.5, 32.0]	16.0 [9.0, 32.0]	11.5 [5.0, 31.0]	0.44
Flap Location (donor site)				0.81
Latissimus/Scapular	33 (43.4)	11 (39.3)	22 (45.8)	
Radial/OsteoRadial	24 (31.6)	10 (35.7)	14 (29.2)	
Fibula	19 (25.0)	7 (25.0)	12 (25.0)	
Flap type				0.70
Soft Tissue	44 (57.9)	17 (60.7)	27 (56.2)	
Soft Tissue and bone	32 (42.1)	11 (39.3)	21 (43.8)	
Pathology: Malignancy	72 (94.7)	26 (92.9)	46 (95.8)	0.62**
TNM stage				0.10
<3		8 (32.0)	7 (15.2)	
>=3		17 (68.0)	39 (84.8)	
Unknown		3	2	
Recurrence*	16/73 (21.9)	5/26 (19.2)	11/47 (23.4)	0.68
Adjuvant therapy*	60/73 (82.2)	21/26 (80.8)	39/47 (83.0)	0.81
Squamous cell carcinoma*	61/72 (84.7)	20/25 (80.0)	41/47 (87.2)	0.50
PEG on Date of Surgery	30 (39.5)	11 (39.3)	19 (39.6)	0.98
Trach on Date of Surgery	55 (72.4)	20 (71.4)	35 (72.9)	0.89
Neuropsych disease	38 (50.0)	16 (57.1)	22 (45.8)	0.34
Chronic pain	4 (5.3)	2 (7.1)	2 (4.2)	0.62**
PEG on Date of Survey	14 (18.4)	4 (14.3)	10 (20.8)	0.48
Trach on Date of Survey	8 (10.5)	1 (3.6)	7 (14.6)	0.25**

*Missing: recurrence n miss=3, Adjuvant therapy n miss=3, Squamous cell carcinoma n miss=4

**Fisher exact test,

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Table 2.-Summary of study surveys score by sex.

Outcomes by sex	Overall	Female	Male	P-value
General (100=better health)	N=76	N=28	N=48	
SF36 PCS Optum (Physical), Mean (SD)	41.1 (10.4)	42.2 (10.1)	40.4 (10.6)	0.49
SF36 MCS Optum (Mental), Mean (SD)	49.6 (10.6)	45.9 (10.5)	51.8 (10.2)	0.02
Disease-specific (100=worse health)	N=76	N=28	N=48	
SMFA Functional Index, Mean (SD)	19.6 (15.7)	21.3 (17.0)	18.7 (14.9)	0.48
SMFA Bothersome Index, Mean (SD)	23.4 (18.1)	24.7 (19.8)	22.7 (17.2)	0.64

		Overall	Female	Male	P-value
Location-specific		N=57	N=21	N=36	
Arm: DASH, Mean (SD) (100=worse health)		20.8 (17.2)	20.5 (18.5)	21.0 (16.6)	0.91
	Median	15.8 [7.5, 30.8]			
	Range	0 - 64.2			
		N=19	N=7	N=12	
Lower Limb: LLO Standardized Mean (SD) (100=better health)		87.1 (16.8)	82.7 (22.3)	89.7 (13.1)	0.4
	Median	91 [82, 100]			
	Range	36 - 100			
		N=19	N=7	N=12	
Lower Limb: LLO Normative Score Mean (SD)		47.5 (12.3)	44.3 (16.4)	49.3 (9.5)	0.4
	Median [IQR]	50 [44, 57]			
	Range	10 - 57			

SF-36 (Short Form 36 Health Survey); SF-36 PCS (Physical Component Summary) and SF-36 MCS (Mental Component Summary),
SMFA (Short Musculoskeletal Function Assessment Questionnaire); FI (the functional index) and BI (the bothersome index).
LLCS (Lower Limb Core Scale)
DASH (Disabilities of the Arm, Shoulder, and Hand).

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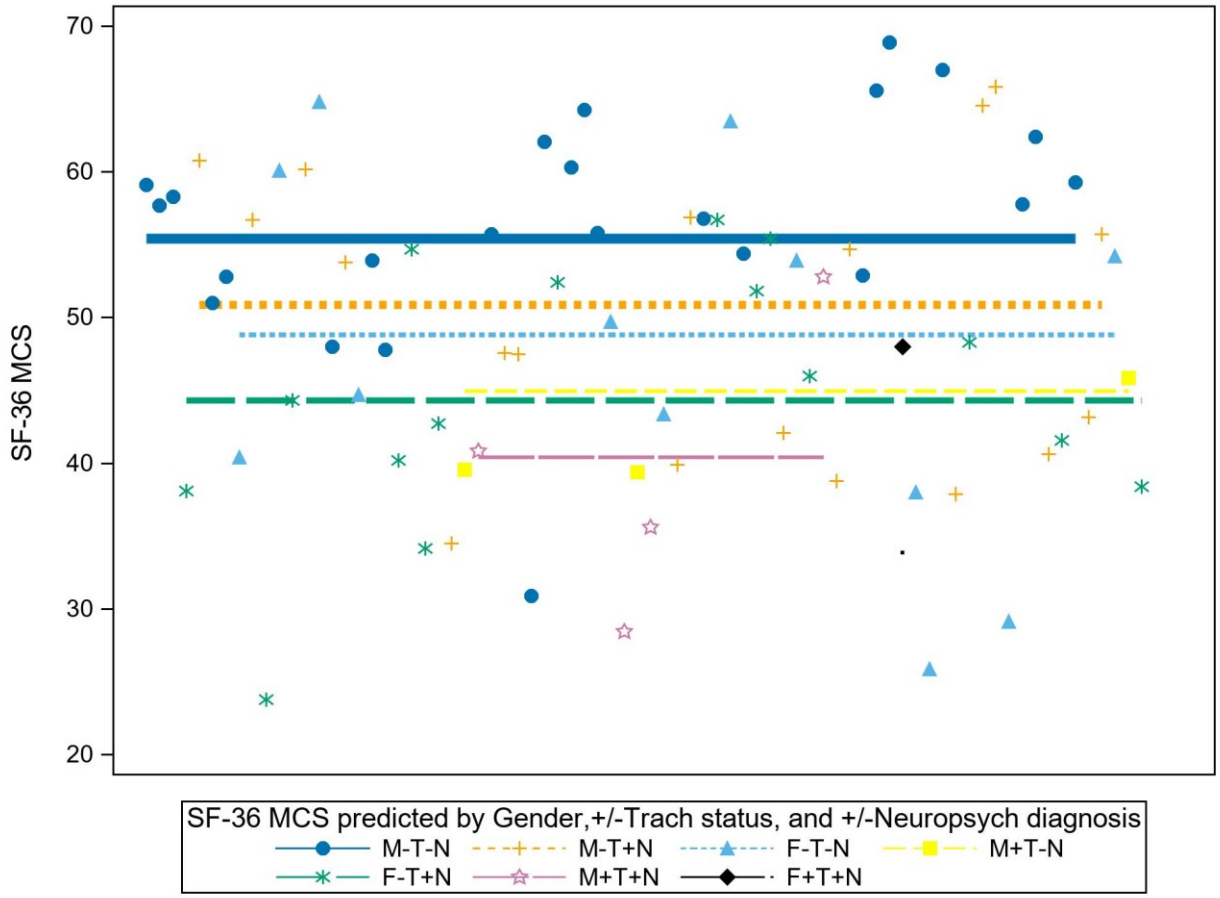
Figure 1. Regression Model: SF-36 MCS and the regression lines predicted by sex, tracheotomy status and neuropsychiatric diagnoses.



Legend:

M: males, F: Females, T: tracheotomy, N: neuropsychiatric diagnosis, +: with, -: without

○**:** Males without a tracheotomy or neuropsychiatric diagnosis.

+**:** Males without a tracheotomy with one or more neuropsychiatric diagnoses.

×**:** Females without a tracheotomy or neuropsychiatric diagnosis.

Note: Only one female with tracheostomy on the date of survey without a neuropsychiatric diagnosis.

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