Physical Activity Levels in Esophageal Cancer Prehabilitation

Master thesis

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“ONDERGETEKENDE

Mitchel Griekspoor,

bevestigt hierbij dat de onderhavige verhandeling mag worden geraadpleegd en vrij mag worden gefotokopieerd. Bij het citeren moet steeds de titel en de auteur van de verhandeling worden vermeld.”

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ABSTRACT

Background: Esophagectomy is associated with poor outcomes in esophageal cancer patients. Prehabilitation programs can improve physical fitness to reduce poor outcomes after esophagectomy. However, tailoring the level of exercise program to individual patients is recommended due to differences between patients in physical fitness and adherence to prehabilitation. This can be facilitated by identifying subgroups of esophageal cancer patients based on levels of physical activity during prehabilitation.

Aim This study aimed to 1) identify subgroups of esophageal cancer patients based on level of physical activity during prehabilitation, 2) determine differences in improved physical fitness within and between the identified subgroups after prehabilitation.

Methods: A cross-sectional design was used for the primary aim and a longitudinal design for the secondary aim of this study based on data of the 'Preoperative intervention to Improve outcomes in Oesophageal cancer patient after Resection' (PRIOR) study. A hierarchical cluster analysis was performed with data of preoperative exercise reports to identify subgroups of esophageal cancer patients based the level of physical activity. Physical activity was measured by four clustering variables regarding; level of aerobic exercises, level of resistance exercises, performed MET-minutes per week, and self-experienced levels of fatigue. Results of the Steep Ramp Test, Chair Rise Time Test (5x), and a subscale of the Research and Development-36 were used to determine differences in improved physical fitness between and within the subgroups after prehabilitation via Kruskal-Wallis tests, and paired samples t-tests.

Results: In total, data of 61 participants was used for the hierarchical cluster analysis. Three subgroups were identified: the fit subgroup, the frail subgroup, and the fatigued subgroup. Kruskal-Wallis Tests did not show statistically significant differences in improved physical fitness between the subgroups after prehabilitation. Paired samples t-tests showed statistically significant differences in improved VO_2max and physical function within two subgroups after prehabilitation.

Conclusion and key findings: This study identified three subgroups of esophageal cancer patients. The study showed no differences between subgroups in improved physical fitness after prehabilitation. Esophageal cancer patients improved in cardiorespiratory fitness and physical function after prehabilitation compared to baseline outcomes.

Keywords: esophageal cancer, prehabilitation, cluster analysis

INTRODUCTION

Esophageal cancer is one of the most fatal malignancies worldwide, with a dramatic increase in incidence in the Western world occurring over the past few decades (1–3). This type of cancer is the sixth leading cause of death and the eight most common type of cancer worldwide with a five-year survival rate of 15%-25% (2). Esophageal cancer is a debilitating disease, frequently diagnosed at an advanced stage, traditionally associated with poor outcomes (4). In the Netherlands, the incidence of the disease is approximately 2500 people per year and more common in men than in woman (4,5).

Surgery is the mainstay of potential curative treatment for the disease (6,7). Despite recent evidence that short- and long-term outcomes are improving, esophagectomy remains a procedure associated with major complications (6,7). This leads to increased functional recovery time, decreased quality of life, and a significant increase in morbidity and mortality after invasive procedures (6–9). Preoperative physical fitness is a predictive factor for postoperative outcome (10,11). Unfortunately, the physical fitness of patients with cancer is often reduced (7). Several studies reported a reduction in exercise capacity, with reductions up to 50% of the VO_2max reference values (12,13). Depletion of skeletal muscle mass and strength is also commonly witnessed and predicts pulmonary complications after esophagectomy (14,15). Therefore, preoperative physical fitness seems to be an important factor for improving postoperative outcomes (7).

Previous research shows that physical activity in prehabilitation can improve physical fitness of oncologic patients prior to surgery (7,16,17). A general recommendation for older adults and cancer survivors is to perform a minimum of 150 minutes of moderate-intensity exercise with two to three exercise sessions per week in combination with an active lifestyle (18–20). In most cases, it would be appropriate to combine aerobic and resistance exercises to obtain positive adaptations in cardiorespiratory fitness, muscular strength, endurance, and respiratory muscle function (21). However, due to differences in physical fitness and adherence among cancer patients, it is not self-evident that all patients can adhere to these general recommendations for prehabilitation (18,22,23).

Several factors predict the adherence to prehabilitation among patients with oncologic diseases in primary practice. Known environmental and personal factors are differences in social support, arranging transportation to the practice for exercise appointments, differences in motivation for exercising, differences in physical fitness, and differences in cancer related fatigue (22–25). When cancer patients have differences in one or more of these factors, heterogeneity in the level of physical activity during prehabilitation in an esophageal cancer population may occur. Prehabilitation is therefore not considered as a 'one size fits all' approach and should be tailored to each individual patient (21,26). For instance, patients who have higher levels of cancer-related fatigue might have less exercise tolerability and may be less physically active compared to patients who are better conditioned and less fatigued (27).

Therefore, this study hypothesized a distinction between subgroups of esophageal cancer patients in physical activity during prehabilitation.

Different subgroups of esophageal cancer patients based on physical activity during prehabilitation can be distinguished by measuring multiple parameters of physical activity simultaneously. Insight in homogeneous subgroups of esophageal cancer patient can be beneficial to develop tailored programs to the patients' personal level of physical fitness and characteristics (7,28,29). Furthermore it is known that physical activity in prehabilitation can improve physical fitness of oncologic patients prior to surgery (7,16,17) but the effect of prehabilitation in different homogeneous subgroups is lacking from literature.

The primary aim of this study is to identify subgroups based on levels of physical activity in patients with esophageal cancer during prehabilitation. The secondary aim is to determine differences in improved of cardiorespiratory fitness (VO2max), muscle strength, and physical function between and within the identified subgroups after prehabilitation.

METHODS

Study design and participants

A cross-sectional design was used for the primary aim and a longitudinal design was used for the secondary aim of this study. For both aims, data from the 'Preoperative intervention to Improve outcomes in Oesophageal cancer patient after Resection' (PRIOR)-study was analyzed. The PRIOR-study is a multi-center longitudinal cohort study that investigates implementation of prehabilitation in esophageal cancer patients before esophagectomy. The inclusion criteria for the current study were: (I) patients scheduled for esophagectomy after chemoradiation; (II) patients participating in a prehabilitation program; (III) exercise reports were delivered to the PRIOR-research team and (IV); patients who had measurements of clinical outcomes after the prehabilitation program. Data was collected between September 2019 and February 2020 at four participating hospitals in the Netherlands.

Preoperative exercise therapy recommendations

Participants in the PRIOR-study were instructed to conduct two exercise sessions under supervision by a physiotherapist in combination with one home-based exercise session per week in the period between chemoradiation and esophagectomy (usually 6-10 weeks). In addition, participants were advised to adhere to the Dutch Standard Health Movement (in Dutch: Nederlandse Norm Gezond Bewegen, (NNGB)). This guideline recommends to perform physical activity on moderate to vigorous intensity with a minimum of 150 minutes per week, distributed over several days. Exercise sessions should have had a minimum duration of 30 minutes and should have consisted of both resistance and cardiorespiratory exercises. Participants were advised to conduct resistance exercises in three sets of 12 repetitions at a level of 4-5 points on Borg Rating of Perceived Exertion Scale. Cardiorespiratory exercises should have been performed on 70% of the maximum exercise capacity based on outcomes on the SRT or the maximum of wattages based on the Short-Time Exercise Capacity.

Clustering variables

Data from exercise therapy reports and OpenClinica was collected and transformed into four clustering variables: (1) level of aerobic exercises in wattages; (2) LASA Physical Activity Questionnaire (LAPAQ) in MET-minutes per week; (3) level of resistance exercises; (4) self-reported levels of fatigue.

The first clustering variable illustrated the mean wattage of aerobic exercises over all exercise sessions per participant. The second clustering variable illustrates the level of physical activity in MET-minutes per participant per week. The LAPAQ measures the frequency and duration of six frequent daily activities during the past two weeks and appears to be a reliable instrument for classifying physical activity in older people (30). Level of physical activity per participant per week was calculated by multiplying the frequency and duration with the corresponding Metabolic Equivalent of Task (MET) value of the six items of the LAPAQ. The third clustering variable illustrates the participants self-experienced levels of fatigue measured with the Short Fatigue Questionnaire (SFQ). The SFQ is very reliable for examining the intensity of experienced fatigue in the two weeks prior to the completion of the questionnaire (31). It is scored on a 7-point Likert scale were the total score ranges from 4 to 28. The higher the score, the greater the intensity of physical fatigue (31). Finally, The Borg Rating of Perceived Exertion Scale (0-10) was used as fourth clustering variable to determine the perceived exertion during resistance training. The mean score of the Borg Rating of Perceived Exertion Scale was computed for every participant over all exercise sessions. Several exercise reports reported the Borg Rating of Perceived Exertion Scale on the 6-20 scale instead of the 0-10 scale. The scores were converted via a conversion model to a 0-10 scale (32).

Sample size

The primary research question was answered by conducting an agglomerative hierarchical cluster analysis. There are no strict guidelines in cluster analysis to determine the required sample size (33,34). A general rule-of-thumb for the number of samples is that the sample size should be equal to or greater than 2_m (34). The 'm' stands for the number of clustering variables. Identification of subgroups was based on four variables and therefore required a minimum sample size of $n \geq 2_4 = 16$.

Demographics and clinical outcomes

The demographics age, gender, and weight were obtained from the OpenClinica database. Clinical outcomes before and after prehabilitation were used to assess mean differences in improved physical fitness between and within the identified subgroups. Lower extremity muscle strength was measured with the Chair Rise Time 5x test. Upper body strength was assessed with a hand-held dynamometer. Both measurement tools have excellent reliability when used as a screening tool in community-dwelling elderly persons (35). Physical function was assessed with the physical function subscale of the Research and Development-36 (RAND-36) (ranging from 10-30). A higher score suggests a better physical function (36). The outcomes on the Steep Ramp Test (SRT) were used to calculate participants' estimated VO_2max before and after prehabilitation. The SRT is a practicable, reliable, and valid test for prescribing the training load and for monitoring training progress in the rehabilitation of cancer patients (37). We calculated the VO_2max through the formula for the estimated VO_2max in the oncology guideline of the Royal Dutch Society for Physical Therapy (KNGF) (38).

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics (Version 26.0). Before analysis, data were checked on missing values and outliers. In addition, the clustering variables were checked for multicollinearity. Variables with a Pearson's correlation coefficient > 0.90 were excluded (39). Due to the skewness of the data, a complete case analysis was used. Age, gender and weight were presented to describe demographics of the study population. Furthermore, the cluster variables were measured on different scales and therefore standardized by converting each variable to z-scores by subtracting the mean and dividing it by the standard deviation for each variable (40). Z-standardization procedures eliminate bias introduced by scale differences of the variables used in the analysis (40).

A hierarchical cluster analysis following Ward's method with Squared Euclidean distance measures was used. Cluster analysis is a commonly used technique to identify relatively homogeneous subgroups that are similar to each other in certain clustering variables and aims to achieve the highest within-group homogeneity and lowest between-group homogeneity (33). The number of subgroups was determined on visual assessment of the dendrogram, and interpretation of the subgroups by the researcher (40).

Differences in demographics and mean differences in clinical outcomes between subgroups were evaluated using one-way ANOVA F-Test for normally distributed data, the Kruskal-Wallis Test for non-normally distributed data, or the chi-square test for categorical or nominal data. Differences in clinical outcomes within each subgroup were evaluated using paired samples t-test. Statistical significance was set at $p<0.05$.

RESULTS

Study population

In total, 96 participants were included in the study. Two participants were excluded from the dataset because outcomes were distanced 6.0 and 3.8 standard deviations from the mean, which strongly affected the clustering procedure. Thirty-three cases in our study were removed from the data due to a missing value on one of the clustering variables. We eventually used data of 61 participants in the cluster analysis. The mean age of the total study population was 66.6 ± 7.9 years and 73.8% of the participants were male.

Cluster analysis

Three subgroups were identified: the *fit subgroup*, the *frail subgroup*, and the *fatigued subgroup.* Identification of the subgroups was based on the dendrogram (Appendix I), proportional change in agglomerative coefficient, and interpretation of the subgroups that indicated best similarities and deviations on physical activity. The analysis resulted in two larger subgroups (n = 22 and n = 32) and one smaller subgroup (n = 7). Table 1 presents the subgroups' mean scores on the clustering variables.

The *fit subgroup* (n = 32) was characterized by the highest level of aerobic exercises (94.5 ± 23.4) and lowest levels of self-experience fatigue (6.0 ± 2.6). The group had an average Borg Rating of Perceived Exertion score during resistance exercises (4.8 ± 0.93) and average levels of performed MET-minutes per week (567.9 ± 231.0) compared with the average score of total study sample.

The *frail subgroup* (n = 7) was characterized as very physically active regarding the large number of MET-minutes per week (877.3 ± 199.4). Despite high levels of physical activity, this subgroup performed the lowest level of aerobic exercises (56.7 ± 11.4) and reported a low SFQ score for self-experienced fatigue (6.1 ± 2.4), which was almost equal to the fit subgroup. The frail subgroup also considered resistance exercise the hardest regarding the highest Borg Rating of Perceived Exertion score (7.3 ± 0.59).

Compared to the other two subgroups, the *fatigued subgroup* (n = 22) was characterized by the highest level of self-reported fatigue on the SFQ of all subgroups. They also performed the lowest amount of MET-minutes per week (234.0 ± 115.1), and the lowest Borg Rating of Perceived Exertion Scale score during resistance exercise (4.5 ± 0.82). The level of aerobic exercises was slightly below the group average.

Table 1: Mean scores on the clustering variables of the identified subgroups (n = 61)

Clustering variables	The fit subgroup (n = 32)	The frail subgroup (n = 7)	The fatigued subgroup (n = 22)	Total study sample (n = 61)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Borg Rating of Perceived Exertion Scale	4.8 (0.93)	7.3 (0.59)	4.5 (0.82)	5.0 (1.2)
LAPAQ in MET-minutes	567.9 (231.0)	877.3 (199.4)	234.0 (115.1)	483.0 (284.4)
Level of aerobic exercises in wattages	94.5 (23.4)	56.7 (11.4)	70.1 (27.9)	81.4 (27.9)
Short Fatigue Questionnaire	6.0 (2.6)	6.1 (2.4)	11.9 (4.7)	8.1 (4.4)

LAPAQ = LASA Physical Activity Questionnaire; MET = Metabolic Equivalent of Task

Demographics and clinical outcomes

Demographics of the subgroups are presented in table 2. Clinical outcome variables of the subgroups at baseline and after prehabilitation are presented in table 3. Chi_2 tests showed no significant differences in age (p=0.782), gender (p=972), and weight (p=0.745) between the three subgroups.

Kruskal-Wallis tests did not show significant differences in improved VO_2max (p=0.447), lower and upper extremity muscle strength (p=0.567 and p=0.094 respectively), and physical function (p=0.236) between the subgroups.

Paired-samples t-test showed statistically significant improvements in VO_2max and physical function (p<0.000 and p=0.005 respectively) within the fit and fatigued subgroup. The improvements in VO_2max were not considered as clinically relevant in any of the subgroups (41). The improvements in physical function was clinically relevant for the fit and fatigued subgroup (42). Muscle strength did not improve statistically significant and clinically relevant after prehabilitation in any of the subgroups (43). The frail subgroup did not improve statistically significant or clinically relevant on any clinical outcome after prehabilitation.

Table 2: Demographics of subgroups

Variables	The fit subgroup	The frail subgroup	The fatigued subgroup	p-value
	Mean (SD)	Mean (SD) n = 7	Mean (SD) n = 22	
	n = 32			
Age in years	65.9 (7.8)	67.4 (9.3)	67.2 (7.7)	0.782 $_a$
Gender (male) n (%)	24 (75)	5 (71.4)	16 (72.7)	0.972 $_b$
	n = 29	n = 7	n = 22	
Weight in kg	81.6 (14.3)	76.5 (14.1)	79.6 (16.6)	0.745 $_a$

n = number of patients; SD = standard deviation; kg = kilogram; s = seconds; a = Kruskal Wallis Test; b = chi_2 test; p-value = statistical value for the mean difference in demographics between subgroups

Table 3: Clinical outcomes of subgroups

Variables			The fit subgroup		The frail subgroup		The fatigued subgroup	p-value
			Mean (SD)		Mean (SD)		Mean (SD)	
VO_2max (Liter/minutes	T0	n = 31	1.96 ± 0.36	n = 7	1.70 ± 0.53	n = 20	1.71 ± 0.48	
	T2	n = 30	2.17 ± 0.36	n = 7	1.84 ± 0.69	n = 20	1.92 ± 0.48	0.447 b
			P<0.000 *		p=0.078		P<0.000 *	
Chair Rise Time Test (s)	T0	n = 29	10.41 ± 3.33	n = 7	9.88 ± 3.81	n = 20	11.28 ± 5.35	
	T2	n = 30	9.40 ± 2.72	n = 6	8.72 ± 3.70	n = 20	9.48 ± 2.85	0.567 b
			p=0.142		p=0.154		p=0.054	
Hand grip strength	T0	n = 31	39.45 ± 12.31	n = 7	33.57 ± 5.47	n = 22	34.68 ± 13.54	
	T2	n = 30	40.29 ± 10.54	n = 7	33.29 ± 7.18	n = 22	36.18 ± 12.81	0.094 b
			p=0.462		p=0.832		p=0.13	
Physical function (RAND-36)	T0	n = 31	26.29 ± 3.39	n = 7	25.57 ± 2.82	n =22	23.91 ± 4.33	
	T2	n = 31	28.29 ± 1.85	n = 6	27.50 ± 1.52	n = 22	27.18 ± 1.99	0.236 b
			p=0.005 *		p=0.175		P<0.000 *	

*n = number of patients; SD = standard deviation; kg = kilogram; s = seconds; T0 = baseline outcome; T2 = outcome after prehabilitation a = Kruskal Wallis Test; b = statistical value for difference in clinical outcomes between subgroups; * = significant difference outcomes T0 vs T2*

DISCUSSION

This is the first study that aimed to identify subgroups of esophageal cancer patients based on levels of physical activity during prehabilitation and three distinct subgroups emerged from the data: the fit subgroup, the frail subgroup, and the fatigued subgroup. All three subgroups had a distinctively different pattern. Second, the study did not show statistically significant differences between the subgroups in improved physical fitness. Third, the study showed statistically significant improvements in VO_2max and physical function within the fit and fatigued subgroup after prehabilitation.

Although no previous study has identified subgroups based on levels of physical activity, our study showed consistency with subgroups of two other studies (44,45). However, both studies based the subgroups on cancer symptoms instead of physical activity. Still, presence of a distinction between patients in levels of fatigue in these studies is consistent with the identified fatigued subgroup in the current study. Several studies have shown that levels of cancer-related fatigue vary between cancer patients. (46). Therefore, the distinction between subgroups in our study with high and low levels of fatigue within the population of esophageal cancer may be plausible. It is also noticeable that the fatigued subgroup was less physically active, since the fit and frail subgroups showed higher levels of performed physical activity in MET-minutes per week. The fit and frail subgroup both performed levels of physical activity above the, in the 'Oncology Movement Guideline', recommended 450 MET-minutes per week, while the fatigued group performed failed to adhere to this recommendation (47). An explanation for the differences in levels of physical activity between the fit and frail subgroup compared to the fatigued subgroup can be given by the distinction in fatigue levels. Literature shows that higher levels of cancer-related fatigue are associated with a decrease in physical activity (22,46), which was consistent with the characteristics of our fatigued subgroup. Physiotherapists should therefore be aware of inactivity in fatigued patients, since decreased physical activity levels during cancer treatment can result in weakness and deconditioning, leading to a cycle of decreasing activity and increasing fatigue, as patients fatigue more quickly during activity (46). On the contrary of this inactive daily lifestyle, the fatigued subgroup surprisingly performed higher levels of aerobic exercise than patients in the frail subgroup. Here as well, levels of cancer-related fatigue between the fatigue and frail subgroup may play an important role. Two studies of Blaney et al. (2010; 2013) stated that cancer-related fatigue acts as a motivator for exercising because exercise related fatigue was perceived as a more natural experience and led to positive experiences on physical and mental well-being (27,48). If differences in motivation between the fatigued and frail subgroup were present, this might be a reason for the observed differences in levels of aerobic exercise. However, since our study did not analyze motivation levels across the different subgroups, it is uncertain whether this known phenomenon applies to our study and so this statement should be interpreted with great caution.

In the secondary analysis of this study, we investigated differences between subgroups in demographics and in improved physical fitness between and within each of the subgroups after prehabilitation. First of all, it is important to mention that there were no causal relationships between age, gender, weight, and the identified subgroups. Higher age for example, could have resulted in a decline in exercise capacity (49), which eventually might have affected physical activity levels. Since demographic outcomes were almost equal in all subgroups, patient demographics were not assumed to be responsible for the differences in physical activity and differences in physical fitness between or within the subgroups. Secondly, the study did only find clinically relevant mean differences in physical function within the fit and fatigued subgroups. The improved VO_2max and muscle strength was higher compared to baseline but was not clinically relevant. However, it should be noted that we used generally known clinically relevant differences from other populations because clinically relevant differences in oncologic patients are lacking from literature. A possible explanation for the lack of clinically relevant improvement in VO_2max can be given by the results of one of the executed sub analysis of our study. This showed that all subgroups failed to adhere to the recommended minimum of 60% of the VO_2max for achieving cardiorespiratory improvements from aerobic exercises (38). Nevertheless, previous research showed mortality in oncologic patients decreased when smaller mean improvements in VO_2max were achieved than the mean improvements from our study (50). Moreover, since this study used generally clinically relevant values for cardiorespiratory improvement and muscle strength for assessing our subgroups, it is unknown whether these values apply to our study population. For these two reasons, the improved VO_2max in our study may still be clinically relevant to our study population. Finally, we have no clear explanation for the small improvements in physical fitness of the frail group. This group performed aerobic exercise at an equal level as the fit and fatigued subgroup and was most physically active of all three subgroups but had the lowest improvement in physical fitness after prehabilitation.

The study has some strengths and limitations. One of the strengths of this study is that the hierarchical cluster analysis was performed with data from real-life usual care. The PRIOR-study did not prescribe a structured exercise protocol, and therefore, the subgroups are considered as a representative and generalizable representation of esophageal cancer patients in clinical practice and can therefore be useful for physiotherapists during prehabilitation of esophageal cancer patients in the Netherlands. However, several limitations of the study should be noticed. One of the limitations was the difference in cluster size of the subgroups. Prior to the study, there were no reasons to expect unequally sized clusters. Therefore, a hierarchical cluster analysis following Ward's method was considered as a suitable method. Nevertheless, one smaller subgroup derived from the analysis, whereby the Ward's method could have negatively affected the clustering mechanism (34). For a subsequent study it may be appropriate to use a different clustering method that is less affected by unequally sized subgroups. In addition, the sample size was quite small. Small sample sizes are less likely to reveal significant relationships (51). It is doubtful if absence of statistically significant differences in improved physical fitness between subgroups is representative for primary practice or caused by the small sample size. Another important limitation to consider is the large number of excluded cases. Hierarchical cluster analysis is a procedure that requires complete cases (34), which resulted in the exclusion of approximately 30% of the data. Due to this large amount of excluded cases, the results could have been biased and the clustering results could have had a different outcome. Finally, the samples size was too small to test the stability and validity of the cluster solution by cross-validation procedures. A common approach is to split the sample into two groups and analyzing the results of every cluster separately (40). Splitting the sample in this study would have led to substantial different results compared to the primary cluster results. Therefore, future studies with larger sample sizes are required to investigate whether the identified subgroups of the current study are valid.

The present study shows a distinction into three subgroups of esophageal cancer patients during prehabilitation, which are important for clinical practice. Since the esophageal cancer population is heterogeneous in levels of physical activity, prehabilitation should be tailored to the current health status and physical fitness to achieve optimal effects of the program. More research with larger samples sizes is needed to test the validity and stability of the subgroups. Despite the fact that subgroups showed differences in level of physical activity and did not comply to the general exercise prescriptions, subgroups were still able to improve in physical fitness compared with baseline. Therefore, future research should aim to test the stability and validity of the identified subgroups in this study. Once the stability and validity is confirmed, insight into the most effective exercise prescriptions for each of the homogeneous subgroups is needed.

CONCLUSION

Based on levels of physical activity during prehabilitation, three subgroups of esophageal cancer patients were identified. Differences between the subgroups regarding improved cardiorespiratory fitness, muscle strength, and physical function after prehabilitation were not present. Furthermore, the study showed differences in improved VO_2max and physical function in two subgroups after prehabilitation compared with baseline. Future studies should test the stability and validity of the identified clusters in this study and determine the optimal level of physical activity to facilitate the development of tailored prehabilitation programs.

Other information

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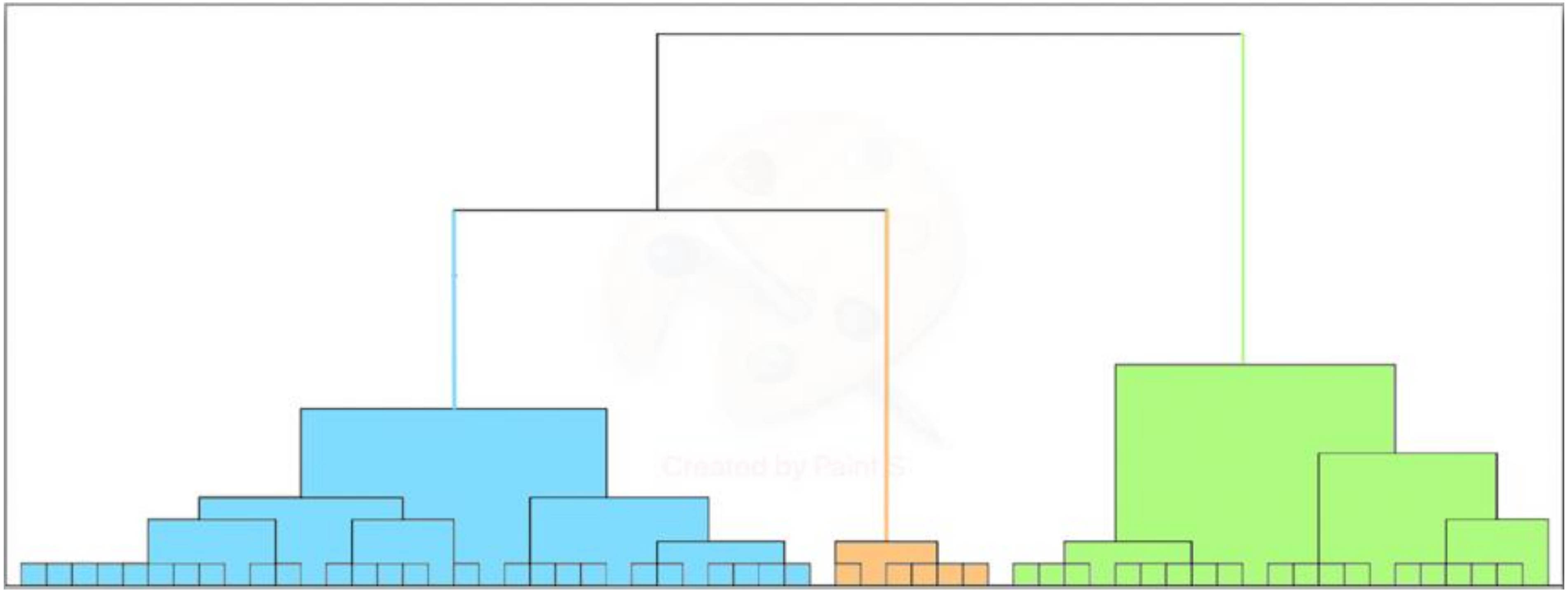
APPENDIX I: Dendrogram illustrating the clustering procedure



Note: Colors indicate the three identified clusters. From left to right: fit subgroup (blue), frail subgroup (orange), and the fatigued subgroup (green).