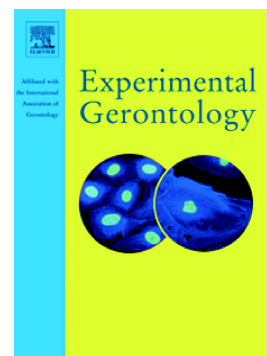


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# **Bioimpedance analysis and physical functioning as mortality indicators among older sarcopenic people**

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**Keywords:** Sarcopenia, Bioimpedance analysis, physical functioning, survival prognosis

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**Abstract**

**Objectives:** To assess the prognostic significance of various characteristics and measurements of sarcopenia and physical functioning on all-cause mortality among home-dwelling older people with or at-risk of sarcopenia.

**Design:** Cross-sectional and longitudinal analyses.

**Setting:** Porvoo sarcopenia trial in open care

**Participants:** Community-dwelling people aged 75 and older (N = 428, of which 182 were re-examined at one year) with four years of follow-up.

**Measurements:** Body mass index (BMI), physical functioning (physical component of the RAND-36) and physical performance tests (Short Physical Performance Battery (SPPB), hand grip strength, walking speed, Charlson Comorbidity Index, bioimpedance-based surrogates for muscle mass: Single Frequency Skeletal Muscle Index (SF-SMI), and Calf Intracellular Resistance Skeletal Muscle Index (CRi-SMI). Date of death was retrieved from central registers. Survival analyses were performed using Life-Table analyses and Cox models.

**Results:** Most test variables (except BMI) were associated with four-year mortality in a dose-dependent fashion. After controlling for age, gender and co-morbidity, physical performance and functioning (both SPPB and RAND-36), muscle strength (hand grip strength) and CRi-SMI appeared to be independent mortality risk indicators ( $p < 0.001$ ) whereas SF-SMI was not. When CRi-SMI values were grouped by gender-specific cut-off points, the probability of surviving for four years decreased by 66% among the older people with low CRi-SMI (HR = 0.34, 95%CI 0.15-0.78,  $p = 0.011$ ). When low CRi-SMI was further controlled for SPPB, the prognostic significance remained significant (HR = 0.55, 95%CI 0.33-0.92,  $p = 0.021$ ). After controlling for age, gender, comorbidity, and CRi-SMI, the

physical component of the RAND-36 ( $p = 0.007$ ), SPPB ( $p < 0.001$ ) and hand grip strength ( $p = 0.009$ ) remained significant mortality predictors. Twelve-month changes were similarly associated with all-cause mortality during the follow-up period.

**Conclusion:** CRi-SMI, muscle strength, physical performance and physical functioning are each strong independent predictors of all-cause mortality among home-dwelling older people. Compared to these indicators, BMI seemed to be clearly inferior. Of two bioimpedance-based muscle indices, CRi SMI was better predictor of mortality than SF-SMI. In this regard, muscle mass, muscle strength and physical performance are all suitable targets for the prevention of sarcopenia-related over-mortality.

## 1. Introduction

Sarcopenia, age-related muscle loss, has been recognized as a major clinical problem among older people as it is common and associates with poorer health outcomes. A recent consensus panel has defined it as low muscle strength, low muscle quantity and quality, and low physical performance (Cruz Jentoft et al. 2019). Compared with the determination of strength and performance, the assessment of muscle mass is challenging in clinical practice.

Different body imaging techniques such as computed tomography, magnetic resonance imaging, dual energy X-ray absorptiometry (DEXA) and Bioimpedance analysis (BIA) have been recommended for the measurement of muscle mass (Cruz Jentoft et al. 2019). However, the three first imaging techniques require a visit to a laboratory or a hospital, which may be problematic for some older sarcopenic people with disabilities. BIA is a portable alternative for assessing body composition (Janssen et al. 2000) and thus suitable for primary health care settings, including home visits. The bioimpedance spectroscopy (BIS) that scans 256 frequencies has been a useful tool for estimating the health status and survival prognosis of selected patient groups such as dialysis patients (Avram et al. 2010; Koh et al. 2011; O'Lone et al. 2014). However, the prognostic significance of BIS has not been studied thoroughly.

The use of different sarcopenia criteria in several studies has shown that increased sarcopenia is associated with over-mortality (Roubenoff et al. 2003; Cesari et al. 2009; Bunout et al. 2011; Studenski et al. 2011; Landi et al. 2011; Landi et al. 2012; Arango-Lopera et al. 2013; Atkins et al. 2014; Batsis et al. 2014; Alexandre et al. 2014). In a recent long-term population-based cohort study, sarcopenia, defined as low muscle mass in BIA and low gait speed, was associated with a 29% increase in all-cause mortality and a 61% increase in cardiovascular mortality among women (Brown et al. 2016). Obesity did not modify the relationships between sarcopenia and mortality in this study. Furthermore, appendicular lean mass (muscle mass) distinguished the mortality risk among prefrail and frail older

people (Brown et al. 2017). However, the relative importance of muscle mass, strength and function, and the role of concomitant obesity has been debated (Visser et al. 2005; Newman et al. 2006) and requires further exploration. For instance, some studies suggested that muscle function may be a more powerful predictor of disability and mortality than muscle mass (Newman et al. 2006; Rantanen 2003). According to a recent meta-analysis, sarcopenic obesity is associated with a 24% increased risk of all-cause mortality (Tian and Xu 2016). In a large English study, sarcopenic obesity did not confer any greater risk than sarcopenia alone (Hamer and O'Donovan 2017). Weight loss combined with sarcopenia presented the greatest mortality risk.

The aim of this study was to explore whether and to what extent the different characteristics of sarcopenia predict mortality among older people at-risk or with sarcopenia. For this purpose, we compared the prognostic significance of two bioimpedance-based muscle indices with that of muscle strength, physical functioning, physical performance and body weight in the four-year follow-up study of the Porvoo Sarcopenia trial. Both baseline data and their 12-month changes were tested as all-cause mortality risk indicators.

## 2. Material and methods

### 2.1. Participants

We derived our data from the Porvoo Sarcopenia and Nutrition Trial (ACTRN12612001253897) (Bjorkman et al. 2013). We approached the population aged 75+ living in Porvoo, Finland (N=3275) by a postal questionnaire (response rate 60.5%) and the research group further examined the individuals at risk of sarcopenia (N= 428). Of these, 182 participated in a three-armed 12-month intervention trial and were re-examined one year later. We obtained the participants' census status and date of death from the bureau of Official Statistics of Finland (SVT) in 2016, 60 months after baseline examination and 48 months after cessation of the trial period.

### 2.2. Data collection and examinations

Demographic data and medical history were collected by postal questionnaire. The questionnaires also included a Finnish translation of the RAND-36 physical functioning scale (Hays and Morales, 2001) as an indicator for physical functioning. Morbidity was classified according to the Charlson Comorbidity Index (Charlson et al. 1987) indicating comorbidity.

To be included in the trial the participants had to be at least at risk of sarcopenia. The inclusion criteria were: 1. low hand grip strength (men  $\leq 30.0$  kg, women  $\leq 20.0$  kg) or slow habitual gait speed ( $\leq 0.80$  m/s) and 2. low SMI (2 standard deviations below young adults) measured by segmental calf BIS). They were clinically examined at a day clinic or during a home visit. A short physical performance battery (SPPB) (Guralnik et al. 1994), with 0 points indicating poorest and 12 points best performance, assessed physical performance. Its three components (balance, gait speed, and chair rise) were also used to calculate continuous summary physical performance scores (CSPPS = 0 to 100) (Nieves et al. 2005). Muscle strength was assessed using a hand grip dynamometer (JAMAR



dynamometer, Saehan Corp., Masan, Korea). We recorded the mean maximum strength of both hands, and used gender specific cut-off points (30kg for men and 20kg for women), as suggested by the European Working Group on Sarcopenia in Older People (Cruz Jentoft et al. 2019). We also assessed two-minute walking distance (Connelly et al. 1996). Cognitive function was evaluated by mini mental state examination (MMSE) (Folstein et al. 1975), with a score ranging from 0 (poorest) to 30 (best).

BIS was performed by a single channel, tetra polar device (SFB7, ImpediMed Ltd., Eight Miles Plains, Queensland, Australia) (ImpediMed SFB7, 2019) that scans 256 frequencies between 4 and 1000 kHz. This device has been shown to give accurate estimates of body composition and good agreement with DXA (Thompson et al. 2007). We recorded the values without further software processing. Segmental calf intracellular resistance skeletal muscle index (CRi-SMI) was calculated from the BIS data of calf measurements as follows:  $CRi-SMI = \text{electrode distance}^2 / Ri_{\text{calf}}$  ( $\text{cm}^2/\Omega$ ), using the means of both calves.

The whole-body single frequency skeletal muscle index (SF-SMI) was calculated from whole-body skeletal muscle mass (SMM) and assessed according to Janssen et al. (2000). We then transformed this into skeletal muscle index as  $SF-SMI = SMM / \text{height}^2$ . The age-specific median values were used as cut-off points for low SMI (6.90  $\text{kg}/\text{m}^2$  for women and 9.31  $\text{kg}/\text{m}^2$  for men). We also calculated Calf Intracellular Resistance Skeletal Muscle Index (CRi-SMI) as described (Bjorkman et al. 2012). The corresponding age-specific cut-off points for low CRi-SMI were 1.50  $\text{cm}^2/\Omega$  for women and 2.06  $\text{cm}^2/\Omega$  for men.

The study was approved by the Ethics Committee of the Helsinki University Central Hospital.

Informed consent was obtained from each patient or, if necessary, from their closest proxy for MMSE of <19 points.

### 2.3. Statistics

We used SPSS software (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) for the statistical analyses. Continuous variables with normal distribution were expressed by means with standard deviations (SD) and those with skewed distribution by medians with first and fourth quartile cut-off points. For the variables with normal distribution, we performed statistical comparisons between the groups using Student's t-test, and for those with skewed distribution we used the Mann-Whitney U test. We used the Chi-Square test to examine the relationships between two categorical variables, and Fischer's exact test when appropriate.

We used Kaplan-Meier analyses to study time-dependent differences in survival, and Cox survival analyses to test the prognostic significance of various risk conditions. Age, gender and comorbidity as common confounders for mortality were forced into the regression analysis as covariates when appropriate.

### 3. Results

#### 3.1. Baseline characteristics as mortality risk indicators

The participants (N = 428) were old ( $83.4 \pm 4.6$  years), women outnumbered men (285 vs 143) and the majority (56%) lived alone. They used a mean of  $5.4 \pm 3.0$  prescribed regular medications. Their mean BMI was  $27.2 \pm 4.6$  kg/m<sup>2</sup> and that of MMSE  $25.6 \pm 3.5$ . Up to 40% were considered to have a sedentary lifestyle.

Of the screened participants, 88 died within four years. Mortality was twice as high among the men than among the women and was closely associated with characteristics of physical functioning (RAND-36), physical performance (SPPB, CSPPS, walking speed, two-minute walking distance, and chair tests) among both genders (Table 1). We found no difference between the BMI of the survivors and deceased women. Of the bioimpedance measures, only CRi-SMI values were significantly lower among the deceased than among the survivors.

The survival analyses (Kaplan-Meier curves) revealed that case-fatality increased with CRi-SMI over time. (Figure 1). The same also held true for several other indicators of sarcopenia, physical functioning and Charlson comorbidity index (data not shown).

We further tested the significance of the risk indicators in Cox regression analyses, into which we entered age, gender and comorbidity as covariates (Table 2). The indices of physical performance and functioning (SPPB and RAND-36), muscle strength (hand grip strength), and CRi-SMI as an indicator of muscle mass appeared to be independent mortality risk indicators. In this analysis, the prognostic value of SF-SMI and BMI remained insignificant. When CRi-SMI values were grouped by age-specific cut-off points, the probability of surviving for four years decreased by 66% among the older people

with low CRi-SMI (Fig. 1). When CRi-SMI was further controlled for SPPB, the prognostic significance of low CRi-SMI remained significant (HR = 0.55, 95%CI 0.33-0.92,  $p = 0.021$ ). Finally, when we forced the muscle mass indicator CRi-SMI into the Cox survival analysis as an additional covariant, both the hand grip strength and physical functioning indices retained statistical significance as mortality predictors, whereas the prognostic value of BMI remained insignificant (Table 2).

### 3.2. Twelve-month changes and mortality

Twelve-month changes in sarcopenia indicators were available from 182 individuals, of whom 33 died within the four-year follow-up. Physical performance decline, measured as twelve-month changes in the SPPB score and weakening of hand grip strength, were significantly associated with four-year mortality (Table 3). Both bioimpedance measures, SF-SMI and CRi-SMI, also decreased to a significantly greater extent among those who later died than among those who survived.

It was interesting to note that the intercorrelation between BMI and bioimpedance data were only moderate. The age- and gender-adjusted correlation between the two bioimpedance datasets at entry was 0.374 and at 12-month changes 0.384. Changes in BMI correlated significantly only with SF-SMI ( $r=0.284$ ,  $p<0.001$ ) but not with changes in CRi-SMI. Of the 80 participants who lost weight during the 12-month follow-up, SF-SMI decreased among 51, CRi-SMI among 56, and CSSP deteriorated among 46. Changes in hand grip strength were associated with those of CRi-SMI ( $r = 0.238$   $p<0.01$ ) but not at all with changes in SF-SMI ( $r = 0.068$ ).

In order to test the extent to which these variables were independent risk indicators, we first forced age, gender and the Charlson comorbidity index into the equation of logistic regression analysis (Table 4). A 1% decrease in CRi-SMI was associated with a 4% increase in four-year mortality. The respective

figure for the loss of hand grip strength was 2%. The prognostic values of changes in the SF-SMI, weight and physical functioning scores were of similar magnitude but did not reach statistical significance.

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#### 4. Discussion

This study shows that most characteristics of sarcopenia and frailty are associated with a significant long-term all-cause mortality risk among older community-dwelling people who are at a high risk of or already suffer from age-related muscle loss. In addition, mortality risk is increased by most test variables in a dose-dependent fashion. The results were essentially similar in the two analyses (baseline measurements vs. 12-month changes) of the present study, although due to the attrition of the study population, the statistical significances were not as strong among the 12-month follow-up participants (N = 182) as among the baseline screening population (N = 428).

When seeking potential prevention targets of sarcopenia-related health consequences, it is important to distinguish between causes and consequences, as well as a plethora of epiphenomena. In this respect, our data provide new valuable information.

Simultaneous testing of muscle mass, muscle strength, physical functioning scores and BMI revealed that the three sarcopenia measures were superior to BMI as mortality predictors. It is worth noting that the intercorrelations of different sarcopenia indicators were rather low at baseline and their changes were not congruent during the one year of this study. It is conceivable that muscle strength and physical functioning are influenced by several factors other than muscle mass. Our data clearly showed that muscle strength (hand grip strength) and physical performance and functioning (SPPB and RAND-36) were mortality predictors independently of CRi-SMI. Compared to these indicators, BMI seemed clearly inferior. This observation accords well with the newest data on sarcopenic obesity (Hamer and O'Donovan 2017). In this regard, muscle mass, muscle strength and physical performance are all suitable targets for the prevention of sarcopenia-related over-mortality.

The superiority of CRi-SMI compared to SF-SMI as a mortality predictor, and their relatively weak intercorrelations, deserve special attention. SF-SMI is based on an algorithm derived from relatively healthy subjects, which may be a source of error among the older multimorbid disabled people of the present study. This is why, in the present study, we used CRi-SMI, which is based on BIS data that does not require population-specific algorithms to avoid these inaccuracies. Muscle atrophy during ageing decreases the intracellular compartment of the muscle, but the extracellular fluid is maintained, resulting in an increase in the proportion of non-functional muscle volume (Yamada et al. 2010, Yamada et al. 2013). This extracellular water compartment may result in overestimation of actual muscle mass with SF-BIA and imaging techniques. This overestimation in turn may mask age-related muscle loss (Yamada 2014). This could explain the low association between SF-SMI and physical performance, as well the mortality in the present study.

CRi-SMI is closely related to the intracellular water compartment, as fat and bone cells have low intracellular water content. Thus, CRi-SMI may be considered a surrogate for skeletal muscle cell mass. The results of the present study are in good accordance with those of our previous longitudinal study, in which the changes in CRi-SMI associated with mobility decline among typical nursing home residents (Bjorkman et al. 2012). Further research for comparisons of these methods are still warranted.

The main weakness of this study is the lack of confirmatory measurement of muscle mass (dual x-ray absorptiometry, etc.). However, the usefulness of bioimpedance analysis in the estimation of muscle mass and quality has been investigated thoroughly (Heymsfield et al. 2014). These measurements require the presence of stable patient conditions at time of measurement, because hydration of the participant, time of day, and meticulous adherence to manufacturer-specific conditions are important for the reliability of the results.

Major strengths in turn are the representativeness of the population sample, the simultaneous use of a large test battery, repeated measurements of key indicators, long follow-up and the consistency of results. Furthermore, this is the first study to investigate the role of CRi-SMI as a mortality predictor among community-dwelling older people.

## 5. Conclusions

CRi-SMI, muscle strength, and physical functioning are each strong independent predictors of all-cause mortality in home-dwelling older people. Compared to these indicators, BMI seemed to be clearly inferior. Of two bioimpedance-based muscle indices, CRi SMI was better predictor of mortality than SF-SMI. In this regard, muscle mass, muscle strength and physical performance are all suitable targets for the prevention sarcopenia-related over-mortality.



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Legends to figure:

**Fig. 1. Calf intracellular resistance muscle index (CRi-SMI) as independent four-year mortality indicator.** The age-specific cut-off points for low Cri-SMI were 1.50 cm<sup>2</sup>/Ω for women and 2.06 cm<sup>2</sup>/Ω for men. Data adjusted for age, gender and Charlson comorbidity index. OR = 0.34 (0.15-0.78, p = 0.011).

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**Table 1. Baseline characteristics of men and women by four-year mortality**

Variable	Men			Women		
	Alive (N= 97)	Dead (n=46)	P-value	Alive (N =243)	Dead (N = 42)	P-value
Age, years	83.2 (4.4)	84.0 (4.2)	0.307	82.9 (4.6)	86.1 (4.4)	<0.001
Charlson Comorbidity Index	2.33 (1.85)	3.43 (3.06)	0.008	1.84 (1.65)	2.86 (1.66)	<0.001
MMSE	25.2 (3,1)	25.0 (5,3)	0.812	26.2 (2.6)	24.1 (5.0)	0.015
RAND-36, Physical function scale	57.8 (28.5)	46.2 (32.9)	0.036	51.4 (25.9)	31.2 (24.7)	<0.001
Short Physical Performance Battery (0–12)	8.7 (2.7)	7.2 (3.3)	0.006	8.7 (2.7)	5.5 (3.4)	<0.001
Continuous summary physical performance score	68.1 (16.4)	57.5 (21.9)	0.002	68.0 (15.1)	47.0 (22.2)	<0.001
Walking speed, m/s	0.95 (0.28)	0.79 (0.35)	0.005	0.93 (0.29)	0.61 (0.34)	<0.001
Chair test, sec.	15.5 (7.8)	18.6 (7.5)	0.028	15.4 (8.0)	22.1 (11.5)	<0.001
2-min walking distance, m	81.3 (27.7)	74.0 (23.6)	0.141	79.1 (23.1)	58.4 (24.1)	<0.001
Hand Grip Strength, kg	28.8 (7.1)	25.9 (6.4)	0.020	18.1 (4.2)	14.1 (4.7)	<0.001
Body Mass Index kg/m <sup>2</sup>	27.3 (4.0)	25.8 (3.7)	0.034	27.4 (4.6)	27.1 (6.6)	0.783
SF-SMI <sup>a</sup> , kg/m <sup>2</sup>	9.83 (1.14)	9.42 (1.29)	0.055	6.96 (0.94)	6.82 (1.34)	0.406
CRi-SMI <sup>b</sup> , cm <sup>2</sup> /Ω	1.74 (0.54)	1.47 (0.40)	0.004	1.40 (0.37)	1.15 (0.42)	<0.001
MMSE=Mini Mental State Examination						
<sup>a</sup> Single Frequency Skeletal Muscle Index						
<sup>b</sup> Calf Intracellular Resistance Skeletal Muscle Index						

<b>Table 2. Baseline measurements of physical functioning, physical performance and sarcopenia as independent indicators of four-year mortality</b>			
Measure	Hazard ratio	95% Confidence Intervals	P-value
Adjusted for age, gender, and comorbidity			
BMI, kg/m <sup>2</sup>	0.96	0.91– 1.00	0.080
SPPB	0.85	0.79 - 0.92	<0.001
RAND-36, physical function scale	0.987	0.978 – 0.995	0.003
Hand grip strength, kg	0.93	0.90 – 0.97	<0.001
CRi-SMI, cm <sup>2</sup> /Ω	0.41	0.28 – 0.69	0.001
SF-SMI, kg/m <sup>2</sup>	0.85	0.70 – 1.04	0.120
Adjusted for age, gender, comorbidity, and CRi-SMI			
BMI, kg/m <sup>2</sup>	0.97	0.92 – 1.02	0.264
SPPB	0.85	0.79 – 0.92	<0.001
RAND-36, physical function scale	0.988	0.979 – 0.997	0.007
Hand grip strength, kg	0.95	0.91 – 0.99	0.009
SPPB = Short Physical Performance Battery (0–12), BMI = Body Mass Index, SF-SMI = Single Frequency Skeletal Muscle Index. CRi-SMI = Calf Intracellular Resistance Skeletal Muscle Index.			



<b>Table 3. Percentage twelve-month changes (SE) of physical functioning, physical performance and sarcopenia measures as predictors of four-year mortality</b>			
Variable	Alive (N= 149)	Dead (N=33)	P-value
Weight	0.38 (4.6)	-0.53 (4.7)	0.453
SPPB	2.0 (2.7)	-12.2 (7.5)	0.045
RAND-36, physical function scale	18.9 (7.8)	-6.2 (8.9)	0.151
CSPPS	-0.4 (1.6)	-6.5 (3.0)	0.108
Hand grip strength	-6.5 (1.6)	-17.7 (4.5)	0.006
SF-SMI	0.3 (0.5)	-2.3 (1.0)	0.035
CRi-SMI	-1.0 (1.1)	-8.5 (2.6)	0.009
SPPB = Short Physical Performance Battery (0–12), BMI = Body Mass Index, CSPPS = Continuous Summary Physical Performance Scores (0-100), SF-SMI = Single Frequency Skeletal Muscle Index, CRi-SMI = Calf Intracellular Resistance Skeletal Muscle Index.			

**Table 4. Percentage changes in physical functioning, physical performance and bioimpedance measures and probability for four-year survival**

Change in	Risk	95% Confidence Intervals	P-value
Body Mass Index	0.95	0.89 – 1.02	0.174
RAND-36, physical function scale	0.995	0.989 - 1.002	0.166
SPPB	0.99	0.98 – 1.01	0.121
Hand grip strength	0.98	0.97 – 0.99	0.037
SF-SMI	0.96	0.91 – 1.01	0.099
CRi-SMI	0.96	0.96 – 0.99	0.010

Data adjusted for age, gender, and comorbidity. SF-SMI = Single Frequency Skeletal Muscle Index.  
CRi-SMI = Calf Intracellular Resistance Skeletal Muscle Index.

**Highlights:**

-We tested the prognostic significance of various characteristics and measurements of sarcopenia in a four-year follow-up of a randomized treatment trial.

-Physical functioning, physical performance including gait speed, hand grip strength, and Calf Intracellular Skeletal Index as a muscle mass surrogate were independent mortality risk indicators in a dose-dependent fashion.

- Among older people at risk of or with sarcopenia, the Calf Intracellular Skeletal Index based on bioimpedance spectroscopy was a superior mortality risk indicator compared to Body Mass Index and muscle mass measured using bioimpedance analysis.

- Muscle mass, muscle strength and physical performance are all suitable targets for the prevention of sarcopenia-related over-mortality.

### Calf Intracellular Resistance Skeletal Muscle Index.

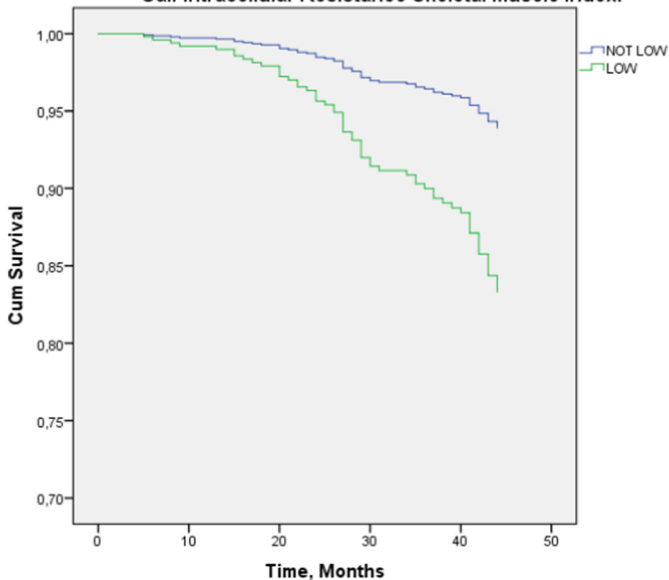


Figure 1