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Handgrip Strength Index: a Novel Parameter which quantifies clinical weakness in people on haemodialysis.

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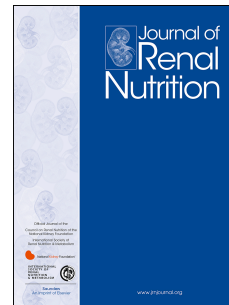
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Handgrip Strength Index: a Novel Parameter which quantifies clinical weakness in people on haemodialysis.

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15 Abstract: 282 words

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17 *Short title:* Handgrip strength in adults on haemodialysis

18

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41

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18

19 Abstract

20 Objective: Muscle strength in people on haemodialysis is associated with nutritional
21 status, quality of life, functional independence and survival. Handgrip Strength
22 (HGS) is simple to measure, but clinical interpretation is limited by the lack of
23 reference ranges for a haemodialysis population. This study aims to define a novel
24 parameter, HGS index, which quantifies degree of clinical weakness specific to a
25 haemodialysis population and to test if this predicts survival.

26 Methods: In a cross-sectional single centre study HGS was measured in stable
27 participants on haemodialysis. HGS in the well-nourished subgroup, was used to
28 develop a predictive equation for “expected” HGS according to demographic
29 variables. This then was compared to observed HGS resulting in HGS index (%), an
30 individualised parameter indicating weakness due to clinical variables whilst
31 accounting for demographic ~~weakness~~ contributors to strength. The association
32 between HGS index and survival was explored in all participants.

33 Results: Amongst 427 well-nourished individuals on haemodialysis, HGS was
34 strongly associated with demographic variables and predicted in males by the
35 equation: $HGS(kg) = 0.38 * height(cm) - 0.31 * age(years) - 18$, and in females by the
36 equation: $HGS(kg) = 0.25 * height(cm) - 0.11 * age(years) - 16$. Amongst 547
37 participants (22% with protein energy wasting), lower HGS index was associated
38 with diabetes ($p=0.004$), lower body mass index ($p=0.005$), lower albumin ($p=0.033$)
39 and longer dialysis vintage ($p=0.007$). Over a mean observation period of 2.8 years,
40 quintile of HGS index was strongly associated with survival ($p=0.023$), and in a Cox
41 Proportional Hazards model, the independent predictors of mortality were age,
42 albumin, body mass index and HGS index.

43 Conclusion: HGS index, defined as observed relative to expected HGS, is an
44 individualised measure of clinical weakness. It is a novel parameter which
45 independently predicts survival. HGS index improves the detection of clinically
46 relevant muscle weakness in people on haemodialysis, opening up the possibility of
47 earlier, individualised interventions and improving outcomes in this vulnerable group.

48

49 Keywords: handgrip; haemodialysis, equation, nutritional status, renal

Journal Pre-proof

50 **Introduction**

51 Despite gradual progress over the last decade, mortality in people on haemodialysis
52 remains high, with many centres reporting median survival around 5 years for people
53 in their 60's ¹. Protein energy wasting, noted in 28-54% of people on haemodialysis,
54 could be a contributor to this as it is associated with decreased quality of life and
55 increased hospitalization ². A key feature of the clinical diagnosis of protein energy
56 wasting is the determination of muscle mass ³. However, research has demonstrated
57 that muscle strength is more strongly associated with the risk of mortality than
58 muscle mass in people on haemodialysis ^{4,5}. Therefore muscle mass alone is not a
59 proxy for strength and therefore muscle quality (ratio of strength to mass) may be
60 better at describing the physiological changes in muscle that occur with aging ⁶.
61 Handgrip Strength (HGS) is a functional measure which has been linked to
62 nutritional decline ^{7,8} and mortality in people on dialysis ⁹, and outside dialysis has
63 been used to predict mortality ¹⁰ and old age disability ¹¹. Functional measures are
64 often the earliest to exhibit change when the clinical condition deteriorates, and are
65 closely linked to other important outcomes, such as ability to self-care and live
66 independently ¹². HGS is cheap and easy to measure and may be useful for early
67 detection of protein energy wasting, as well as a potential surrogate outcome
68 measure for interventional studies. In addition, HGS is often used in evaluation of
69 sarcopenia, in particular in older people on dialysis ^{13,14}. In these studies, a wide
70 range of cut-offs and reference ranges are used to determine weakness that is
71 beyond aging, exposing a gap in the determination of the presence sarcopenia and
72 potentially frailty.

73 Abnormal HGS may be defined by deviation from reference ranges ¹⁵⁻¹⁷, often
74 stratified by factors such as age, gender, height and ethnicity ^{18,19}. Additionally HGS

75 cut-off values have been used to identify clinically relevant (26 and 16kg) and
76 mobility limiting (30 and 20kg) weakness in males and females over 65, respectively
77 ^{20 21}. These reference ranges are problematic when applied to HGS values from
78 people on haemodialysis as they have been derived from community dwelling
79 populations and thereby generally reflect weakness of aging. As such, the values
80 from people on haemodialysis fall predominantly within the weakest categories as
81 the inherent clinical weakness and reduced function associated with being on
82 haemodialysis is unaccounted for, thereby leading to a nonspecific tool with limited
83 clinical applications. Haemodialysis specific HGS cut-offs have been used to help
84 identify malnutrition ²² and predict mortality ⁵ e.g. 28.3kg for males and 23.4kg for
85 females ⁵. However, they are based on crude gender categories without further
86 demographic characterisation according to variables that are strong determinants of
87 HGS e.g. age, height. It is challenging in a study of n=436 to produce reference
88 ranges for all variables which is the approach undertaken in large population studies
89 such as Spruit's UK biobank study with over 500,000 participants ¹⁷ which provides
90 HGS ranges for several discrete demographic categories (age, height, sex). An
91 alternative approach is to develop a predictive equation that determines "expected"
92 HGS from demographic features, which can overcome the need to have thousands
93 of participants for every subcategory. Currently, without haemodialysis-specific
94 normative values, abnormal HGS is only obvious in the individual through repeated
95 measures and noting a decline over time, which is how renal clinical guidelines
96 recommend its clinical usage ²³.

97 The lack of reference ranges highlights an important knowledge and clinical
98 assessment gap to be addressed. The aims of this study are: (1) to determine the
99 demographic variables that influence HGS in a well-nourished haemodialysis

100 population; (2) to determine a prediction equation to calculate an individual's
101 "expected" HGS from these demographic variables; (3) to define a novel,
102 demographically adjusted parameter, HGS index, as the observed HGS as a
103 percentage of the expected HGS to determine degree of clinical weakness observed;
104 and (4) to test if HGS index predicts survival in this group.

105

106 **Methods**

107 In this cross-sectional study, clinically stable adults were recruited from nine satellite
108 haemodialysis units in an urban mixed-ethnicity renal centre in XXX. Adults (aged
109 18 years or older) were eligible if receiving dialysis for at least three months, without
110 hospital admission in the previous month, able to consent, did not have a fistula in
111 their dominant arm and able to stand for HGS measurement.

112

113 ***Data collection***

114 HGS was measured once in each participant, immediately prior to a haemodialysis
115 session, to avoid dialysis-associated fatigue²⁴ which leads to a weakening of
116 maximal grip over the session^{25,26}. HGS was measured in the dominant non-fistula
117 hand, using a Jamar® Hand Dynamometer (Sammons Preston, Bolingbrook, Illinois,
118 US). Measurements were undertaken under standard testing conditions: in the
119 standing position, with elbow at full extension, and palm facing inwards, with people
120 supporting themselves as necessary with their free arm. This standing position was
121 selected as opposed to the sitting position as the chair available (e.g. with arms,
122 without arms) is likely to vary between dialysis units. To allow participants to
123 become familiar with the dynamometer, a training (warm up) measurement preceded
124 the single recorded HGS measurement. This is thought to result in an increased grip

125 strength and could reflect a truly physiological maximum ²⁷. It has also been shown
126 to be as reliable and instigate less pain than the best of (or mean of) two or three
127 trials ^{28,29}. A unique assessment feature of this study was including a recording for
128 pain. As this group are vulnerable to hand conditions such as carpal tunnel, pain
129 was recorded on a 100mm visual analogue scale before and after measurements:
130 those with pain scores above 20mm (value selected by researchers) were excluded,
131 since pain confounds the measurement of maximal strength ³⁰. It was felt to be
132 important by the authors to determine if significant pain was influencing an
133 individual's maximal grip and to exclude these values.

134

135 Participants were divided into well and poorly nourished groups using the seven-
136 point Subjective Global Assessment (SGA). SGA is a well validated global
137 nutritional assessment tool used to determine if a person is well-nourished (score 6-
138 7), mildly to moderately malnourished (score 3-5) or severely malnourished (score 1-
139 2) ³¹. Demographic and clinical data were also recorded.

140

141

142 **Statistical analyses**

143 ~~This study was powered so that several groups (age $>$ or \leq 65 years, ethnic~~
144 ~~background of black, white and asian and gender) would be well represented.~~
145 ~~Enough dialysis shifts were targeted with the aim to recruit at least 500 people in~~
146 ~~total (anticipating at least 20% of this sample to have protein energy wasting).~~

147 This study size was determined so that the subgroups of age $>$ or \leq 65 years, ethnic
148 background of Black, White and Asian; and gender would be well represented. A
149 sample size of 30 is commonly considered sufficient (based loosely on the

150 convergence of normal and t-distributions) for representative parameter estimation in
151 a predictive equation. The study sample size was designed by anticipating protein
152 energy wasting in 20% of participants, a total sample size of 500 was therefore
153 selected to achieve at least 30 well-nourished participants in each of the 12 planned
154 subgroups.

155

156 Initial HGS analysis was restricted to well-nourished people (SGA 6 or 7) to define
157 “expected” HGS in well-nourished, relatively stable, individuals on haemodialysis
158 from demographics. Demographic variables associated with HGS were explored
159 with ~~5-fold~~ k-fold cross-validation, which separates training and validation subgroups
160 to ensure development of a generalisable model, but without loss of data ^{32,33}. The
161 well-nourished group was first separated by gender and then randomly split into five
162 subgroups: for each subgroup, linear regression was used to define predictors of
163 HGS in the remaining well-nourished patients (with the subgroup removed), with
164 prediction by the ~~final~~ resulting model tested and thereby validated in the subgroup
165 (which did not contribute to model development). The mean of each coefficient
166 averaged over ~~An average~~ of these five models was used to provide the coefficients
167 for the prediction equation. Coefficient accuracy (number of significant figures) was
168 selected so that increased accuracy would improve R^2 by less than 0.01. The aim of
169 this stage was to define “expected” HGS in well-nourished dialysis patients, so only
170 demographic predictors (such as age, gender, height and ethnicity) were assessed,
171 and variables influenced by illness (such as comorbid conditions, weight and
172 albumin) were not included.

173

174 Subsequently, a novel parameter, HGS index, was defined to quantify the degree of
175 HGS clinical weakness, by comparison with the expected HGS for a stable, well-
176 nourished individual of the same age, height and gender. HGS index was therefore
177 defined as the ratio of observed to expected HGS, expressed as a percentage.

178

179 Simple HGS and HGS index were compared using multivariable linear regression in
180 the whole group, in order to define the extent to which each overlaps with clinical and
181 demographic predictors of weakness. Kaplan-Meier survival analysis was used to
182 demonstrate the effect of HGS index on survival, and Cox Proportional Hazards
183 models were used to compare HGS and HGS index as independent predictors of
184 survival, alongside other risk factors.

185

186 There was minimal missing data (dialysis vintage was unknown for two participants
187 and was coded as two years). SPSS v25.0 (IBM, New York) was used for survival
188 and regression analyses.

189

190 ***Ethics***

191 This study was approved by the XXX and was performed in accordance with the
192 Declaration of Helsinki, with written informed consent from all participants.

193

194 **Results**

195 Between May 2010 and June 2015, HGS was measured in 547 participants (aged
196 18-92, 52% male), of whom 427 (78.1%) were considered to be well-nourished, with
197 SGA score 6 or 7, the rest having mild/moderate (SGA 3-5, n=118, 21.6%) or severe
198 protein energy wasting (SGA 1-2, n=2, 0.4%). Amongst males mean(+/-sd) age was

199 63.2(14.1) with height 172.6(7.3)cm, weight 76.2(17.1)kg, and BMI 25.5(5.2)kg/m²,
200 whereas amongst females mean(+/-sd) age was 61.9(15.1), with height
201 159.7(8.0)cm, weight 70.0(17.2)kg, and BMI 26.2(6.4)kg/m². One-hundred and three
202 patients (18.8%) had a BMI over 30kg/m² (categorised as obese). A diagram
203 illustrating an overview of patient flow through each stage of the study can be found
204 in supplementary information (Figure S1). Other characteristics of the whole group,
205 well-nourished and poorly nourished subgroups, are provided in Table 1. This
206 sample was drawn from a total population of 1350 people on haemodialysis (in flux
207 over time with new people starting dialysis and some discontinuing due to withdrawal
208 or death or having a transplant). Aside from the participants that were not eligible
209 due to being unable to consent or unable to stand (wheelchair or bedbound), only
210 5.9% declined to take part in the study.

211
212 Amongst the 427 well-nourished participants (aged 18-92, 54% male) mean(+/-sd)
213 HGS was 28.1(10.6)kg with a right-skewed distribution in males and 17.3(6.5)kg in
214 females (Figure 1A). This distribution is however very different from a healthy, non-
215 dialysis population: using large population studies from healthy individuals stratified
216 by age and gender ¹⁹ or age, gender and height ¹⁷, HGS values in our study are
217 seen to cluster predominantly below the 10th percentile (Figure S2 in supplementary
218 information).

219
220 Demographic variables associated with HGS were explored separately in males and
221 females with 5-fold cross-validation and showed strong associations with age and
222 height and gender, and a weaker no consistent association with ethnic background
223 (Table 2).

224 Averages across the five models were used to derive coefficients for a male and
 225 female prediction equations:

226

227 $\text{Predicted HGS(kg)} = 0.38 \cdot \text{height(cm)} - 0.31 \cdot \text{age(years)} - 18$ (males)

228 $= 0.25 \cdot \text{height(cm)} - 0.11 \cdot \text{age(years)} - 16$ (females)

229

230 HGS index was then defined as the observed HGS relative to this prediction as a
 231 percentage:

232

233 $\text{HGS index (\%)} = 100 \times [\text{observed HGS} / \text{expected HGS}]$

234

235 HGS index in the whole group (N=547, including well and poorly nourished
 236 participants) was normally distributed with mean(+/-sd) 98.5(33.9)%. Mean(+/-sd)
 237 HGS index in well-nourished patients was 100.4(32.5)% and in malnourished
 238 patients was 91.7(37.6)%. The distribution of HGS index was similar in males and
 239 females (Figure 1B). As an example, where the observed HGS matches the
 240 expected HGS derived from the predictive equation based on demographics of well-
 241 nourished individuals on haemodialysis, the HGS index would be 100%. Where the
 242 observed is lower than the expected, the HGS index would be less than 100%.

243

244 In linear regression models, simple HGS is associated strongly with demographic
 245 variables (age, gender and height) and with the addition of clinical data (dialysis
 246 vintage, diabetes status, albumin, BMI) much of the variation in HGS can be
 247 explained ($R^2=0.430$) as is shown in Table 3. In contrast HGS index is most closely
 248 associated with illness variables (dialysis vintage, diabetes status and BMI), however
 249 these variables only mildly influence it ($R^2=0.039$, Table 3). In addition, as is

250 expected, HGS index is not associated with demographic variables as these are
251 included in the prediction equation when calculating expected HGS. Therefore,
252 unlike simple HGS measurement which overlaps substantially with the clinical and
253 demographic data, HGS index adds new information reflecting muscle weakness
254 beyond aging and being on haemodialysis.

255 Over a mean follow-up duration of 2.8 years (1,530 patient-years total), there were
256 138 deaths (25.2% of the group). Dividing participants into quintiles of HGS index
257 (with quintile cut-offs at 72, 91, 107 and 126%), higher HGS index quintile at
258 baseline predicted longer survival ($p=0.023$, Figure 2).

259

260 In Cox Proportional Hazards models, HGS index quintile performed at least as well
261 as simple HGS quintile, as being an independent predictor of survival after
262 adjustment for age, albumin and body mass index ($p=0.049$, Table 4). Being two
263 quintiles weaker (e.g. being in the lowest vs middle quintile of HGS index) was
264 associated with a 26% increased mortality hazard, equivalent on average to an
265 additional mortality of 2.7%, and equal to the mortality disadvantage of being 4 years
266 older, having 3.2 g/L lower albumin, or 7.5 kg/m² lower body mass index.

267

268 **Discussion**

269 This study of 547 participants describes the distribution of HGS in people on
270 haemodialysis and develops a predictive equations for males and females to
271 determine expected HGS values based on people who are well-nourished. Defining
272 HGS index as the ratio of observed to expected HGS as a method to determine
273 degree of weakness, was found to be a strong independent predictor of survival. By
274 defining what is 'normal for haemodialysis' and having a parameter that represents

275 individualised as opposed to generic weakness, HGS index facilitates early and rapid
276 detection of muscle weakness through a single as opposed to serial measurements,
277 paving the way for potential targeted and timely interventions.

278

279 This study confirms the near universal presence of muscle weakness in people on
280 haemodialysis when compared with similar aged individuals without kidney disease.

281 For example, in a study of 3700 healthy volunteers (mean age 63, range 52 – 82

282 years) from the English Longitudinal Study of Ageing³⁴, investigators reported a

283 mean HGS of 42.9 and 26.0kg in males and females respectively, which by

284 comparison with these data suggests that HGS is reduced by approximately 30%

285 even in well-nourished people on haemodialysis, regardless of gender. The

286 ~~comparative distribution illustrated in~~ supplementary information demonstrates the

287 limited utility of assessing weakness in people on haemodialysis compared to a

288 healthy reference range since the vast majority of individuals would be defined as

289 weak. A method specific to people on haemodialysis that more accurately

290 determines degree of weakness, which might respond to targeted intervention, is

291 certainly of value in clinical practice.

292

293 In other studies of people on haemodialysis, similar demographic predictors of HGS

294 have been observed: in 156 participants from Brazil, Pinto found both height

295 ($R=0.57$) and age ($R=-0.35$) to be closely correlated with HGS, suggesting that these

296 predictive relationships are reproducible in different haemodialysis populations. In

297 healthy populations, height is also an important predictor of HGS. With such a

298 strong contribution from a continuous variable, one approach, for example adopted

299 by Spruit in a study of over 500 000 participants¹⁷, is to provide reference ranges

300 stratified by height. We adopt the alternative strategy, more suited to a smaller
301 population, of defining the expected HGS predicted by demographic variables
302 including height and describing observed HGS as a percentage of this prediction
303 (HGS index). This approach is well-established in other areas of clinical nutrition
304 and physiology: target energy requirements, for example, are calculated using
305 equations which include age, weight, and ethnicity. Similarly, lung function tests are
306 commonly reported as a percentage of the expected value, predicted by height
307 amongst other variables. The concept of HGS index therefore has reasonable
308 precedent in clinical practice.

309

310 HGS index is (mostly) not predicted by demographic variables as one component of
311 the index (expected HGS) is already adjusted for age, height and sex.

312 ~~Demographic variables are mostly not predictive of HGS index since expected HGS~~
313 ~~is already adjusted for these variables. This independence from demographic~~
314 ~~variables makes HGS index a more meaningful measure of weakness, since simple~~
315 ~~HGS may be appropriately low due to older age or shorter stature, in the absence of~~
316 ~~any reduction in strength due to clinical reasons. As expected, illness variables,~~
317 such as diabetes status and BMI, however, remain associated with HGS index.

318 HGS index was also found to reduce by 1% for each additional year on
319 haemodialysis (dialysis vintage). HGS declines more rapidly than HGS index over
320 time in people on haemodialysis as it is influenced by aging as well as clinical
321 variables. In Kaysen's paper, males on haemodialysis lost a mean of 3.9% of their
322 HGS over 12 months ³⁵.

323

324 A similar relationship between HGS and haemodialysis mortality has been observed
325 previously: for example, Matos reported baseline handgrip in 443 adults and
326 subsequent mortality over a median follow-up of 34 months, finding 17% increased
327 mortality in those with low HGS compared to those with high HGS ⁵. The association
328 has been confirmed also in a meta-analysis in which low HGS was predictive of
329 mortality ³⁶, and the relationship between reduced muscle mass and poor survival
330 has been observed in a number of settings ³⁷⁻³⁹. Muscle strength rather than muscle
331 mass is thought to be the dominant factor, so it is not surprising that HGS would be
332 associated with increased mortality ^{9,10}. But since there is much co-linearity between
333 HGS and other clinical parameters as well as aging ^{10,22} it can be difficult to be clear
334 that HGS is indicating something beyond older age and kidney failure.

335

336 ~~HGS index however indicates weakness beyond that to be expected from having~~
337 ~~end stage renal disease on treatment.~~ Since HGS index performs as well as simple
338 HGS as an independent predictor of survival, it can be seen that HGS index captures
339 the value of HGS yet enhances this further by accounting for individual demographic
340 values e.g. height, age, as well as quantifying degree of weakness. This makes HGS
341 index a more useful clinical tool than simple HGS and allows a single measurement
342 to be clinically meaningful.

343

344 Being a single centre study enables accurate outcome data and consistency of
345 treatment practices but the external validity is less clear, and it is possible that some
346 of the conclusions are centre specific. In addition, HGS was measured at a single
347 timepoint, with a limited set of other variables available. One challenge in comparing
348 studies is lack of consistency in the method of HGS measurement. Hwang's meta-

349 analysis describes variability in dynamometer type and calibration, arm side
350 (dominant vs non-fistula) and position, duplicate measurement and statistical
351 handling of repeated measures. A recent study determined a standardised method
352 of HGS assessment, which does differ from our study, which was completed
353 previously ⁴⁰. Our study was however large and broadly inclusive, with reasonable
354 duration of post-measurement observation, so it is likely that findings are broadly
355 generalisable.

356

357 In conclusion, the reduced HGS of people on haemodialysis is influenced by
358 demographic and clinical variables. HGS index, already demographically adjusted,
359 reflects mostly clinical weakness and is a strong independent predictor of mortality.
360 HGS index therefore detects the degree of muscle weakness in people on
361 haemodialysis, allowing for potential earlier intervention and detection of responses
362 to therapy. Further research demonstrating the clinical utility of this novel parameter
363 is anticipated.

364

365 **Practical applications**

366

367 This study illustrates the need for haemodialysis specific reference ranges and
368 discusses a novel and demographically adjusted index to interpret handgrip strength
369 developed for people on haemodialysis and predictive of survival.

370 Handgrip strength has the potential to be implemented routinely in clinical practice
371 providing objective and individualised data on muscle weakness derived from a
372 reference group of well-nourished people on haemodialysis. Our method enables a
373 single (versus ongoing) handgrip strength measurement to provide valuable clinical
374 information, which has not been available to date.

375

376

377

378 **Authors' contributions**

379

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382 **References**

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Table 1. Patient characteristics and Handgrip Strength in the well-nourished, poorly nourished and whole group.

	Well-nourished (N=427)		Poorly nourished (N=120)		Whole group (N=547)	
	Med(IQR) / N(%)	HGS(kg)	Med(IQR) / N(%)	HGS(kg)	Med(IQR) / N(%)	HGS(kg)
All patients		22 (16.5-28)		18.5 (12-25)		21 (15.5-28)
Age (years)	63 (52-75)		65 (53-74)		64 (53-75)	
< 65	227 (53.2)	24 (18-32)	58 (48.3)	19 (13.5-29)	285 (52.1)	23 (18-30)
> 65	200 (46.8)	19 (15-25)	62 (51.7)	18 (11-23)	262 (47.9)	19 (14-25)
Gender						
Male	232 (54.3)	27.5 (21-33)	50 (41.7)	23.5 (17-30)	282 (51.6)	26.5 (20-32)
Female	195 (45.7)	18 (13-21)	70 (58.3)	15 (10-20)	265 (48.4)	18 (12-21)
Ethnicity						
Black	119 (27.9)	24 (18-32)	26 (21.7)	19 (12-28)	145 (26.5)	22 (17-30)
White	143 (33.5)	23 (18-29.5)	41 (34.2)	20 (13-27.5)	184 (33.5)	22 (16.5-29)
Asian/other	165 (38.6)	20 (16-26)	53 (44.2)	16 (11-24)	218 (39.9)	19 (14-26)
Height (cm)	1.68 (1.60-1.73)		1.65 (1.57-1.73)		1.68 (1.59-1.73)	
< 170	248 (58.1)	18 (14-23)	78 (65.0)	16 (11-21)	326 (59.6)	18 (14-22)
> 170	179 (41.9)	28 (22-34)	42 (35.0)	25 (17-31.5)	221 (40.4)	28 (21-33)
BMI (kg/m ²)	25.9 (22.6-29.6)		21.8 (19.7-24.4)		24.8 (21.7-28.9)	
< 25	184 (43.1)	22 (17-28)	94 (78.3)	18 (12-24)	278 (50.8)	20 (15-28)
> 25	243 (56.9)	21 (16-28.5)	26 (21.7)	20 (11-28)	269 (49.2)	21 (16-28)
Vintage (years)	2.1 (1.0-4.3)		2.5 (1.0-6.2)		2.1 (0.9-4.6)	
< 2	212 (49.6)	23 (16-30)	53 (44.2)	17 (13-23)	265 (48.4)	21 (15-29)
> 2	215 (50.4)	21 (17-28)	67 (55.8)	19.5 (11-26)	282 (51.6)	20.5 (16-28)
Comorbidity						
Diabetes	193 (45.2)	20 (16-26)	39 (32.5)	16 (11-23)	232 (42.4)	20 (15-26)
Vascular	103 (24.1)	20 (14.5-26)	32 (26.7)	17 (13.5-21)	135 (24.7)	20 (14-25.5)
Albumin (g/L)	35.0 (32.0-38.5)		33.5 (31.0-37.0)		35.0 (32.0-38.0)	
< 35	196 (45.9)	21 (16-27)	69 (57.5)	19 (13.24)	265 (48.4)	20 (14-27)
> 35	231 (54.1)	22 (18-30)	51 (42.5)	18 (12-27)	282 (51.6)	21 (16-30)

Characteristics are given as N(%) or median(IQR)

HGS: Handgrip Strength (kg)

Table 2. Prediction of HGS by demographic (~~non-illness~~) variables, confirmed by cross-validation in 5 subgroups of well-nourished group (N=427), separated by gender.

	Group 1		Group 2		Group 3		Group 4		Group 5		Final model*	
Males	Coeff	p value	Coeff	p value	Coeff	p value	Coeff	p value	Coeff	p value	Coeff	SE
Height (cm)	.453	.000	.433	.000	.326	.000	.374	.000	.330	.001	0.38	.080
Age (years)	-.310	.000	-.253	.000	-.353	.000	-.303	.000	-.345	.000	-0.31	.043
Model fit	R ²	p value	R ²	p value	R ²	p value	R ²	p value	R ²	p value	R ²	SEE
Training set	.316	.000	.291	.000	.301	.000	.267	.000	.290	.000		
Validation set	.185	.004	.285	.000	.233	.001	.434	.000	.291	.000	.290	8.94
Females	Coeff	p value	Coeff	p value	Coeff	p value	Coeff	p value	Coeff	p value	Coeff	SE
Height (cm)	.263	.000	.247	.000	.193	.001	.307	.000	.235	.000	0.25	.052
Age (years)	-.086	.009	-.090	.013	-.146	.000	-.093	.004	-.118	.000	-0.11	.029
Model fit	R ²	p value	R ²	p value	R ²	p value	R ²	p value	R ²	p value	R ²	SEE
Training set	.164	.000	.144	.000	.204	.000	.196	.000	.163	.000		
Validation set	.209	.004	.332	.001	.064	.087	.088	.050	.191	.007	.168	5.89

Validation group characteristics are given as mean sd or N %, as appropriate.

HSG: handgrip strength

SE: standard error of the coefficient

SEE: standard error of the estimate

*Final model validated in the complete data set

Table 3. Demographic and clinical predictors of Handgrip Strength and Handgrip Strength Index in the whole group (N=547)

	Handgrip Strength (kg)				Handgrip Strength Index (%)			
	Univariable		Multivariable ^a		Univariable		Multivariable ^b	
	R	p value	B	p value	R	p value	B	p value
Age (year)	-0.277	.000	-0.169	.000	0.037	.390		.083
Gender (Female)	-0.504	.000	-6.637	.000	0.019	.649		.881
Ethnicity (Black)	0.129	.003		.294	0.061	.153		.305
Height (cm)	0.537	.000	0.322	.000	-0.019	.655		.662
BMI (kg/m ²)	0.040	.345	0.186	.002	0.107	.012	0.122	.005
Vintage (year)	-0.097	.024	-0.243	.007	-0.105	.014	-0.118	.007
Diabetes	-0.119	.005	-2.370	.001	-0.086	.045	-0.128	.004
Vascular	-0.107	.013		.219	-0.103	.016		.130
Albumin (g/l)	0.138	.001	0.169	.008	0.111	.010	0.090	.033

^aadjusted R² = 0.430 for the final model

^badjusted R² = 0.039 for the final model

Beta missing for terms excluded from the final model

Table 4. Predictors of survival by Cox Proportional Hazards model in the whole group (N = 547)

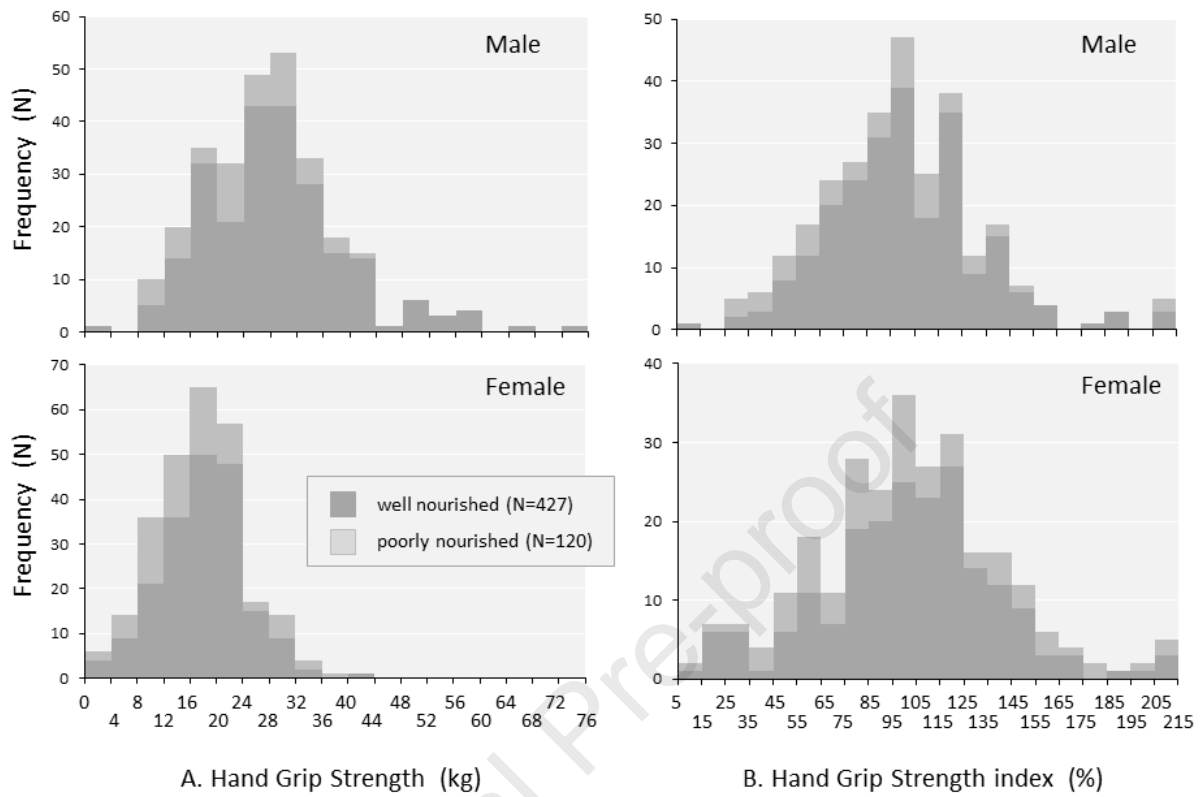
		Univariable			Multivariable			Multivariable		
		HR	(95% CI)	p value	With HGS	(95% CI)	p value	With HGS index	(95% CI)	p value
Age	(year)	1.06	(1.05-1.08)	.000	1.06	(1.05-1.08)	.000	1.06	(1.05-1.08)	.000
Albumin	(g/L)	0.92	(0.89-0.96)	.000	0.92	(0.89-0.96)	.000	0.93	(0.89-0.97)	.000
BMI	(kg/m ²)	0.96	(0.93-0.99)	.009	0.96	(0.93-0.99)	.014	0.97	(0.94-0.99)	.029
HGS	(quintile)	0.74	(0.65-0.84)	.000			.053			
HGS index	(quintile)	0.87	(0.77-0.98)	.023				0.89	(0.78-0.99)	.049
Ethnicity	(Black)	0.49	(0.30-0.79)	.004			.250			.303
Vascular		1.49	(1.04-2.12)	.028			.296			.394
Vintage	(year)	1.02	(0.98-1.06)	.290			.382			.467
Gender	(Female)	0.84	(0.60-1.18)	.309			.734			.689
Diabetes		1.20	(0.85-1.68)	.289			.899			.962

Survival censored for moving out of area or at study end, not censored at transplantation

HGS: Handgrip strength

HR: hazard ratio

CI: confidence interval



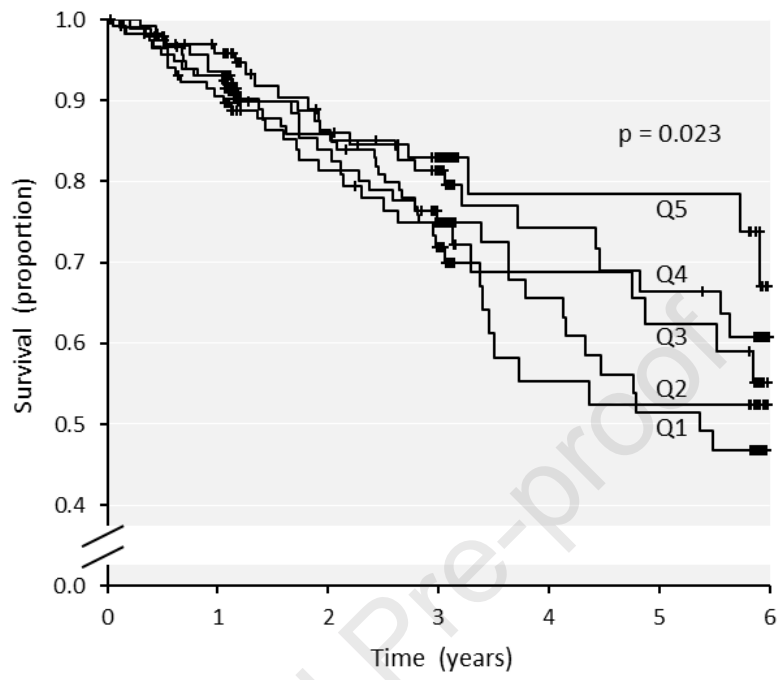


Figure 1. Distribution of Handgrip Strength and Handgrip Strength index. (A)

Left panels: Handgrip Strength (simple, without any adjustment) in well-nourished and poorly nourished participants (B) Right panels: Handgrip Strength index (percentage of HGS expected derived from a well-nourished haemodialysis population, adjusted for age, gender and height) in well-nourished and poorly nourished participants. Upper panels: males. Lower panels: females.

Figure 2. Patient survival by Handgrip Strength index. Patients were separated by baseline Handgrip Strength Index into quintiles (Q1-Q5) with quintile cutoffs at 72, 91, 107 and 126%. Survival was censored at the end of observation, or at transplantation or transfer to another centre.

Credit Author Statement

Tina Dilloway: Investigation, Resources, Data curation, Writing – Original draft, Project administration, Funding acquisition.

Damien Ashby: Formal analysis, Visualization, Writing – review and editing.

Mary Hickson: Conceptualization, Methodology, Writing – review and editing, Supervision.

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