Association of Handgrip Strength With Mortality in Hemodialysis Patients in Taiwan: A Prospective Cohort Study

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Research Article

Keywords: Handgrip strength, mortality, end-stage renal disease, hemodialysis, Asian, Taiwan

Posted Date: February 19th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-213240/v1

Abstract

Background:

Poor muscle quality has been associated with mortality in patients undergoing hemodialysis (HD). Handgrip strength (HGS) has gained considerable attention as a marker of nutritional status and muscle function. The aim of this study was to verify the association between HGS and mortality in patients undergoing maintenance HD in Taiwan.

Methods:

A total of 188 stable HD patients from January to December 2009 were enrolled in the study. We used a standard handgrip dynamometer to measure the HGS. HGS was measured on enrolment at the beginning of the study. Each measurement was repeated three times for each patient, and the average value was recorded for analysis.

Results:

During a mean follow-up period of 47 ± 11 months, 34 of the 188 patients died. The all-cause mortality rate was 18%. Higher HGS (hazard ratio [HR] 0.891, 95% confidence interval [CI] 0.838–0.948; $p < 0.001$) and Kt/V (HR 0.086, 95% CI 0.018–0.421; $p = 0.002$) were independent factors associated with survival in HD patients. For female patients, an HGS < 17 kg had a positive predictive value (PPV) of 39% and a negative predictive value (NPV) of 96% for predicting mortality. For male patients, an HGS < 26 kg had a PPV of 29% and an NPV of 84% for predicting mortality.

Conclusion:

HGS provides a good marker for survival in HD patients. Our results indicate that HGS can identify male and female patients undergoing maintenance HD with an increased risk of all-cause mortality, with different cut-off values for each sex.

Background

Previous studies have suggested that markers of muscle mass and muscle function could have important prognostic values for patients with end-stage renal disease [1-3]. Poor muscle quality has been associated with mortality in patients undergoing hemodialysis (HD). In the past decades, handgrip strength (HGS) has gained considerable attention as a marker of nutritional status and muscle function. HGS measurement is a validated method of assessing nutritional status [4]. It is a simple, safe, non-invasive, radiation-free, and low-cost technique. According to a recent study, HGS seems to be unaffected by hydration status [5], thus making it a potentially better indicator of muscle mass or quality in maintenance HD (MHD) patients. HGS has been recognized as a reproducible and easy-to-measure variable that correlates with lean body mass. It predicts malnutrition and prognosis in patients with chronic kidney disease. However, how well HGS can predict mortality in HD patients has not been

investigated in Taiwan. Therefore, the aim of this study was to verify the association between HGS and mortality in patients undergoing MHD in Taiwan.

Methods

Study design and subjects

A total of 188 stable HD patients (78 males, 110 females) at Kaohsiung Chang Gung Memorial Hospital from January to December 2009 were enrolled in the study. The inclusion criteria were age >20 years and regular 4-h HD sessions 3 times per week for at least 3 months. The exclusion criteria were viral hepatitis, active malignancy, acute infection, or hospitalization within 3 months before enrolment.

Assessment of muscle function

We used a standard handgrip dynamometer (Fabrication Enterprises, White Plains, NY) to measure HGS. The dynamometer was adjusted according to the hand size of each patient. HGS was measured on enrolment, at the beginning of the study. In patients without an arteriovenous fistula (AVF), HGS was measured in the dominant arm. In patients with an AVF, HGS was measured in the arm without the AVF.

Mid-arm circumference (MAC) and triceps skinfold thickness (TSFT) were determined using a plastic tape measure and a Lange skinfold caliper (Beta Technology, Santa Cruz, CA) [6]. Mid-arm muscle circumference (MAMC) was calculated as MAC – (π × TSFT). The MAMC area was calculated as $(MAMC)^2 / (4 \times \pi)$. Each measurement was repeated three times for every patient, by experienced research staff who were blinded to all clinical and biochemical data, and the average value was recorded for analysis.

Statistical analysis

Statistical analysis was performed using SPSS (version 12.0; IBM, Armonk, NY). The results are expressed as mean ± standard deviation or median (interquartile range) for non-parametric data, and frequencies are expressed as percentages. Comparisons between sexes and between surviving and non-surviving patients were performed using Student's t test. Cox regression hazard analysis was used to assess the relationship between HGS and survival time. A receiver operating characteristic curve was also used to establish an optimal HGS cut-off point for males and females.

Results

During a mean follow-up period of 47 ± 11 months, 34 (17 men) of the 188 patients died. The all-cause mortality rate was 18% (34/188). The baseline biochemical data and demographic features of the 188 stable HD patients are shown in Table 1. The underlying etiologies of end-stage renal disease in these patients included chronic glomerulonephritis (35%), diabetes mellitus (27%), hypertension (17%), polycystic kidney disease (7%), interstitial nephritis (4%), and unknown (10%). The mean age was 59.5 ±

10.6 years. HGS (19.6 ± 6.3 vs. 28.4 ± 10.4 kg [males], p < 0.001), waist circumference (82.2 ± 10.9 vs. 89.1 ± 13.4 cm [males], p < 0.001), MAMC area (34.5 ± 11.5 vs. 39.4 ± 9.9 cm^2 [males], p = 0.004), and serum creatinine level (10.4 ± 1.8 vs. 11.5 ± 2.2 mg/dL [males], p < 0.001) were significantly lower in females.

Univariate analysis showed that survivors had significantly higher HGS and Kt/V, and lower waist circumference and interleukin-6 level. Survivors also included a lower proportion of patients with diabetes (23% [35] vs. 47% [16], p = 0.004) and cardiovascular disease (41% [63] vs. 62% [21], p=0.027) (Table 2). To identify the independent predictors for survival, Cox regression hazard analysis was performed. Cox regression hazard analysis identified higher HGS (hazard ratio [HR] 0.891, 95% confidence interval [CI] 0.838–0.948; p < 0.001) and Kt/V (HR 0.086, 95% CI 0.018–0.421; p = 0.002) as the two independent factors associated with survival in HD patients. We also used receiver operating characteristic curves to determine the best HGS cut-off points for each sex. For female patients, an HGS of <17 kg had a positive predictive value (PPV) of 39% and a negative predictive value (NPV) of 96% for predicting mortality, with an area under the receiver operating characteristic curve of 0.864 (95% CI 0.761–0.966, p < 0.001) (Fig. 1). For male patients, an HGS of <26 kg had a PPV of 29% and an NPV of 84% for predicting mortality, with an area under the receiver operating characteristic curve of 0.747 (95% CI 0.589–0.904, p = 0.016) (Fig. 2).

Table 3 summarizes the univariate associations between HGS and other variables. In our study, HGS was correlated with serum albumin level (positively), serum creatinine level (positively), MAMC area (positively), age (negatively), and TSFT (negatively).

Discussion

Our study demonstrated the utility of HGS in predicting mortality in MHD patients. Utilizing this simple tool to identify MHD patients at an increased risk of death may be beneficial for healthcare systems. The results of the present study can be used to identify MHD patients who are at a high risk for mortality. Together with the **subjective global assessment or** malnutrition inflammation score, HGS offers other important tool for nutritional assessment.

HGS is a widely used measure in clinical practice because it is a simple, easy-to-determine, non-invasive, and reliable nutritional marker [5]. In fact, HGS has been recognized as a simple and easy-to-measure variable that correlates with lean mass in patients soon after the start of dialysis [7]. Additionally, several studies have shown that HGS is a good indicator of nutritional status, enabling the early diagnosis of malnutrition due to changes in muscle function [5, 8-10].

Moreover, our results indicated that HGS can identify an increased risk of mortality in both male and female MHD patients, with a different cut-off for each sex. This study provides direct evidence supporting HGS as a valid tool for predicting mortality in Taiwanese MHD patients. The optimized cut-off point for HGS as a predictor for mortality in males was 26 kg and 17 kg in females. According to the 2019 Asian

Working Group for Sarcopenia (AWGS) recommendation [11, 12], the diagnostic cut-off point for low muscle strength is HGS < 28.0 kg for men and <18.0 kg for women among elderly Asian populations (age > 65 years). In comparison, the HGS cut-off points for poor outcomes in dialysis patients are relatively lower than those in the elderly population.

The mechanisms and mediators underlying the association between low HGS and high mortality risk are not fully understood. Several mechanisms have been hypothesized to explain the significant association of muscle strength and mortality. Physical disability and cognitive decline are risk factors for higher mortality in old-aged populations, which may be a result of reduction in muscle mass [13-17]. For example, low muscle mass may increase the risk of falls in elderly people, resulting in a greater risk for disability and, consequently, death. However, previous reports have shown that resistance training enhances muscle quality, reduces the risk of cardiovascular disease, and improves the quality of life in the general population [18]. In our study, the non-surviving group had a higher proportion of patients with cardiovascular disease. Moreover, muscle strength is considered a marker of nutritional status [19, 20]. Malnutrition has been recognized as a definite predictor of mortality in HD patients [21]. Nutritional status is usually reduced in chronic diseases, and malnutrition also exerts a substantial impact on muscle strength. A poor nutritional status is more associated with increased risk factors for death, such as infection. The above reasons may explain the association between HGS and mortality risk (Fig. 3).

Most previous studies that examined the association between muscle strength and death were performed in Caucasian patients or in patients of African descent. Recent studies investigated the association between muscle strength and death in the Japanese population [1, 22]. These studies confirmed that low muscle strength is associated with an increased risk of mortality in Asian populations. Similarly, we applied HGS to the Taiwanese dialysis population, and our results also proved the correlation between muscle strength and mortality.

Although diagnostic cut-off points for low muscle strength of HGS < 28.0 kg for men and HGS < 18.0 kg for women were recommended by the AWGS 2019 for elderly Asian populations [11, 12], there is a lack of consensus on HGS reference values for dialysis patients. Leal et al. [23] showed in their systematic review that the HGS values of dialysis patients range from 12 to 38 kg in men and from 12 to 26 kg in women. In the study by Vogt et al. [24] (N = 265; HD: 82.3%, peritoneal dialysis: 17.7%), the HGS cut-off values were 24 kg for men and 12.5 kg for women. In the study by Matos et al. [3] (N = 443), HGS values of 28.3 kg for men and 21.5 kg for women were the best cut-off points for predicting mortality in Brazilian HD patients. Moreover, the values were 26 kg for males and 17 kg for females in our study. As in the general population, a large discrepancy in muscle strength is observed in MHD patients according to age, race, and sex. In summary, the difference of muscle strength between the sexes is already well known. Moreover, recent studies have proved that different races and ages are associated with different cut-off values [3, 12, 22, 24, 25].

Muscle mass assessed using MAMC area and TSFT had no significant difference between survivors and non-survivors in our analysis. In contrast, higher HGS and higher Kt/V were both significant independent

predictors for better outcome in HD patients, similar to the results of previous studies. In the study by Isoyama et al. [2] (N = 330), decreased muscle strength was more strongly associated with mortality than decreased muscle mass in dialysis patients. Lopes et al. [25] included 413 patients with <3 months of HD in their study. However, other studies that investigated the association between HGS and mortality in the MHD population mainly comprised prevalent patients with >6 months of dialysis. The results presented here might have been influenced by the HD vintage, which was 72–75 months in our study. Another previous study suggested that muscle mass wasting is highly prevalent among MHD patients, with significant evidence of wasting in 18–75% of the patients [26]. The longer the HD vintage, the greater the possibility for muscle strength reduction. Therefore, the cut-off point might be different in patients with different dialysis vintages. However, uremic toxins may play an importance role in muscle wasting, which might explain why the cut-off for low muscle strength in HD patients is lower than that in the general population. Furthermore, a lower mortality rate was observed in patients with higher uremic toxin clearance in our study.

Strength training is associated with important clinical outcomes, including increased muscle strength and improved self-rated physical health and function. However, particularly in HD patients, it may be difficult to increase muscle mass with strength training. Muscle growth may be impaired as a result of several catabolic conditions, such as insulin resistance, reduced levels of and resistance to anabolic hormones, acidosis, or chronic inflammation [27]. In our analysis, patients with high Kt/V had a lower mortality rate. Therefore, a high quality of HD can reduce the accumulation of uremic toxins and consequently reduce muscle wasting. In other words, simple muscle training might play a limited role in improving muscle strength in HD patients. Clinicians should pay more attention to the dialysis quality or the nutritional status of patients rather than to muscle training.

Limitations

This study had several methodological limitations. First, our sample was limited to the Taiwanese population, which mainly consisted of Asian patients. Therefore, this may limit the extrapolation of our findings to other ethnic groups. Second, definite causal conclusions cannot be reached in our analysis owing to its prospective observational nature. For example, it is not possible to evaluate whether the association of HGS with mortality varies according to the cause of death. Nevertheless, previous studies have indicated that the mortality risk associated with nutritional indicators is usually due to cardiovascular disease [28].

Although the results of this study showed the association of HGS with mortality in both male and female MHD patients, randomized controlled trials are still required to confirm our results. Third, our sample size was small, and patients were enrolled from a single medical center. Finally, we addressed the mortality risk based on single-point measurements of muscle strength in the beginning of the study. Because HGS was measured only at the start of the study, our data were not suitable for determining the influence of changes in muscle strength during the follow-up on mortality risk. A time-averaged analysis based on

sequential measurements during the follow-up period may provide more direct evidence on the association between muscle strength and prognosis in MHD patients.

Further studies are required to assess whether serial changes in muscle function may better predict mortality than a single measurement in MHD patients. Age-specific HGS should also be assessed in future investigations. In addition, further studies should be conducted to evaluate the association between HGS and mortality risk in PD patients. HGS may also play a role in predicting mortality in the PD population.

Conclusion

This study has important implications for clinical practice in MHD patients. It provides evidence that HGS can predict mortality in MHD patients. Thus, this simple, objective, non-invasive tool can be used in the clinical setting to identify MHD patients at an increased risk of death. In addition, our results indicate that HGS can identify male and female MHD patients with an increased risk of all-cause mortality, with different cut-off values for each sex. The HGS cut-off points for predicting mortality are 26 kg for males and 17 kg for females in Asian populations. In conclusion, this study shows that HGS is a good marker for survival in HD patients.

Abbreviations

HD, hemodialysis; MHD, maintenance hemodialysis; HGS, handgrip strength; AVF, arteriovenous fistula; MAC, mid-arm circumference; MAMC, mid-arm muscle circumference; TSFT, triceps skinfold thickness; PPV, positive predictive value; NPV, negative predictive value

Declarations

Ethics approval and consent to participate:

This study was conducted according to the Declaration of Helsinki and approved by the Institutional Review. Board and Ethics Committee in Chang Gung Memorial Hospital (IRB No. 98-2685B), and informed consents were obtained from all participants.

Consent for publication: Not applicable.

Availability of data and materials: Not applicable at this stage.

Competing interests:

The authors declare that they have no competing interests.

Funding:

This study was supported by funding from the Kaohsiung Chang Gung Memorial Hospital, Taiwan (CMRPG890171).

Authors' contributions:

Y.T. Chu and Terry T.Y. Chiou made conception and design of this study. P.C. Hsu, C.H. Liu and Terry T.Y. Chiou acquired the data. Y.T. Chu and Terry T.Y. Chiou did analysis besides Terry T.Y. Chiou, W.C. Lee and C.H. Wu interpreted the data. Y.T. Chu drafted the manuscript and prepared all figures and tables as well. Terry T.Y. Chiou and W.C. Lee revise the manuscript critically for important intellectual content. All authors reviewed the manuscript.

Acknowledgements:

We gratefully acknowledge the biostatistics center in Kaohsiung Chang Gung Memorial Hospital for their valuable comments on this study.

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Tables

Table 1. Baseline characteristics of 188 HD patients and comparison between male and female patients

Characteristics	Total (N=188)	Male (N=78)	Female (N=110)	P-value
Age (years)	59.5 ± 10.6	61 ± 9.1	58.4 ± 11.4	0.093
HD vintage (months)	61(36.3-107.3)	55.5(34.8-110.8)	68(40.0-105.8)	0.957
BMI (kg/m2)	22.9 ± 3.9	23.4 ± 4.4	22.5 ± 3.6	0.103
HGS (kg)	23 ± 9.2	28.4 ± 10.4	19.6 ± 6.3	<0.001
Waist circumference (cm)	85 ± 12.5	89.1 ± 13.4	82.2 ± 10.9	<0.001
TSFT (mm)	15.9 ± 6.4	12.6 ± 5	18.3 ± 6.3	<0.001
MAMC area (cm^2)	36.6 ± 11.1	39.4 ± 9.9	34.5 ± 11.5	0.004
Kt/V (dialysis adequacy)	1.7 ± 0.3	1.5 ± 0.2	1.8 ± 0.3	<0.001
Hemoglobin (g/dL)	10.5 ± 1.2	10.5 ± 1.2	10.6 ± 1.2	0.612
Serum albumin (g/dL)	3.9 ± 0.2	3.9 ± 0.2	3.9 ± 0.3	0.531
Serum creatinine (mg/dL)	10.9 ± 2.1	11.5 ± 2.2	10.4 ± 1.8	<0.001
Serum calcium (mg/dL)	9.3 ± 0.8	9.2 ± 0.8	9.4 ± 0.8	0.041
Serum phosphate (mg/dL)	4.9 ± 1.4	4.8 ± 1.4	4.9 ± 1.4	0.411
Hs-CRP (mg/L)	2.9(1.3-6.8)	3.7(2.0-7.4)	2.4(1.1-6.1)	0.158
Interleukin-6 (pg/mL)	2.6(1.5-4.3)	2.8(1.6-4.1)	2.4(1.4-4.6)	0.159
TNF-α (pg/mL)	6.4(4.1-10.7)	6.5(4.6-11.0)	6.4(3.8-10.6)	0.385

HD, hemodialysis; BMI, body mass index; HGS, handgrip strength; TSFT, triceps skinfold thickness; MAMC, mid-arm muscle circumference; Hs-CRP, high-sensitivity C-reactive protein; TNF-α, tumor necrosis factor alpha.

Table 2. Clinical and nutritional characteristics and comparison between survivors and non-survivors					
Univariate analysis				Multivariate analysis with Cox proportional hazards models	
Characteristics	Non-survival (N=34)	Survival (N=154)	P-value	Hazard Ratio (95% CI)	P-value
Age (years)	62±9	59±11	0.148	—	0.559
HD vintage (months)	51.0(28.8-98.3)	63.0(36.8-108.3)	0.79	—	—
Male (%)	50	40	0.266	—	0.769
Diabetes mellitus (%)	47	23	0.004	—	0.226
CVD (%)	62	41	0.027	—	—
BMI (kg/m^2)	23.2±3.6	22.8±4	0.567	—	—
HGS (kg)	16.4±8.4	24.2±8.8	<0.001	0.891(0.838-0.948)	<0.001
Waist circumference (cm)	89.3±10	84.1±12.8	0.028	—	0.766
TSFT (mm)	15.4±6.5	16.0±6.4	0.638	—	—
MAMC area (cm^2)	36.1±10.2	36.8±11.8	0.735	—	—
Kt/V (dialysis adequacy)	1.3±0.2	1.4±0.2	0.022	0.086(0.018-0.421)	0.002
Hemoglobin (g/dL)	10.4±0.9	10.6±1.3	0.301	—	—
Serum albumin (g/dL)	3.9±0.2	3.9±0.3	0.141	—	0.119
Serum creatinine (mg/dL)	10.3±2.2	11±2	0.087	—	—
Serum calcium (mg/dL)	9.3±1	9.3±0.8	0.702	—	—
Serum phosphate (mg/dL)	5.1±1.5	4.8±1.4	0.267	—	—
Hs-CRP (mg/L)	4.2(2.4-9.9)	2.5(1.2-6.2)	0.073	—	0.677
Interleukin-6 (pg/mL)	3.4(1.7-7.5)	2.3(1.4-4.0)	0.048	—	0.136
TNF-α (pg/mL)	5.7(3.4-10.4)	6.5(4.1-	0.472	—	—

	10.8)

CI, confidence interval; HD, hemodialysis; CVD, cardiovascular disease; BMI, body mass index; HGS, handgrip strength; TSFT, triceps skinfold thickness; MAMC, mid-arm muscle circumference; Hs-CRP, high-sensitivity C-reactive protein; TNF-α, tumor necrosis factor alpha.

Table 3. Correlation between handgrip strength and other variables

Variables	Pearson correlation	P-value
Age	-0.249	0.003
HD vintage	-0.002	0.982
BMI	0.162	0.056
Waist circumference	0.118	0.164
TSFT	-0.185	0.037
MAMC area	0.221	0.012
Serum albumin	0.245	0.004
Serum creatinine	0.357	<0.001
Hs-CRP	-0.040	0.641
Interleukin-6	-0.143	0.093

HD, hemodialysis; BMI, body mass index; TSFT, triceps skinfold thickness; MAMC, mid-arm muscle circumference; Hs-CRP, high-sensitivity C-reactive protein

Figures

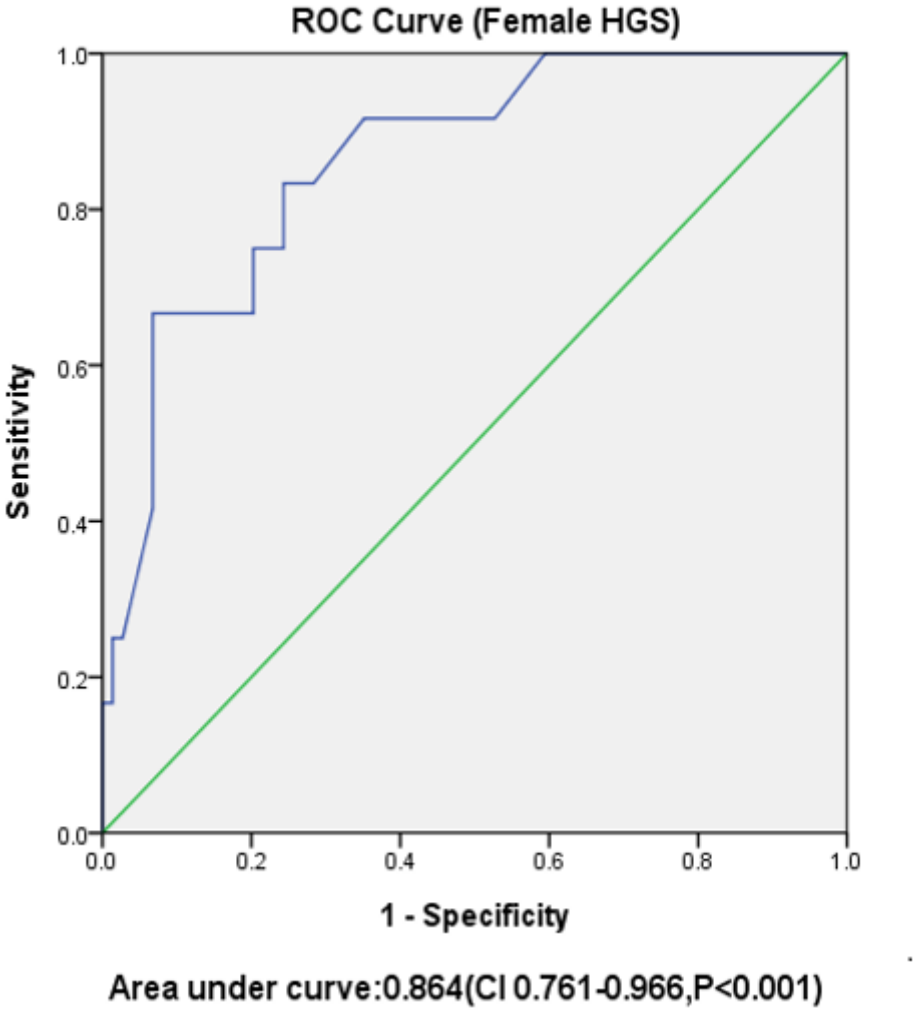

Figure 1

Receiver operating characteristic curve for handgrip strength (HGS) of female maintenance hemodialysis patients. CI, confidence interval.

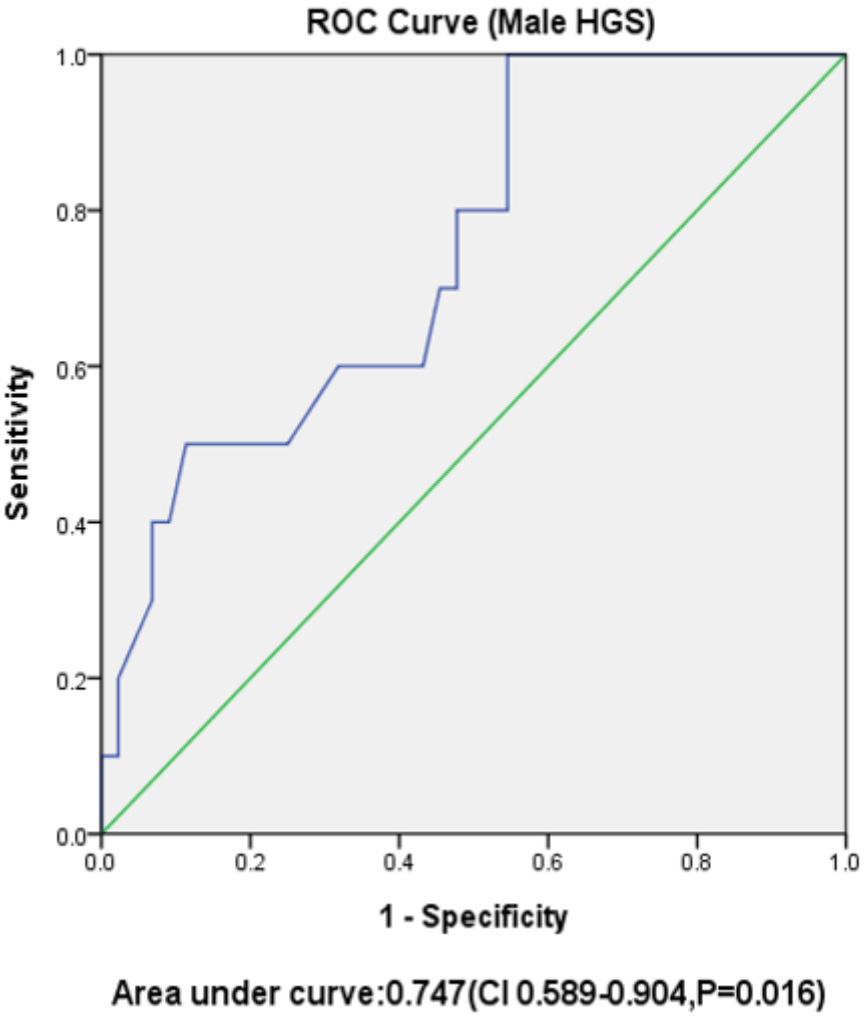

Figure 2

Receiver operating characteristic curve for handgrip strength (HGS) of male maintenance hemodialysis patients. CI, confidence interval.

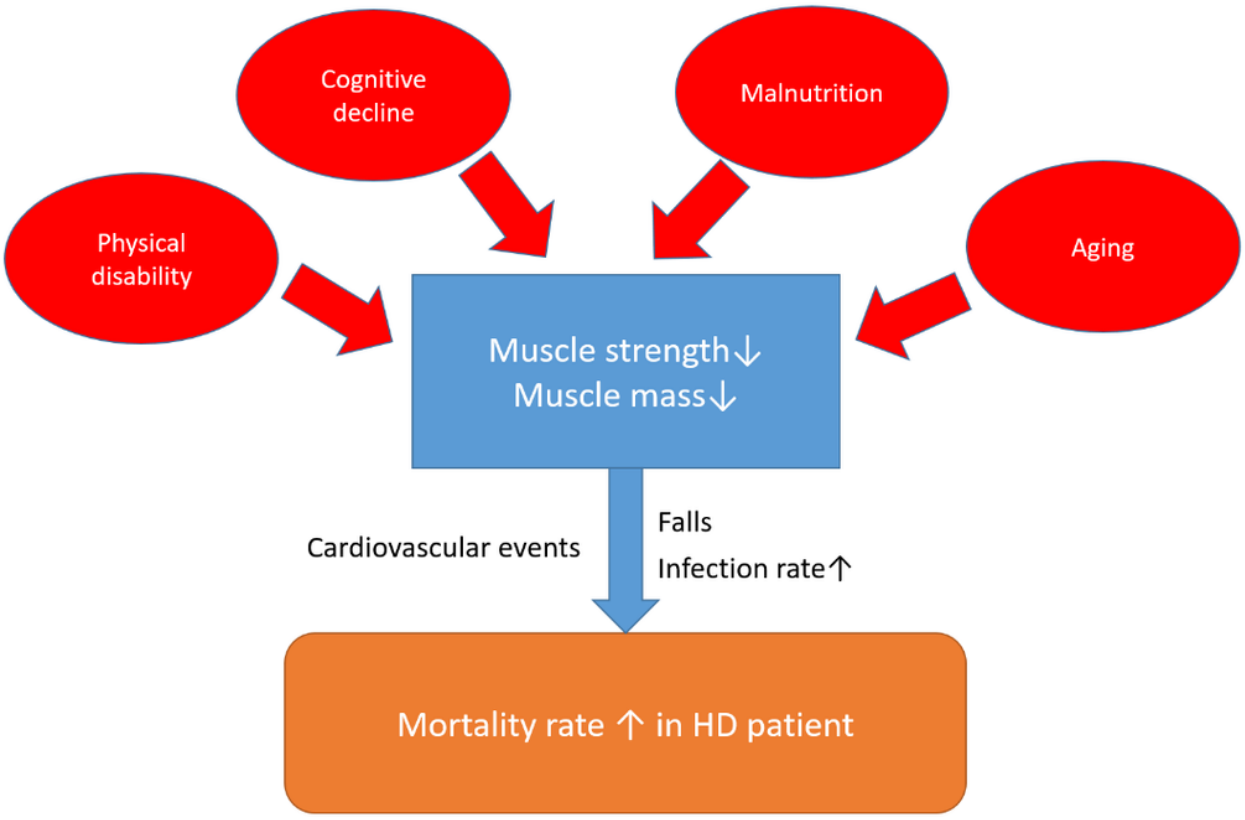

Figure 3

Several mechanisms may explain the significant association between muscle strength and mortality risk. HD, hemodialysis.