UNIVERSITÉ DU QUÉBEC À MONTRÉAL

ASSOCIATION BETWEEN STANDARD BIOCHEMISTRY MARKERS AND HAND GRIP STRENGTH IN CANCER SURVIVORS: A CROSS-SECTIONAL ANALYSIS OF NHANES DATA

THESIS

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ASSOCIATION ENTRE LES MARQUEURS BIOCHIMIQUES STANDARD ET LA FORCE DE PRÉHENSION DES MAINS CHEZ LES SURVIVANTS DU CANCER : UNE ANALYSE TRANSVERSALE DES DONNÉES DU NHANES

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LISTE DES ABRÉVIATIONS, DES SIGLES ET DES ACRONYMES

HGS	Handgrip strength
BMI	Body mass index
CBC	Complete Blood Count
ACSM	American College of Sports Medicine
NHANES	National Health and Nutrition Examination Survey
NA	Not Applicable
AIC	Akaike Information Criterion
VIF	Variance Inflation Factor

LISTE DES SYMBOLES ET DES UNITÉS

Symbol	Unit
Albumine	g/dl
Alanine aminotransferase	U/L
Aspartate aminotransferase	U/L
Blood urea nitrogen	mg/dl
Body mass index	kg/m2
Creatine Phosphokinase	IU/L
Handgrip straight	kg
Phosphorus	mg/dl
Potassium	mmol/L
Sodium	mmol/L
Total calcium	mg/dl
Total calcium	mg/dl
Total protein	g/dl

RÉSUMÉ

L'objectif de cette étude était d'évaluer l'association entre la force de préhension et 10 marqueurs biochimiques standards chez les survivants du cancer âgés de 25 à 80 ans. En outre, les valeurs normales de la force de préhension pour 3 groupes d'âge différents ont été rapportées, calculées comme la somme de la force de préhension pour trois essais, en utilisant les données représentatives de la National Health and Nutrition Examination Survey (NHANES).

Méthodes :

Nous avons inclus les participants survivants du cancer des cycles NHANES 2011-2012, et 2013- 2014 qui ont effectué un test de force de préhension. Ce test a été défini comme la valeur maximale atteinte en utilisant la main droite ou la main gauche exprimée en kilogramme (kg). Des modèles de régression multivariés ont été utilisés pour identifier les facteurs les plus influents sur la force de préhension de la main. Les modèles incluaient les variables indépendantes suivantes : l'âge, le sexe, la race, l'Indice de Masse Corporelle (IMC), la circonférence du bras, l'activité physique, le tabagisme, la main dominante et les 10 facteurs biochimiques (Mesurés à partir d'échantillons de sang).

Nous avons effectué deux modèles de régressions descendants qui utilisaient la valeur du Critère d'information d'Akaike comme indice de sélection du modèle. Nous avons systématiquement utilisé les valeurs de pondération dans nos modèles. Chaque modèle était testé dans un premier temps en excluant les données manquantes puis à la suite d'une imputation de données.

Résultats :

Parmi les 537 survivants du cancer (52,1% de femmes et 47,9% d'hommes, âge = 64,3 ± 13,7 ans), les cancers les plus fréquents étaient respectivement la prostate, le cancer

du sein, le mélanome, le côlon, le poumon, l'utérus, l'ovaire, le rein, la vessie, le cerveau / le larynx / l'œsophage et autres.

Dans le modèle de régression ajusté avec données manquantes, nous avons identifié les facteurs biochimiques suivants comme associés significativement à la force de préhension : azote uréique sanguin, créatine phosphokinase, potassium, aspartate aminotransférase et alanine aminotransférase ($R^2 = 0.66$).

Le second modèle de régression ajusté utilisant les données imputées, les variables suivantes étaient associées à la force de préhension : azote uréique sanguin, créatine phosphokinase, calcium, potassium, aspartate aminotransférase et alanine aminotransférase ($R^2 = 0.64$)

Conclusions :

Sur la base de nos analyses, les facteurs biochimiques suivant sont associés à la force de préhension chez les survivants du cancer : azote uréique sanguin, créatine phosphokinase, calcium, potassium, aspartate aminotransférase et alanine aminotransférase. En revanche, le facteur d'albumine, de phosphore, de sodium et de protéine totale n'a pas été retenue dans les deux modèles. La détection précoce des changements dans le profil biochimique et la classification des performances de préhension, ainsi que la prise de conscience de la relation entre la force des mains et les marqueurs sanguins chez les patients atteints d'un cancer avancé peuvent fournir aux médecins des indices pronostiques utiles qui peuvent les inciter à prendre des mesures de traitement en temps opportun ou à effectuer des interventions ciblées. Enfin, des interventions de changement de comportement ciblant le régime alimentaire et l'activité physique pourrait favoriser un meilleur contrôle de ces facteurs déséquilibrés chez les adultes avec un antécédent de cancer. Cela pourrait inciter les personnes touchées par un cancer d'adopter un mode de vie plus actif si leur condition le permet.

Mots clés : Force de préhension, profil biochimique, survivants du cancer, NHANES.

ABSTRACT

The objective of this study was to evaluate the association between handgrip strength (HGS) and 10 standard biochemistry markers in cancer survivors between 25 to 80 years old. In addition, the norm ranges of handgrip strength for 3 different age groups was reported, which was calculated as the summation of handgrip strength for three trials, using representative National Health and Nutrition Examination Survey (NHANES) data.

Methods:

We included cancer survivor participants from the NHANES cycles 2011-2012, and 2013- 2014 who did handgrip strength test. This test is defining as the maximum value achieved using either right or left hand in kilogram (kg). Multivariate Regression models were used to identify the most influential factors on hand grip strength as dependent variable. The models included the following independent variables: age, sex, race, body mass index (BMI), arm circumference, physical activity, smoking status, dominant hand and 10 biochemical factors (measured from blood samples).

Two Backward regression models were built using Akaike's Information Criterion (AIC) value as the index to fit the final model. We systematically used weighted values in our models. Each model was first tested by data missing values (with NAs) and then by imputed data (without NAs).

Results:

Among 537 cancer survivors (52.1% women and 47.9% men, age = 64.3 $\pm$ 13.7 years), the most common cancers were prostate, breast cancer, melanoma, colon, lung, uterus, ovary, kidney, bladder, brain / larynx / esophagus, and others, respectively.
In the adjusted regression model with missing data, we identified the following biochemical factors that were significantly associated with handgrip strength: blood urea nitrogen, creatine phosphokinase, potassium, aspartate aminotransferase and alanine aminotransferase (R2 = 0.66). On the other hand, in the second adjusted regression model using the imputed data, the following variables were associated with hand grip strength: blood urea nitrogen, creatine phosphokinase, calcium, potassium,

phosphorus, aspartate aminotransferase and alanine aminotransferase (R2 = 0.64). In contrast, the albumin, sodium and total protein were not significant in either model.

Conclusions:
Early detection of changes in the biochemistry marker and classification of handgrip performances, as well as awareness of the relationship between hand strength and blood markers in patients with advanced cancer may provide physicians with useful prognostic clues that may prompt them to take treatment steps in an appropriate time or do targeted interventions. Finally, behavioral change interventions targeting diet and physical activity may promote better control of these unbalanced factors in adults with a history of cancer. This could prompt people with cancer to adopt implement a more active lifestyle if their condition allows it.

Keywords: Handgrip strength, biochemistry marker, cancer survivors, NHANES.

INTRODUCTION

Clinical research has shown that weak muscle strength is associated with longer hospital stays, lower physical function, poorer quality of life, and that it contributes to the disability of older people. Having a normal range of muscle strength plays an important role in the prevention and treatment of almost all chronic diseases that are very prevalent in older age. One of the best ways for measuring the overall and the upper body muscles' strength is to use handgrip strength (HGS) test. This test can also be used as an indicator of muscle mass since muscle force is directly proportional to muscle mass [1]. All over the world, due to the use of calibrated equipment and dynamometers to measure hand force, this test is adopted as a common and reliable method and as a reference test [1]. In addition, measuring the HGS shows how skeletal muscles are functional in generating forces, and through this, the inability and weakness of the muscles that may predict future dysfunction to maintain daily life activities can be determined [2]. Different types of cancer have long been known as a deadly disease through which the muscle strength is altered. Advanced cancer is also associated with many clinically related conditions such as anorexia, anemia, and abnormal biochemical markers such as a wide range of pro-inflammatory markers [3]. Therefore, HGS, biochemical factors and the association between them are crucial factors in studies related to cancer.

Most of available studies have classified muscle forces according to gender and age, while a limited number of studies categorized the forces based on the right and left

hand or the dominant and non-dominant hand. Some research found that the HGS of men was higher in all age groups compared to women [4]. In addition, Hermoso et al examined the effect of muscle strength on all-cause mortality between sexes. After measuring HGS, people with more strength showed reduced risk of all-cause mortality by 31 percent [2]. In women, this relationship between HGS and reduced all-cause mortality was slightly stronger accompanied with lower heterogeneity when compared to men. In terms of age, the HGS typically reaches a peak value in the fourth decade of life followed by a gradual decrease [1].

In terms of methodology for measuring HGS, the sitting position is one of the most reliable and widely used postures [2]. In addition, different number of trials for measuring HGS are performed by participants in different studies depending on their purpose. The highest or mean value of grip strength in kilograms is then used for the analyses [4].

HGS used to investigate in a few studies in patients with cancer [5-9]. The term "cancer survivor" refers to a person who has been diagnosed with cancer and has spent the rest of his/her life with it. Some studies have measured the physical activity and mental state of cancer survivors in association with chemical factors [8, 10-13]. This relationship is important because biochemical marker imbalances in survivors of cancer can impact on the metabolic homeostasis of their body. Post-cancer care can lead to more effective outcomes and improve physical performance in individuals. In this study, we proposed to analyze various factors in cancer survivors such as age, sex, education, marriage, physical activity, smoking, BMI and 10 biochemical factors (e.g., alanine aminotransferase, aspartate aminotransferase, proteins, albumin, blood urea nitrogen, creatine phosphokinase, calcium, sodium and potassium). The main objective

of the current study was to identify the most influential factors on HGS by introducing these factors into a multiple regression model.

1 CHAPITRE I
LITERATURE REVIEW

1.1 Measurement of the hand grip strength

1.1.1 Importance of hand grip strength and its predictability

The HGS test can be used both as an indicator of muscle mass and overall muscle strength of the body. Different body positions have been suggested to measure grip strength, nonetheless, the sitting position is one of the most reliable and widely used methods. Regardless of the measurement approach, the relationship between HGS and age, sex, and different diseases have been assessed and reported in previous research. In this section, different positions for measuring grip strength are primarily summarized. Then, the relationship between HGS and different factors will be reviewed.

1.1.2 Different positions to measure hand grip strength

Several situations and positions have been used to measure HGS, so it is not the same between different studies. For example, the study of National Health and Nutrition Examination Surveys (NHANES) did not follow the protocol recommended by the American Society of Hand Therapists (ASHT) for measuring grip strength, which was sitting position without arm rests [14]. In fact, the AHST approach is with the elbow flexed at 90°, forearm in neutral position, and wrist pronated between 15° and 30° with a recommendation of using three trials for measuring the grip strength of each hand with the Jamar dynamometer (Figure 1.1). However, the position in NHANES studies

was in standing position, as proposed by the American College of Sports Medicine (ACSM), with arm straight downwards, elbow fully extended and feet apart at hip width. Regarding the measurement tool, the Jamar dynamometer was recommended by the American Society for Surgery of the hand and the ASHT approach for grip strength measurement. However, in the NHANES study, the Takei digital dynamometer, model T.K.K.5401, was used to record three trials of grip strength, with 60-second break between trials. The combined grip strength was calculated as the sum of the largest reading from each hand and expressed in kilograms [4, 14].

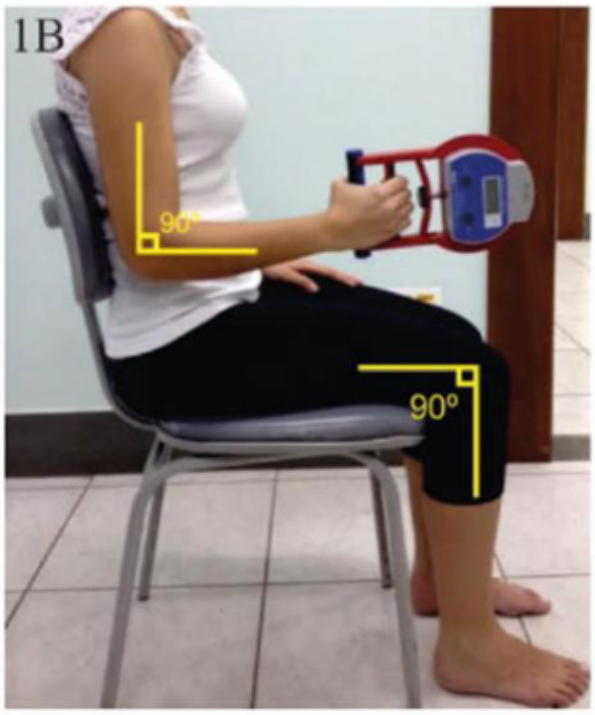


Figure 1.1: The position used by American Society of Hand Therapists to measure HGS [15]

In an effort to look at the effect of body position, Balogun et al compared four different positions in a population of 61 people in the age range of 16 to 28 to understand the differences in HGS scores. The positions were: 1) sitting with elbow in 90° flexion, 2) sitting with elbow in full extension, 3) standing with elbow in 90° flexion, and 4) standing with elbow in full extension. They found significant differences between sitting and standing positions and different elbow joint angles for both sexes. The highest grip strength belonged to the standing position with elbow in full extension, yielding a strength of 31.1 ± 8.8 kg. On the other hand, the lowest score was observed in sitting position with elbow at 90° flexion with the range of 29.5 ± 9.3 kg [16]. Based on these results, it might be difficult to compare the results of grip strength between studies which used different positions of measurement. However, individual studies that use the same approach with all their included participants to report the association between grip strength and other factors should be comparable regardless of their measurement approach.

In the next section, the association of grip strength and other factors are summarized.

1.1.3 Effect of gender, age, dominant hand and race on grip strength

Some studies reported the effect of different age groups, gender, dominant hand, race and body mass index (BMI) on the function of muscles using the HGS test [4]. For example, Wang et al used the NHANES database from 2011-2014 to categorize muscle strength based on age groups of 6-80 years, gender and dominant side. Three trials of the HGS were measured for each hand using the ACSM recommended approach with a Takei digital handgrip dynamometer, and the highest recorded force was used for analysis. The highest mean grip strength was equal to 50.3 kg and was observed in the dominant hand of the men aged in the range of 30-34 years old, while the lowest mean

grip strength was equal to 10.0 kg belonging to the 6 year-old girls' category in their non-dominant hand. In addition, the highest average strength for women was reported in the age group of 40-49 compared to men in the age group of 20 to 39 [4]. Bohannon et al compare two Data: the first one with 13,918 participants from the 2011–2014 National Health and Nutrition Examination Survey (NHANES) and the second one with 3,594 participants the 2011 normative phase of the National Institutes of Health (NIH) Toolbox project. In fact, the NHANES values used were the mean and best of three trials but the NIH Toolbox value used was the one maximum trial after a practice trial. When they compared NHANES mean values to NIH handgrip values, the results showed that grip strength values were higher for the NHANES group than the NIH Toolbox group ($F = 98.6$, $p < .001$). In addition, grip strength values were higher or males than for females ($F = 3{,}967.6$, $p < .001$), for the dominant side than the non-dominant side ($F = 9{,}497.9$, $p < .001$), and for some age groups than others ($F = 1{,}406.9$, $p < .001$) [17]. Hand grip strength measurements were performed on a population of 1,023 Swiss people aged 18 to 96 using a Jamar dynamometer. The test was performed according to the American Society of Hand Therapists (ASHT) with a sitting position. The peak value of grip strength for males was observed in ages of 35-39 and for female in the range of 40-45 years. The test of the hand grip was repeated three times and due to the fatigue of repeating the tests, the average difference was 1.3 kg in the right hand and 1.53 kg in the left hand [18]. In addition to considering the effect of age and sex, some studies considered the impact of other factors such as race. Leong et al have reported the differences in hand grip strength due to differences in the geographic regions of participants. The results corresponding to the participants from 2121 countries in the range of 35-70 years old were summarized as follows: the men of Europe/north America, <40 years, with power of 50 kg had the highest and the women from South East Asia, >60 years with power of 18kg had the lowest handgrip strength.

In general, all regions from the least hand grip strength to the highest one were expressed in this order: South Asia, South East Asia and Africa, China, South America, the Middle East, and Europe/North America. Additionally, in the absence of obesity, the relationship between hand grip strength and BMI was positive [19]. Based on the results of this study, age, gender and the dominant side had significant impact on HGS and have to be considered in future studies.

1.2 Association between hand grip strength and chronic disease

The association between HGS and physical or mental health consequences has also been studied in recent years. This section focused on understanding the relationship between muscle strength and mortality in people with chronic diseases, as well as the predictability of mortality by HGS.

Jochem et al evaluated the relationship between mortality risk and muscle strength in acute and chronic diseases such as cancer, chronic obstructive pulmonary disease (COPD), renal disease, and cardiovascular disease. They conducted a systematic review and random-effects meta-analysis of prospective cohort studies on 39 studies and a total of 39,852 participants. They performed statistical analysis using R (v.3.4.4) and the Metaphor package. This study reported that six out of 39 studies investigated all-cause mortality in patients with cancer. Based on these studies, the risk of all-cause mortality in individuals with the lowest and highest levels of muscle strength was significant. Decreases in muscle strength were associated with 1.8-fold increase in the risk of mortality. On the other hand, it was reported that each 5 kg increase in muscle strength was related to 28% reduction in all-cause mortality risk. Regarding cancer patients, the lowest amount of HGS was related to risk of mortality. This was in

agreement with the results of two previous studies who reported the decrease in muscle strength was directly related to increased mortality in heart disease and cancer [3].

In addition to the previously mentioned literature in this section, there are other studies available that examined the relationship between HGS and mortality over different years of follow-up. Such studies might help researchers to see whether time or other mediating factors affect the relationship between mortality and HGS. In fact, Rantanen et al studied 919 women in the age range of 65 to 101 that were surveyed, and the participants were followed for 5 years. They reported that HGS was a strong predictor of all cause, cardiovascular and respiratory mortality. However, HGS was not related to cancer mortality, which was not in agreement with previous studies [20].

Gale et al evaluated 800 men and women aged 65 and over who lived in eight different areas of Britain. They assessed the relationship between HGS and total mortality during 24 years of follow-up using Cox proportional hazard models. They found that lower HGS was associated with higher rate of mortality from all causes, cardiovascular disease, and cancer in men. This finding was preserved even when they adjusted this relationship with other factors like arm muscle area, BMI, fat free mass or percentage of fat. For men with higher HGS, the risk of mortality decreased, and this relationship remained significant after multivariate adjustment for fat-free mass, BMI and % body fat. After adjusting mean grip strength for sex and age, they found that HGS amount was higher for non-smokers compared to smokers, in healthy people compared to those diagnosed with disease, and in those who had hobbies involving high levels of physical activity compared to those having no hobbies outdoors. On the other hand, following multivariate analyses, the association between grip strength and risk of mortality from cancer was not statistically significant in women. In addition, a reduced risk of cancer

mortality was observed in men with greater grip strength [21]. These results were partly in agreement with the results of meta-analysis study performed by Jochem et al [22].

A further study was performed by Celis-Morales et al which evaluated the relationship between grip strength and age with the risk of all causes of mortality and the incidence of specific disease and mortality from cardiovascular disease, respiratory disease, COPD, all cancers and sub-types of cancer in 502293 participants aged 40 to 69 years from the UK Biobank. They used nonlinear regression Cox proportional hazard models for investigating the association between grip strength with the all-cause mortality and incidence through a follow-up approach. Grip strength was considered as a continuous variable. The results of this study showed that adding grip strength as a predictor parameter improved the predictability of the models. It was also observed that a higher hazard for all-cause mortality, incidence and mortality from cardiovascular disease, all respiratory disease, COPD, all cancer, as well as colorectal, lung, and breast cancer in both men and women were associated with a 5 kg lower grip strength, which was in agreement with the previous studies. On the other hand, in men and women, the mortality hazard ratio per 5 kg lower grip strength was 1.31 and 1.24 for all respiratory disease, 1.24 and 1.19 for COPD, 1.19 and 1.24 for cardiovascular disease, 1.20 and 1.16 for all-cause mortality, 1.24 for breast cancer, 1.17 and 1.18 for colorectal cancer, 1.17 and 1.08 for lung cancer, and 1.17 and 1.10 for all cancer mortality, respectively. However, no association between grip strength and prostate cancer mortality was observed. The muscle weakness was defined as HGS $\leq$ 26.0 kg for men and $\leq$ 16.0 kg for women, and it was shown that muscle weakness was associated with an increased risk of all health outcomes. The main finding of this study was that a strong association existed between a wide range of adverse health outcomes and lower grip strength [5].

Finally ,Gale et al reported that none of the indicators of body composition and muscle size could predict mortality, but that grip strength was a good predictor of mortality for a lot of cases [21]. Although some studies have found that all-cause mortality in patients was not significantly associated with muscle strength, most of them have suggested that muscle strength affects cause-specific and all-cause mortality as well as differences in muscle strength between the sexes. These results highlight the importance of HGS in different sources of disease and mortality, and might play an important role in the prediction of survival rate regarding cancer survivors. In the next section, we will focus specifically on cancer/cancer survivors and examine the relationship between HGS and cancer.

1.3 Association between hand grip strength and cancer /cancer survivors

1.3.1 The prevalence of different cancer types

Cancer is a disease in which abnormal cells grow and divide uncontrollably and spread to other parts of the body. In Table 1.1, the amount of new cancer cases and cancer death in the United States is shown in 2021 according to national cancer institute website. This table includes the types of cancer that accounts for approximately 50% of new cancer cases in the United States, including breast, lung and bronchial, prostate, and colon cancers [23].

Table 1.1: Amount of new cancer cases and cancer death in USA 2021

Type of cancer	New cancer cases	Type of cancer	New cancer cases
Prostate	248,530 (13%)	Melanoma	106,110
Breast	284,200 (15%)	Uterus	66,570

Colorectal	149,500 (8%)	Bladder	83,730
Lung	235,760(12%)	Kidney	76,080

Although cancer is one of the leading causes of worldwide death, there is little data about the prevalence of cancer in the world. Research has examined the prevalence of cancer in high-income countries, while the ones with highest prevalence are lung, colorectal, breast and prostate cancers, which is similar to the most common types of cancer in U.S. In low-middle-income countries, these cancers include stomach, liver, and cervix. There are many measures to reduce the incidence of cancer including tobacco control, early detection, lifestyle improvement and appropriate treatment and care [24].

Cancer survivor is a person with any type of cancer who is still living. The time of being recognized as cancer survivor is considered as the first time that the patient is diagnosed with cancer or after completing treatment through the rest of his life. In 2001, the population of cancer survivors in the United States was as follows: more than one million people aged 60 to 69, and more than 2 million people aged 70 and over. As of January 1, 2012, approximately 13.7 million cancer survivors were living in the United States. Table 1.2 shows an estimated number of Cancer Survivors in the United States from January 1, 2012, aged 20 to 79, from highest to lowest [25]. In addition, there were an estimation of reaching 18 million cancer survivors in the United States by 2022 which represents an increase of more than 4 million survivors in 10 years.

Table 1.2: Estimated number of Cancer Survivors in the United States by age as of January 1, 2012

Type of cancer	20-39 years	40-59 years	60-79 years	total
Breast	42,826	825,965	1,504,670	2,373,461
Prostate	781	259,245	1,789,680	2,049,706
Colorectal	11,798	203,097	646,508	861,403
Melanoma	70,844	352,840	423,819	847,503
Corpus	5,144	114,327	331,093	450,564
Bladder	4,771	82,312	328,423	415,506
Lung	2,117	68,294	246,489	316,900
Kidney	13,806	95,946	184,014	293,766
Cervix	16,156	93,091	99,857	209,104
Ovary	9,835	60,068	90,261	160,164

A further recent study showed the population of cancer survivors as of 16.9 million in 2019 in the United States. This study also reported the most common types of cancer survivors for males and females separately. For men, the most common cancers were prostate (3,650,030), colon and rectum (776,120), and melanoma of the skin (684,470), while for women the most common types were breast (3,861,520), uterine corpus (807,860), colon and rectum (768,650) [26].

Various studies have compared physical function in cancer patients and cancer survivors. Decreased physical function, on the other hand, is more common in cancer patients than in healthy individuals. There are several factors that can explain the decline in muscle strength in cancer patients and cancer survivors. Regardless of

chemotherapy, the relationship between muscle strength and different types of cancer and cancer survivors has been evaluated and reported in previous research. In the following sections, physical function in healthy groups and different stages of cancer are primarily summarized. Then, the relationship between HGS and various factors such as chemotherapy and blood biomarkers are examined.

1.3.2 Physical function in healthy groups and different stages of cancer

Studies have shown that physical dysfunction occurs in cancer patients after one or two years of treatment, but then the body begins to recover and improve its function [8]. Sweeney et al assessed the physical function of a population consisting of women having a mean age of 72 years. A total of 25,719-people from the United States were included in this study in 1986 and then retaken and followed up in 1997. Participants were then classified into three groups based on their own report about the time since diagnosis: 2 years after diagnosis, and 5 years after diagnosis regarded as long-term cancer survivors and no-cancer participants. To assess physical performance, participants answered the question "for which of these tasks are you healthy enough to do them without help? a) heavy work around the house like shoveling snow or washing walls, windows, and floors? b) walk a half mile? c) go out to a movie, to church or a meeting, or to visit friends? d) walk up and down a flight of stairs? e) prepare most of your own meals?" . Using logistic regression, a relationship was found between cancer survivors and limited physical function. The results also showed that women who survived from cancer less than two years after cancer diagnosis had the lowest mobility between the three groups, and the women who survived from cancer after five years or more had lower mobility than those without cancer. In fact, 5-year cancer survivors were statistically significantly more likely to report limitations than women who had never had cancer like that: 1) for ability to do heavy work (OR = 1.47, 95% CI = 1.27 to 1.69; PR = 1.22, 95% CI = 1.10 to 1.34), 2) for walking a half mile (OR = 1.31, 95%

CI = 1.11 to 1.55; PR = 1.16, 95% CI = 1.02 to 1.32), 3) for walking up and down stairs (OR = 1.34, 95% CI = 1.05 to 1.72; PR = 1.25, 95% CI = 1.00 to 1.56) [12]. The result of this study was in agreement with the research by Keating et al who compared the physical and mental condition in 9064 people with different types of cancer survivors over 4 years to a group of 14,333 healthy people in USA. The findings of this study similarly showed that cancer survivors were worse than the non-cancer group in terms of physical health and function [27]. In addition, Petrick et al reported a similar finding in a group of people with lung cancer where their physical performance was significantly lower three years after cancer diagnosis [11].

A further study reported the HGS in cancer survivors, but their results were in disagreement with the two previous studies. Looijaard et al assessed the differences in physical function between two groups that included 1321 healthy people who did not have cancer versus 414 people who developed cancer within 10 or 20 years, so that the physical function of these people before cancer was also available. The mean age of participants was 67.8. Three approaches to measure physical activity for these individuals included HGS (Takei instrument), six-meter walking (6MWT) and Chair stand test. Two linear regression models were used to find the relationship between cancer diagnosis and physical function measurement. The first model was adjusted for age and gender, and the second model was adjusted for height, weight, current smoking status and number of chronic diseases and chair stand test. The results showed that physical performance of people who reported cancer in the range of 2 to 4 years ago was not lower than that of people without cancer. The mean of HGS for cancer group was 32.8 kg and for non-cancer was 32.6 kg [8].

1.3.3 The relationship between muscle strength and various factors in cancer patients

A. Chemical therapy

Chemical therapy in cancer patients might impose negative impacts on physical function, decreased muscle mass, and obesity. Here, an overview of these associations is provided.

Due to the rapid growth of cancer cells, chemical drugs have been used for many years to counteract the growth of these cells. Chemical drugs travel throughout the body, and they can affect normal cells and damage healthy cells. Therefore, chemotherapy could be accompanied with side effects. It seems that decreased physical function is related with mortality in cancer patients and chemotherapy-related toxicity [8]. Watters et al measured the effect of chemotherapy for two age groups of women with breast cancer who were considered "young" (less than 65 years) and "older" (> 65 years). To measure physical function, they recorded the highest hand strength of the participants. They concluded that physical function initially decreased, then improved after 6 months of treatment. The decrease in physical function was greater in young women in the age range of 31 to 64 years than in older women in the age range of 65 to 80 years ($P < 0.05$).

It was also observed that changes in physical function of older women was better maintained compared to young women during chemotherapy. However, previous research has shown that 6 months after chemotherapy, physical function could recover [7].

In addition to the effect of chemical therapy on physical function, it might also result on an increase in BMI and obesity, which is a further problem following cancer diagnosis. In people undergoing chemotherapy, decreased muscle mass is common due to metabolic changes in skeletal muscles. In order to clarify these changes, it is important to assess the nutritional status and the body composition of cancer patients. Bioelectrical impedance analysis (BIA), is a common method for estimating body

composition [6]. Frenzel et al assessed 70 women with breast cancer in a cohort of patients undergoing chemotherapy, 77% were initially overweight and 73% had excess of body fat. In this study, body composition was estimated through bioelectrical impedance. The results showed a significant increase in fat-free mass ($p > 0.001$), body mass index ($p = 0.03$) and weight ($p = 0.02$) [6]. However, another study reported a decrease in muscle mass and an increase in fat mass following one year of treatment in women undergoing chemotherapy [28].

B. Biochemical factors and inter-related clinical conditions

Advanced cancer has been associated with a multitude of inter-related clinical conditions like anorexia and anemia and abnormal biochemical factors like high range of pro-inflammatory markers. Surviving from advanced cancers has been associated with many clinical and functional abnormalities. Several studies have shown that hand strength can be considered as a predictor of survival and sarcopenia for subjects with reduced muscle mass and malnutrition. However, it is still unknown whether advanced cancer causes early muscle loss or not.

Kilgour et al measured HGS in 245 patients aged 18 years and older in patients with lung and gastrointestinal cancer as well as cancer survivors. HGS percentiles were categorized into three categories (≥50th, 25th, and ≤10th). Then, they investigated the relationship between three HGS percentiles, the biological markers like hemoglobin, albumin as well as numerous crucial body composition markers (such as sarcopenia) while controlling for age, gender, cancer diagnosis, treatment (chemotherapy/radiotherapy), and medications using multivariate regression analysis. The results of their study showed that the HGS score in more than 70% of patients was below the 50^{th} percentile and in 27% of patients was in the 10^{th} percentile. In addition,

there was a significant decrease in BMI, hemoglobin, and albumin when HGS range was ≥50th or ≤10th percentiles. Furthermore, the prevalence of sarcopenia in the 10th percentile was ten times more than the other percentiles. The important finding of their study was that grip strength measurement can be regarded as a very reliable parameter to predict disease and mortality in advanced cancer patients [3].

A further study examined the biochemical markers in addition to HGS in cancer patients. In these studies, more biochemical factors were tested compared to the previous study by Kilgour et al. Hikaru Ihira et al evaluated whether there were any differences between cancer survivors and healthy people in terms of physical function such as HGS, knee extension power, health outcomes, nutritional status, and blood markers. They compared 37 older adults' community-dwelling cancer survivors aged 75 years and older to 238 older adults without any history of cancer. HGS was measured twice with handheld dynamometer on the dominant hand and the best HGS score was recorded. Self-reported food intake questionnaires were filled out during 1 week to have access to the participants' dietary habits. Blood samples were collected for measuring serum total protein (biuret assay), albumin (BCG assay), total cholesterol (cholesterol oxidase assay), aspartate aminotransferase (enzyme assay), alanine aminotransferase (enzyme assay), c-reactive protein (latex agglutination assay), white blood cells and red blood cells. The results of this study showed that regarding physical activity, females had lower knee extension power compared to males and for blood markers, albumin was at a higher level for female cancer survivors than healthy ones. However, there was no significant difference for men between the two groups. The mean of HGS for cancer survivors was 31.3 kg for men and 19.4 kg for women. In addition, they used three groups to measure the knee power and albumin. These groups were divided to no cancer history, cancer survivors within 5 years, and cancer survivors

who were diagnosed 5 years ago or longer. They considered age and BMI as covariates for knee extension power and albumin. This comparison showed that cancer survivors who were diagnosed within the recent 5 years had more deterioration in knee extension power than those who were diagnosed 5 years ago or longer [13].

C. Sarcopenia and cachexia

There are different challenges that patients face in caring for cancer. For example, late side effects of cancer treatment can cause a lot of problems. Late side effects may not show up for months or years after treatment. In this section, we focused on two other challenges for cancer patients and cancer survivors: sarcopenia and cachexia.

Definition of sarcopenia according to European Working Group on Sarcopenia in Older People (EWGSOP) is low muscle mass plus low grip strength or low gait speed. If the body activity decreases, it causes sarcopenia, followed by a decrease in skeletal muscle contractile proteins, which can make people more vulnerable to accidents, particularly falls. Therefore, it is important to understand the impact of medical treatment on functional performance and muscular capacity in cancer survivors.

Rodriguez et al examined 98 women that survived from breast cancer by using sarcopenia-mediated factor in Colombia. For this purpose, BMI and waist circumference were measured. A linear regression model was used to assess the association between HGS as an independent variable and muscle mass as a dependent variable. In one regression model, they found that HGS and the anthropometric parameters (body mass, BMI and waist circumference) were negatively associated ($p < 0.01$). In the second regression model, HGS was positively associated with muscle

mass ($p = 0.002$). The results of their study finally showed that the prevalence of sarcopenia was one in five for breast cancer survivors. On the other hand, the prevalence of sarcopenia was 46.3% in women having a weak HGS [10]. Muscle dysfunction, sarcopenia and sarcopenia obesity were mentioned to be the consequences of cancer drugs.

On the other hand, cachexia means the waste of muscle tissues associated with severe chronic diseases. Cancer might be a cause of cachexia. Many mortalities of cancer are not due to the local effects of the tumors but rather due to the systemic and extensive changes induced by these tumors. One of the worst symptoms of this condition is wasting syndrome, called cachexia, which is the biggest problem in cancer and side effect of cancer treatment. About 10% of body weight is lost during the disease in 45% of cancer patients [29]. Cong et al considered a total of 4231 patients with cancer, where the most common cancer diagnosis were lung cancer and breast cancer in this study. 351 patients (8.3%) were diagnosed with cachexia who were grouped into pancreatic cancer (32.5%), esophageal cancer (21.5%) and gastric cancer (17.9%). Malnutrition is defined as a deficiency or imbalance in food intake. It has serious adverse consequences, such as decreased muscle mass, impaired immune function, increased risk of complications, decreased response or tolerance to treatment. In fact, they reported that the prevalence of malnutrition in advanced cancer patients was more than 50%. They also compared cancer patients with cachexia to cancer patients without cachexia and the results showed lower BMI (18.90±2.61 kg/m2 vs 23.77±3.38 kg/m2, $p<0.05$), lower HGS (18.84±7.02 kg vs 24.83±9.68 kg, $p<0.05$), lower total protein (61.84±7.85 g/L vs 66.66±7.10 g/L, $p<0.05$), pre albumin (0.19±0.19 g/L vs 0.23±0.23 g/L, $p<0.05$) and albumin (35.15±5.72 g/L vs 39.28±5.16 g/L, $p<0.05$). In addition,

c-reactive protein levels were significantly lower in cancer patients who did not have malnutrition [9].

In addition to the previously mentioned problems in cancer patients, the lack of absorption of nutrients will cause disorders of serum biochemical factors [9]. The prevalence of malnutrition in cancer patients is 40% to 80%, which can lead to decreased muscle mass and impaired immune function, excess morbidity and mortality and finally increased muscle protein breakdown.

1.4 Knowledge of biochemistry markers in cancer/cancer survivors

In recent years, some studies have examined whether blood markers in people with cancer or cancer survivors differ from those with healthy symptoms. Assessing standard biochemical factors and blood markers can give some clues to the doctors about what is happening in the body and help them to diagnose and treat cancer. The focus of this section is on the knowledge of standard biochemistry markers in cancer and cancer survivors, including separate sections such as: alanine aminotransferase, aspartate aminotransferase, total proteins, albumin, blood urea nitrogen, creatine phosphokinase, calcium, sodium and potassium.

Alanine aminotransferase and aspartate aminotransferase: Not only alanine aminotransferase and aspartate aminotransferase are the enzymes found mostly in the cells of the liver and kidney but also much smaller amounts of them can be found in the heart and muscles[30]. In healthy individuals, alanine aminotransferase and aspartate aminotransferase levels in the blood are low but when the liver is damaged, both of them are released into the blood. The amount of these two enzymes may be

calculated to help distinguishing the severity of liver injury and distinguish liver injury from damage to heart or muscles[30]. Kunlin Xie et al investigated the relative elevation of alanine aminotransferase and aspartate aminotransferase for all-cause, liver-related, and non–liver-related mortality. They considered alanine aminotransferase and aspartate aminotransferase defined as ⩾40 IU/L. Participants of this study included 3.4 million people per year who were followed up until December 31, 2008. The multivariate analysis was performed with Cox proportional hazards models controlling for age, sex, education, body mass index, smoking status, drinking status, physical activity, hypertension and diabetes. They were presented for 5 levels of alanine aminotransferase and aspartate aminotransferase with elevated alanine aminotransferase and aspartate aminotransferase defined as ⩾40 IU/L. It was observed that alanine aminotransferase was three times more than alanine aminotransferase. The results also showed that aspartate aminotransferase values above 25 IU/L, had a strong association with all-cause mortality, but for alanine aminotransferase, the relationship was found only above 40 IU/L. In fact, both alanine aminotransferase and aspartate aminotransferase were significant for all-cause, liver disease, non-liver disease, and cancer mortality. The results also demonstrated that aspartate aminotransferase was a better predictor of liver cancer and increased risks for both all-cause and liver-related mortality. In addition, aspartate aminotransferase was a cause of excess mortality from all-causes, as the results are show respectively: all cancer (HR, 3.57), non-liver cancer (HR, 1.45), colon cancer (HR, 1.46), and lung cancer (HR, 1.34) [31].

Protein: Proteins are important components of all cells and tissues. The total protein test measures the total amount of two classes of proteins named albumin and globulin. Albumin makes up about 60% of the total protein and globulin makes up 40% of total protein [32]. The total protein test compares the amount of albumin with globulin. The

amount of total protein varies under different conditions, while an increase in total protein due to inflammatory disorders is due to multiple myeloma, and a decrease in this amount is due to multivitamin, liver or kidney disease[33]. Al-Muhtaseb et al investigated the total protein changes in the serum of 40 women with breast cancer and 40 healthy individuals in the age range of 50-70 years. The results showed that total serum protein in breast cancer patients (7.63±0.41 g/dl) was higher than healthy individuals (6.14±1.84 g / dl) **[34]**. In addition, Kathy Pan et al investigated total protein intake in 100,024 women after 14 years of follow-up. They used Cox proportional hazards regression to estimate the associations between breast cancer incidence, deaths from breast cancer, deaths after breast cancer and total, animal, and vegetable protein intake. The results showed that there were 6340 incidences of breast cancer, 764 deaths from breast cancer, and 2059 deaths after breast cancer. The results of multivariable analyses showed that incidence or deaths from or after breast cancer was not associated with higher calibrated total protein intake. Lower breast cancer incidence and lower risk of death after breast cancer was associated with higher vegetable protein intake. In addition, higher animal protein intake was associated with higher breast cancer incidence [35].

Albumin: Albumin is a protein that is produced in the liver that is carried in blood. A typical reference range for normal albumin levels is 3.5 to 5.5 g/dl. Chronic conditions affecting the liver are associated with decreased albumin levels [36]. Ku¨hn et al evaluated whether albumin level is associated with the risk of the most common cancers. They used a case–cohort sample including a random sub cohort (n=2739) and all incident cases of breast cancer (n=627), prostate cancer (n=554), colorectal cancer (n=256), and lung cancer (n=195) as well as cancer death (n=761) that occurred between baseline (1994–1998) and 2009. Cox proportional hazards regression models

were used to analyze the associations between albumin levels and end points (breast, prostate, colorectal and lung cancer as well as cancer death). The results showed that risks of breast cancer and overall cancer mortality were significantly inversely associated with the albumin levels but the risks of lung, prostate and colorectal cancer had no significant associations with albumin levels. Albumin levels were significantly inversely associated with colorectal cancer mortality [37]. In another study, it was shown that lower serum albumin levels impacted on the decreased survival for gastric cancer patients and also they showed that albumin level were significantly different between gastric cancer patients and healthy ones [38].

Blood urea nitrogen: Blood urea nitrogen is an indication of renal (kidney) health that measures the amount of nitrogen in blood which comes from the waste product urea. Unhealthy kidneys have trouble for removing blood urea nitrogen and leave higher amount of it in blood [39]. The normal range of blood urea nitrogen is between 7 to 20 milligrams per deciliter. one study has shown the influence of cytotoxic drugs used to treat cancer in children. In fact, the main question of this study was to recognize whether childhood cancer survivors could be at risk for kidney function due to long-term effects of medications. The results showed that the use of this kind of cancer treatment drug increases renal disease and kidney injury by increasing serum creatinine and blood urea nitrogen levels [40].

Creatine phosphokinase: Creatine phosphokinase is an enzyme that is found in the heart, brain, and skeletal muscle. When our body's creatine phosphokinase level is very high, it leaks into the bloodstream, indicating that muscle tissue, the heart, or the brain has been injured or stressed, and it also indicates the presence of some types of muscular dystrophies. Normal range of total creatine phosphokinase is 1 to 12

microgram/deciliter (mg/dL) [41]. Guo et al investigated antitumor activity across various solid tumors with the novel MEK-pan-RAF inhibitor during 6 years. This study included 58 patients to assess whether they were resistance to conventional treatment and in histologically or cytologically confirmed advanced or metastatic solid tumors. There were 2 phases in this study: the dose-escalation phase included 29 patients with solid tumors and the second included 29 patients with solid tumors or multiple myeloma (12 non-small-cell lung cancer, five gynecological malignancy, four colorectal cancer, one melanoma, and seven multiple myeloma). They considered 3 oral schedules during 28 days for solid tumors patients in dose-escalation phase: (1) 4.0 mg or 3.2 mg CH5126766 three times per week; (2) 4.0 mg CH5126766 twice per week; and (3) toxicity-guided dose interruption schedule. Finally, they found that the impact of the most common treatment (type 3) were creatinine phosphokinase elevation (six [11%]), hypoalbuminemia (six [11%]), and fatigue (four [7%]) [42]. Suggesting cytotoxic damage to various tissues, including skeletal muscle.

Calcium: Calcium is one of the most important minerals in our body. If our body has symptoms such as bone disease, thyroid disease, or kidney disease, it may be due to a high or low amount of calcium in the blood. If certain types of cancer or malnutrition are present, a calcium test may be required, because these conditions may affect the serum calcium levels[43]. The normal ranges of calcium are between 8.6 to 10.3 mg/dl. Women undergoing breast cancer treatment are at risk of osteoporosis and fractures. This is due to lower estrogen levels in breast cancer patients, which protects the bones. In fact, low estrogen levels are caused by the use of medications or surgery in breast cancer survivors.

One study explained the pattern of medication used by early-stage breast cancer survivors. This pattern consisted of the stage from diagnosis to 1-year post-chemotherapy and, as well, data on the medication use for each patient. This study included 107 patients with mean age of 51.1 but the majority of the patients [83 (77.6 %)] were 45 years old and above. The results showed that the most common chronic medication types used before chemotherapy were calcium channel blockers (12.1 %) and lipid-modifying agents (11.2 %). Both of these group medication types continued firmly during chemotherapy (10.3 and 11.2 %, respectively) and after chemotherapy (11.2 and 13.1 %, respectively). The predominant post-chemotherapy medication (77.6 %) was hormonal therapy. The most important changes in medication of post chemotherapy was related to hormonal therapies and medications for controlling long-term psychosocial effects of cancer. The use of aromatase inhibitors or tamoxifen, for example, might cause side effects such as vaginal dryness, arthralgia, and an increased risk of osteoporosis and fractures. Therefore, all of these types of medication must be managed [44].

Sodium/ Calcium/ Potassium: Kidney-related complications associated with cancer also have consequences on sodium, calcium, potassium and magnesium are part of the electrolytes in our body that are dependent from the foods and drinks we consume. When the body becomes low on electrolytes, some body functions, such as blood clotting, muscle contractions, acid balance, and fluid regulation can be negatively altered. Low levels of electrolytes may lead to irregular heartbeat, confusion, blood pressure changes, nervous system or bone disorders [45, 46]. A normal blood sodium level is between 135 and 145 mill equivalents per liter (mEq/L). Hyponatremia (serum sodium <135 mEq/L) and hypernatremia (serum sodium concentration >145 mEq/L) are the most common electrolyte abnormalities happening in a variety of malignancies

that cause main morbidity and mortality. Development of hyponatremia can have negative impact in cancer survivors, such as developing new comorbidities or toxicity, cardiomyopathy, advanced liver disease, or signal as a biomarker of advanced or unresponsive disease. In addition, confusion, behavioral changes, headaches, irritability, nausea and vomiting, lethargy, drowsiness/coma, seizures, and respiratory arrest are related with both hypo- and hypernatremia [46].

Rosner et al evaluated the kidney disease and electrolyte disorder in different stages of cancer patients that may appear by malignancy or concurrent chemotherapy. Patients with advanced cancer, in particular lung, breast and hematological malignancies are more at risk for hypercalcemia. Complaints of nausea, vomiting, weakness, anorexia, polyuria, constipation, or depression may be related to patients with mild hypercalcemia (corrected serum calcium >12 mg/dl). On the other hand, hypocalcemia (serum calcium <8.5 mg/dl) can happen in 30 % of patients with advanced prostate cancer who have proven bone metastases. Some symptoms of hypocalcemia are muscle cramps, confusion, numbness, and tingling in the lips and fingers. As for potassium, normally, blood potassium level are 3.6 to 5.2 mEq/L. Hypokalemia (serum potassium level < 3.5 mEq/L) is the other common problem in patients who have cancer that are associated with many complications confronted by cancer patients like anorexia, nausea, mucositis, vomiting and chemotherapy borne diarrhea [47].

Thus, the current study presented herein focuses on whether HGS is related to common biological/biochemical factors (e.g., alanine aminotransferase, aspartate aminotransferase, total proteins, albumin, blood urea nitrogen, creatine phosphokinase, calcium, sodium and potassium) and other important characteristics (such as age, sex,

race, BMI, arm circumflexion, physical activity, smoking status, dominant hand) in a cohort of NHANES cancer survivors.

1.5 Problem

Alterations in different biochemistry factors might cause changes in muscle strength in cancer survivors. To our knowledge, no previous study exists to look at the association between biochemical factors as well as individual characteristics and the physical function in cancer survivors. Therefore, the main question of this study was that whether there is any association between standard biochemistry markers and HGS in cancer survivors with exploring the mediating factors? In order to measure the strength of this association, a big set of data extracted from NHANES was used to build multiple regression models. Our overall goal was to create a biochemistry marker that could perhaps predict HGS in cancer patients.

1.6 Specific objectives and hypothesis

- The primary goal was to examine the cross-sectional associations between HGS, as the dependent variable, associated to the following independent variables that were extracted from a national representative sample of cancer survivors accessible in the NHANES database: age, sex, race, BMI, arm circumflexion, physical activity, smoking status, dominant hand and 10 biochemical factors.

- A secondary objective was to establish normative ranges of HGS based on the national representative sample of cancer survivors in the NHANES database (same as above).

Hypothesis:

- We hypothesized that in the whole sample, cancer survivors in the age group of 60-80 years had lower HGS than other cancer free similar age groups.

- The second hypothesis was that among the 10 biochemical factors multiple factors would be associated with HGS in cancer survivors in a cross-sectional analysis of the NHANES database (same as above).

2 CHAPITRE II
METHODOLOGY

2.1 National Health and Nutrition Survey

The National Center for Health Statistics (NCHS) manages the NHANES, a popular survey research program in United States population for people up to 85 years old. In fact, this information is used to determine the prevalence and risk factors of different diseases. Extensive collection of this information can help in developing public health policy, directing and designing health programs, and spreading health knowledge in the United States community. NHANES is involved in evaluating all children and adults' health and nutrition programs by collecting all information in accordance with interviews, physical examinations and laboratory tests. Each year, approximately 7,000 participants are randomly selected originally from 15 counties in the United States population. All personal information is written and recorded confidentially and with voluntary consent. Participants are first interviewed and asked about their health, medical history, and diet. Each participant is interviewed at his home. Then, they are asked to go to the mobile examination center for all health examinations including physician examinations, height, weight and other body measures, laboratory urine tests, blood laboratory tests, etc. Mobile examination center then collects the data on each individual. In fact, such research benefits the participants as well. One of the advantages is that the participants would be aware of all their physical examinations and do not need to go to the doctor's office [48].

This cross-sectional analysis study used a sample from NHANES extracted from 2011–2012 and 2013-2014 available data and aggregated data of HGS, standard biochemistry marker, and other characteristics from cancer survivor patients. In 2011-2012, 13,431 people were selected from which 9,756 completed the interview and 9,338 were examined. In 2013-2014, 14,332 people were selected from which 10,175 completed the interview and 9,813 were examined. The participants were chosen from 30 different study locations for NHANES.

2.2 Inclusion / Exclusion criteria

The sample (n=537) cancer survivors for this study consisted of people from the NHANES 2011-2012 and 2013-2014 data that were aged 25-80 years old from the extracted NHANES data, individuals within the age range of 25-80 years were included. The distribution of cancer survivors was not the same in different age groups. We had the lowest range of cancer survivors in age 25 to 40, a middle range of cancer survivor in age 40-60 and the most number of patients in age 60-80 years old. We decided to do this category in order to take into account the distribution of cancer survivor in different age groups. The exclusion criteria for participants were having arthritis, muscles sore/painful, difficulty to use fork, knife, or drinking from cup, hand surgery, non-melanoma or other unknown skin cancer.

2.3 Questionnaire Data:

In the procedure of data collection by NHANES, participants were asked to provide the following information:

- Age

- Gender
- Race
- Civil status
- Dominant hand
- Level of education:

Education was categorized as less than high school, high school graduate, some college and college graduate. The questions in NHANES specified the education level categories.

In addition, the participants were asked to answer the following questions:

- Cancer:

Have you ever said you have cancer or a malignant tumor? If so, what type of cancer and at what age was it first diagnosed?

- Smoke:

Do you currently smoke cigarettes?

- Physical activity:

Physical activity was measured with a global physical activity questionnaire file from NHANES 2011-2012 and 2013-2014. In fact, physical activity was categorized into moderate physical activity and vigorous physical activity. Moderate physical activity was derived from the question "moderate work activity": those with moderate-intensity activity that make small increases in breathing or heart rate for at least 10 minutes continuously (such as brisk walking or carrying light loads).Vigorous work activity was derived from the question "vigorous work activity": those which involve vigorous-intensity activity that causes large increases in breathing or heart rate for at least 10 minutes continuously (like carrying or lifting heavy loads, digging or construction work).

2.4 Examination Data

- Body Mass Index (BMI):

BMI was calculated from the study population weight in pounds and height in inches.

- Handgrip strength:

Isometric HGS test was performed on participants using the Tanei handgrip dynamometer while in standing position. At first, the grip strength was adjusted to the size of the hands. Each hand was tested three times. The examiner asked the participants to use their dominant hands and squeeze the dynamometer as hard as possible. Between each trial, participants rested for 60 seconds as a recovery section. The posture for HGS test and the model of dynamometer can be observed in Figure 2.1 [4].

Figure 2.1: The position used by NHANES for measuring hand grip strength: elbow fully extended andwrist in neutral position while standing [4].

In this test, not only the combined maximum value of hand grip strength achieved by each hand was calculated, but also the best resistance data from three trials for each hand was extracted and used for further analysis.

2.5 Laboratory Data

Standard Biochemistry markers:

For the standard biochemical marker levels, we included albumin (g/dl), alanine aminotransferase (U/L), aspartate aminotransferase (U/L), blood urea nitrogen (mg/dl), total calcium (mg/dl), creatine phosphokinase (IU/L), phosphorus (mg/dl), total protein (g/dl), sodium (mmol/L) and potassium (mmol/L). Blood test series were performed using complete blood count to measure the biochemical marker which is very effective and useful for assessing the functional capacity of several critical organs and systems. Complete blood count can be used for evaluation of the cells that circulate in the blood and it can help to evaluate general condition of health and discover a variety of diseases such as infections, anemia and leukemia. measurements of standard biochemistry markers. In terms of the laboratory methodology, it should be mentioned that serum specimens were processed, stored under appropriate frozen conditions (–30°C) and shipped to the NHANES laboratory services for further analysis. Different methods have been used in Beckman Unicel DXC 800 system to analyte these 10 biochemistry markers. Here, each analyte is described separately.

2.5.1 Albumin

Albumin is dependent on protein intake. Measurement of albumin are used in the diagnosis and treatment of diseases primarily involving the liver and/or kidneys. The

value of the albumin reference range for adults (>18 years) established in the NHANES 2011-2012 and 2013-2014 laboratory methods was 3.7-4.7 g / dl.

Summary of methodology: DcX800 system monitors the changes in absorbance at 600 nm when albumin combine with bromcresol purple reagent to form a complex. This method measured the albumin concentration as a bichromatic digital endpoint. Here, we see the albumin chemical reaction scheme showed by Beckman coulter, Inc. at chemistry information sheet.

$$Albumin + BCP \rightarrow Albumin - BCP\ complex \qquad (2\text{-}1)$$

2.5.2 Alanine aminotransferase

An alanine aminotransferase test measures the amount of this enzyme in the blood, and alanine aminotransferase test is a blood test that checks for liver damage. Alanine aminotransferase measurements are used in the diagnosis and treatment of certain liver diseases and heart diseases. The elevated levels of alanine aminotransferase can indicate myocardial infarction, hepatic disease, muscular dystrophy, or organ damage. The value of the alanine aminotransferase reference range for adults (>20 years) established in the NHANES 2011-2012 and 2013-2014 laboratory methods was 11- 47 IU/L for males and 7-30 IU/L for females.

Summary of methodology: The DxC800 measures the alanine aminotransferase activity in serum or plasma by a kinetic rate method. In the reversible transamination reactional, the alanine aminotransferase catalyzes the L-alanine and α-ketoglutarate to pyruvate and L-glutamate. The pyruvateis then reduces to lactate in the presence of lactate dehydrogenase with the concurrent oxidation of reduced β-nicotinamide

adenine dinucleotide to β-nicotinamide adenine dinucleotide. The system monitors the changes in absorbance at 340 nanometers. This change in absorbance is directly proportional to the activity of alanine aminotransferase in the sample and is used by the system to calculate and express the alanine aminotransferase activity. Here, we see the alanine aminotransferase chemical reaction scheme showed by beckman coulter, Inc. at chemistry information sheet.

$$L-alanine+\alpha-Ketoglutarate \xleftrightarrow{ALT} Pyruvate+L-glutamate \quad (2\text{-}2)$$

$$Pyruyate+NADH+H^{+} \xleftrightarrow{LDH} Lactate+NAD^{+} \quad (2\text{-}3)$$

Abbreviations: ALT=alanine aminotransferase, NADH=adenine dinucleotide, LDH=lactate dehydrogenase, NAD=adenine dinucleotide.

2.5.3 Aspartate aminotransferase

Aspartate aminotransferase measurements is important for the diagnosis and treatment of certain types of liver and heart disease. The elevated levels of alanine aminotransferase can indicate myocardial infarction, hepatic disease, muscular dystrophy, or organ damage. The value of the aspartate aminotransferase reference range for adults (>20 years) established in the NHANES 2011-2012 and 2013-2014 laboratory methods was 13-33 IU/L.

Summary of methodology: The DxC800 measures the aspartate aminotransferase activity in serum or plasma by an enzymatic rate. In the reversible transamination reactional, the aspartate aminotransferase catalyzes the L-aspartate and α-ketoglutarate to poxaloacetate and L-glutamate. The oxaloacetate is then reduced to malate in the presence of malate dehydrogenase with the concurrent oxidation of β-bicotinamide adenine dinucleotide (reduced form) to β-nicotinamide adenine dinucleotide. The system monitors the changes in absorbance at 340 nanometers. This rate of change in

absorbance is directly proportional to the activity of aspartate aminotransferase in the sample and is used by the SYNCHRON system(s) to calculate and express the aspartate aminotransferase activity. Here, we see the aspartate aminotransferase chemical reaction scheme showed by beckman coulter, Inc. at chemistry information sheet.

$$L-Aspartate+\ \alpha-ketoglutarate \overset{AST}{\longleftrightarrow} Oxaloacetate + L-glutamate \quad (2\text{-}4)$$

$$Oxaloacetate\ +\ NADH\ +\ H^{+} \overset{MDH}{\longleftrightarrow} Malate + NAD^{+} \quad (2\text{-}5)$$

Abbreviations: AST=aspartate aminotransferase, NADH=adenine dinucleotide, MDH=malate dehydrogenase, NAD=adenine dinucleotide.

2.5.4 Blood urea nitrogen

A blood urea nitrogen serum test measures the amount of urea in a blood sample. This type of test is requested in combination with the serum creatinine test to diagnose prerenal, renal, and post renal uremia. Kidney dysfunction, increased protein catabolism, nephritis, intestinal obstruction, urinary obstruction, metallic poisoning, cardiac failure, peritonitis, dehydration, malignancy, pneumonia, surgical shock, addison's disease, and uremia can all be associated with high blood urea nitrogen levels. The value of the blood urea nitrogen reference range for adults (>15 years) established in the NHANES 2011-2012 and 2013-2014 laboratory methods was 6-23 mg/dl.

Summary of methodology: The DxC800 modular chemistry by means of the enzymatic conductivity rate method are used to determine the concentration of blood urea nitrogen in serum or plasma. At first, urea is hydrolyzed by urease to ammonia and carbon dioxide, and then concentration of urea in the sample is determined by electronic circuits. Here, we see the blood urea nitrogen chemical reaction scheme showed by beckman coulter, Inc. at chemistry information sheet.

$$Urea + H_2O \xleftarrow{Urease} 2NH_3 + CO_2 \quad (2\text{-}6)$$

$$NH_3 + \alpha - Ketaglutarate + NADH + H^+ \xrightarrow{GLDH} Glutamate + NAD^+ + H_2O \quad (2\text{-}7)$$

Abbreviations: GLDH = glutamate dehydrogenase, NADH=adenine dinucleotide, NAD=adenine dinucleotide.

glutamate dehydrogenase catalyzes the condensation of ammonia and α-ketoglutarate to glutamate with the concomitant oxidation of reduced β-nicotinamide adenine dinucleotide to β-nicotinamide adenine dinucleotide.

2.5.5 Total calcium

Calcium measurement is important for diagnosis and treatment of some diseases like parathyroid disease, bone diseases, chronic renal disease and tetany. The value of the total calcium reference range for adults (>12 years) established in the NHANES 2011-2012 and 2013-2014 laboratory methods was 8.5-10.5 mg/dl.

Summary of methodology: The DxC800 system uses ion selective electrode methodology to measure calcium concentration in serum or plasma by indirect potentiometry utilizing a calcium ion selective electrode in conjunction with a sodium reference electrode. Calcium concentration is determined by calcium ion in solution. The activity of calcium ions in solution is measured when the sample buffer mixture with the electrode contacts the ionophore at the electrode surface. These changes in potential are referenced to the sodium reference electrode. The "referenced potential" is used in calculating the analyte concentrations based on the Nernst equation, which

allows the calculation of calcium concentration: Here we see the total calcium chemical reaction scheme showed by beckman coulter, Inc. at chemistry information sheet.

$$E = Constant + (sslope)(\log[Ca^{2+}]) \qquad (2\text{-}8)$$

2.5.6 Creatine Phosphokinase

Level of the enzyme creatine phosphokinase is important for heart tissue and skeletal muscles and brain. The level of this enzyme is checked by creatine phosphokinase test. Measurements of creatine kinase are useful for recognition and treatment of many diseases like myocardial infarction, skeletal muscle diseases, and diseases of the central nervous system. The value of creatine Phosphokinase reference range for adults (>15 years) established in the NHANES 2011-2012 and 2013-2014 laboratory methods was 22-334 IU/L for males and 22-199 IU/L for females.

Summary of methodology: The DxC800 measures the creatine phosphokinase activity in serum or plasma by an enzymatic rate method. In this reaction, creatine phosphate is converted by creatine phosphokinase to adenosine diphosphate. Hexokinase catalyzes adenosine triphosphate which results in the production of ß Nicotinamide Adenine Dinucleotide (reduced form) from ß Nicotinamide Adenine Dinucleotide. The activity of creatine phosphokinase is measured by system which monitors the rate of changes in absorbance at 340 nm over a fixed time interval. Here, we see the creatine phosphokinase chemical reaction scheme showed by beckman coulter, Inc. at chemistry information sheet.

$$Creatine\ phosphate + ADP \xrightarrow{CK} Creatine + ATP \qquad (2\text{-}9)$$

$$ATP + glucose \xrightarrow{HK} Creatine + ADP \quad (2\text{-}10)$$

$$Glucose - 6 - phosphate + NADP^{+} \xrightarrow{G6PDH} 6 - Phosphogluconate + NADPH^{+} + H^{+} \quad (2\text{-}11)$$

Abbreviations: ADP= adenosine triphosphate, ATP= adenosine triphosphate, HK=hexokinase NADH=adenine dinucleotide, NAD=adenine dinucleotide.

2.5.7 Phosphorus

Phosphorus is a mineral found in our bones along with calcium and is needed to build strong healthy bones. Measurements of phosphorus are used in the diagnosis and treatment of various disorders like: parathyroid gland and kidney diseases, and vitamin D imbalance. The value of Phosphorus reference range for adults (>15 Y) established in the NHANES 2011-2012 and 2013-2014 laboratory methods was 2.6-4.4 mg/dl.

Summary of methodology: The DxC800 system determine the concentration of phosphorus in serum or plasma. A colored phosphomolybdate complex are make in reaction of inorganic phosphorus with ammonium molybdate in an acidic solution. The DxC800 system monitors the change by use a timed-rate method in absorbance at 365 nm. This change in absorbance is directly proportional to the concentration of phosphorus in the sample. Here we see the phosphorus chemical reaction scheme showed by beckman coulter, Inc. at chemistry information sheet.

$$Phosphorus + Molybdate \xrightarrow{H_2SO_4} Phosphomolybdate\ Complex \quad (2\text{-}12)$$

2.5.8 Total protein

Total protein measurement is important for the diagnosis and treatment of a variety of diseases related to the liver, kidney or bone marrow, and other metabolic or nutritional disorders. The value of total protein reference range for adults (>19 Y) established in the NHANES 2011-2012 and 2013-2014 laboratory methods was 6.4-7.7 g/dL.

Summary of methodology: The DxC800 measures the concentration of total protein in serum or plasma using a timed rate biuret method. Total protein reagent is used timed-endpoint biuret method to measure the total protein concentration. In the reaction, the peptide bonds in the protein sample bind to cupric ions in an alkaline medium to form colored peptide/copper complexes. The system monitors the change in absorbance at 545 nanometers. The observed rate of chelate formation is directly proportional to the total protein concentration in the sample and is used by the system to calculate and express the total protein concentration. Here, we see the total protein chemical reaction scheme showed by beckman coulter, Inc. at chemistry information sheet.

$$Protein + Cu^{++} \xrightarrow{Alakali} Protein - copper\ complex \quad (2\text{-}13)$$

Abbreviations: CU= cupric ions

2.5.9 Sodium

Sodium is measured to diagnose and treatment of electrolyte imbalance conditions. The value of the Sodium reference range for adults (>10 Y) established in the NHANES 2011-2012 and 2013-2014 laboratory methods was 136-144 mEq/L.

Summary of methodology: The DxC800 system uses ion selective electrode methodology to measure sodium concentration in serum or plasma by indirect potentiometry utilizing a sodium ion concentration by measuring electrolyte activity in solution. The sample contacts the electrode and sodium ions undergo an ion exchange in the hydrated outer layer of the glass electrode. Change in electrode potential occur as sodium ion exchange takes place. The potential follows the Nernst equation and allows the calculation of sodium concentration in a solution. Here, we see the Sodium chemical reaction scheme (nernst equation) showed by beckman coulter, Inc. at chemistry information sheet.

$$E = constant + (slope)(\log[NA^+]) \quad (2\text{-}14)$$

Abbreviations: NA= sodium

2.5.10 Potassium

Potassium measurements are necessary for treatment and diagnosis of hypokalemia, hyperkalemia, renal failure and addison's disease or other diseases involving electrolyte imbalance. The value of the potassium reference range for adults (>10 Y) established in the NHANES 2011-2012 and 2013-2014 laboratory methods was 3.5-5.0 mEq/L.

Summary of methodology: The DxC800 system uses ion selective electrode methodology to measure potassium concentration in serum or plasma by indirect potentiometry utilizing a potassium ion concentration by measuring electrolyte activity in solution. The potassium electrode consists of valinomycin membrane. change in electrode potential occur as potassium ions react with valinomycin. These changes in potential are referenced to the sodium reference electrode. The "referenced potential" is used in calculating the analyte concentrations based on the nernst equation and allows the calculation of potassium concentration. Here, we see the potassium chemical reaction scheme (nernst equation) showed by beckman coulter, Inc. at chemistry information sheet.

$$E = constant + (slope)(\log[K^+]) \quad (2\text{-}15)$$

Abbreviations: K= potassium

2.6 Data Analysis

Previous studies have shown that people with the disease have lower grip strength than their healthy peers. One of the objectives of this test was to study the relationship

between HGS as independent variable and 10 standard biochemistry marker and other various factors in cancer survivors such as age, sex, race, BMI, arm circumflexion, physical activity, smoking status, dominant hand as dependent variables. All analyses were performed in R version 3.6.3.

Several steps were performed to do the data analysis in this study, as followed:

Extracting descriptive tables: all the data from NHANES existed as SAS files, which could be directly imported into R. First table was plotted to summarize the data about sex, age, race, educational background, marital status, BMI, smoking status, physical activity, dominant hand (right or left), combined HGS only for cancer survivors people. In addition, another table of ten biochemical marker variables associated with cancer survivors were descriptive and in a separate table. In both tables the mean (standard deviation (SD)), median, minimum/maximum and the numbers of participants were calculated and shown.

After summarizing the available data, we examined whether the variables have normal distribution or not. we evaluated the distribution only for numeric variables. It is important to check the distribution of data before further statistical analysis because it helps to reach representative results. In fact, the bell-shaped curve distribution (normal distribution) is important in simplifying the model and reaching higher accuracy for our predictions.

Combined HGS of participants is an important parameter, and was considered as the dependent variable in this study. The combined grip strength among participants was divided into five groups (quantiles), from Q1 to Q5, where Q1 corresponds to participants with the lowest range of HGS and Q5 to participants with the highest range

of grip strength. The classification of participants based on the quantiles of HGS were then plotted for different age groups, and right or left handed in cancer survivors. Based on these plots, we could easily observe the exact number of people in each quantile (kg). The library (ggpubr) in R was used for this purpose. This library is used for visualization, meaning that it makes it easier to better see the distribution of variables by creating images, graphs, and diagrams.

Since we intended to perform regression analysis, each of the variables that did not have normal distribution had to be normalized. This was performed to achieve a better linear relationship between the variables. Briefly, we transformed numeric variables to normal distribution by computing the skewness of variables. We used skewness to evaluate and measure symmetry for a distribution. Whether a variable has a positively skewed (or skewed right) distribution or a negatively skewed (or left-handed) distribution, this means that the central tendency measures (mean, median, mode) are not equal. This positive or negative or zero value of skewness is given by the sign of the skewness coefficient. If skewness is between -0.5 and 0.5, the distribution is approximately symmetric, and that the mean is approximately equal to the median. If skewness is between -1 and -0.5 or between 0.5 and 1, the distribution is moderately skewed, so we did square-root (sqrt(x)) as transformation method to transform the variable to normal distribution. If the value of skewness is less than -1 or greater than 1, the distribution is highly skewed, and we did log10() function. In addition, for severe skewness with values much lower than -1 or much higher than +1, inverse approach was used to normalize the distribution. We used library "moments" in R for computing the skewness of each variable (Table 2.1).

Table 2.1: Transformation methods for different ranges of skewness.

Amount of skewness	value of skewness	Transformation Methods
< -0.5 and > 0.5	symmetric distributions	
< -0.5 or > -1 < 0.5 and > 1	moderate skewness	sqrt(x) for positively skewed data, sqrt(max(x+1) - x) for negatively skewed data
< -1 and > 1	high skewness	log10(x) for positively skewed data, log10(max(x+1) - x) for negatively skewed data
much lower than -1 or much higher than +1	severe skewness	1/x for positively skewed data 1/(max(x+1) - x) for negatively skewed data

After generating normally distributed variables, we performed correlation analysis. Pearson r correlations (Pearson's r) is a measure of linear correlation between covariance of two variables, divided by the product of their standard deviations. Correlation analysis is statistically used to see how two variables are related to each other and can vary between -1 and 1. When it is closer to +1, it means that two variables are highly and positively correlated, when it is closer to -1, it means that two variables are highly but inversely correlated, and when it is closer to zero, it means that they are less correlated to each other. The purpose of using this function in this study was to find the correlation between combined HGS as dependent variable and all other variables as independent variables. We produced scatterplot matrices in R, which makes it easy to quickly visualize the correlations that may exist between combined HGS and all physical characteristics and standard biochemistry marker variables. Correlation function was used to produce scatterplot matrix, with histograms of distribution of each parameter, kernel density overlays, correlation coefficients

(pearson r values), and significance level (P value). In addition, we calculated P-values in a separate table that could help us to know whether the correlation between each independent variable and dependent variable are significant or not. A higher |r| value means that there is a stronger relationship between the variables, while $p<0.05$ shows the statistically significant correlations.

Two regression models were performed on our data. We weighted our data for two regression models separately. Initially, we used the R library (olsrr) to build a backward regression model using Akaike Information Criterion (AIC) for data with undefined values Not Applicable (NAs). Secondly, the R Mice package was used to impute the data and fill the undefined values, followed by building the backward regression model using AIC on the imputed data. The purpose of both models was to find out which clinical markers and other factors such as age, sex, race, BMI, arm circumflexion, physical activity, smoking status, dominant hand was associated with combined HGS in surviving cancer.

In backward regression models, predictors were selected using AIC values. Through a stepwise approach, this model eliminates the variables (the predictors) associated with the smallest, non-significant reduction in R-square. It then proceeds to remove variables that did not significantly contribute to the model. There are two general approaches available in the 'olsrr' package. In the first one, predictors are selected using p-values. However, we performed the "ols_step_backward_aic" function, in which the AIC values were used as a criterion to keep or remove the potential predictors. The final output gives us the variables that can be removed from the final model. In fact, those variables that would result in a reduction in AIC relative to the full model are candidates for exclusion. The backward model for this study was shown as a plot

to easily find out which parameters were removed first, and which parameters would increase the AIC by removing them, respectively.

As missing data will reduce the statistical power, we used mice package to fill the gaps in available data (delete missing data). In fact, creating multiple models and comparing them to an average unit takes care of the missing values. We created 5 numbers of imputed datasets, in each of which the missing values were replaced with the imputed values. Finally, the second model of mice package was used to build the backward regression model. As the last step of results, the results from two regression models were compared: the one with NAs and the one with imputed data.

The R plot_Summs was used to quickly convey the results of correlation coefficients. Coefficients of correlations is the degree of relationship between HGS as dependent variable and 18 various factors (10 biochemistry marker and 8 other various factors) as independent variables. In plot_summs, adding a new predictor causes another one's estimate of r to get much closer to zero.

3 CHAPITRE III
RESULT

3.1 Population

After inserting all available SAS files in R, 537 cancer survivors were included in our study. After extracting the data, we had 11,539 participants in the NHANES for the 2011-2012 and 2013-2014 cycles (492 variables). At first, 3,015 participants were excluded, as they had arthritis (N= 1229), muscle pain (N=1435), difficulty for using fork and spoon (N=191), hand surgery (N=69), and non-melanoma or other unknown skin cancer (N=91). Then, people aged 25-80 were selected for this study. (N=7,288). Finally, we excluded participants who did not provide information about cancer and who did not survive from cancer. The final sample size included in this study was 537 cancer survivors (Figure 3.1).

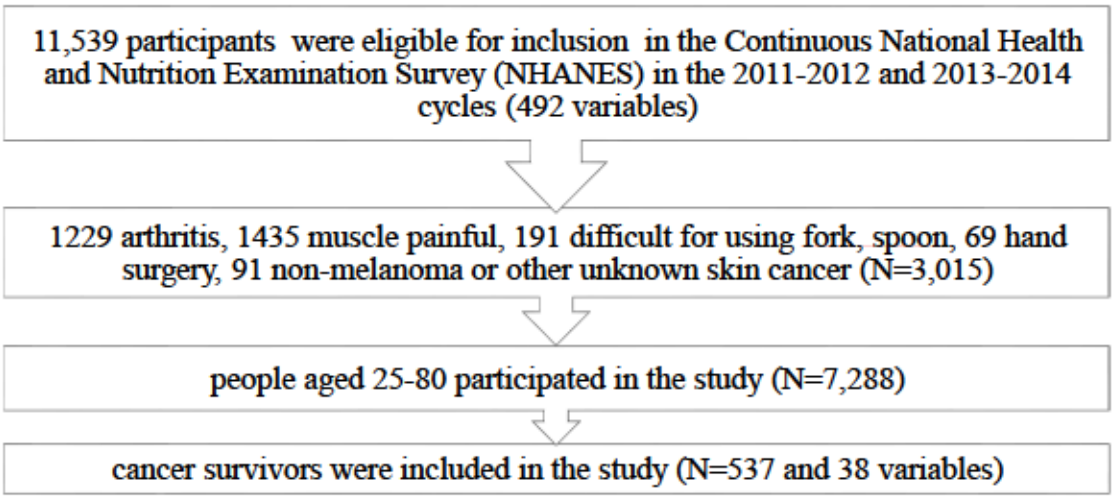


Figure 3.1: Flowchart of selecting participants

The demographics characteristics of the respondents in this study can be observed in Table 3-1. The majority of cancer survivors were between the ages 60-80 years old (N=356). The number and type of cancer in cancer survivor participants were: prostate 106, breast cancer 96, melanoma 66, colon 47, cervix 41, lung 25, uterus 18, ovary 17, kidney 16, bladder 2, brain / larynx / esophagus 7, and others 104. The mean age of the participants was 64.3 years old (SD =13.7). 52.1% of the participants were women and 47.9% of the participants were men. The average for the combined grip strength of the participants was 62.5 kg and median [minimum, maximum] were 60.3 [20.3, 122] kg, respectively.

Table 3.1: The characteristics of cancer survivor participants included in our analyses.

Cancer Survivor (N=537)	
Sex % (N)	
Female	280 (52.1 %)
Male	257 (47.9 %)
Age	
Mean (SD)	64.3(13.7)
Median [min, max]	67.0 [25.0 , 80.0]
Race (N)	
Black	121 (22.5 %)
Other	130 (24.2 %)
White	286 (53.3 %)
Education % (N)	
Less than high school diploma	61 (11.4 %)
College/university/bachelor's degree	119 (22.2 %)
Other	357 (66.5 %)
Marital statuts % (N)	
Alone	89 (16.6 %)
Couple	301 (56.1 %)
Other	147 (27.4 %)
Body mass index (kg/m^2) (SD)	
Mean (SD)	28.6 (6.60)
Median [Min, Max]	27.5 [14.3, 55.8]
Current daily smoker % (N)	
No	461 (85.8 %)
Yes	76 (14.2 %)
Physical activity	
Activity	15 (2.8 %)
No activity	522 (97.2 %)
Dominant hand % (N)	
Equal	16 (3.0 %)
Left hand	32 (6.0 %)
Right hand	489 (91.1 %)

Abbreviations: N: number, SD: standard deviation

3.2 Standard biochemical levels

We investigated standard biochemistry marker levels as defined by NHANES measures. The mean (SD), median [minimum, maximum] of all standard biochemistry marker variables for people with self-reported diagnosed cancer are shown in Table 3.2.

Table 3.2: Summary of the mean (SD), median [minimum, maximum] of all standard biochemistry marker variables for cancer survivors.

Cancer Survivor (N=537)		Cancer Survivor (N=537)	
Albumin		**Creatine Phosphokinase**	
Mean (SD)	4.19 (0.344)	Mean (SD)	125 (103)
Median [min, max]	4.20 [2.80, 5.20]	Median [min, max]	96.0 [18.0, 862]
Alanine aminotransferase		**Phosphorus**	
Mean (SD)	23.3 (18.2)	Mean (SD)	3.75 (0.643)
Median [min, max]	19.0 [7.00,247]	Median [min, max]	3.70 [1.60, 7.20]
Aspartate aminotransferase		**Total protein**	
Mean (SD)	25.5 (14.0)	Mean (SD)	7.01 (0.523)
Median [min, max]	22.0 [10.0, 199]	Median [min, max]	7.00 [5.30, 8.80]
Blood urea nitrogen		**Sodium**	
Mean (SD)	15.6 (3.7)	Mean (SD)	140 (2.46)
Median [min, max]	14.0 [3.00, 95.0]	Median [min, max]	140 [129, 145]
Total calcium		**Potassium**	
Mean (SD)	9.42 (0.398)	Mean (SD)	4.04 (0.391)
Median [min, max]	9.40 [6.50, 11.2]	Median [min, max]	4.00 [3.00, 5.40]

Abbreviations: N: number, SD: standard deviation

3.3 Quantiles based on handgrip strength

The participants in age groups of (25-40), (40-60) and (60-80) were classified, as shown in Table 3.3, into quantiles based on their HGS, while the maximum HGS in the last quantile was 122.3 kg. It was observed that the highest number of people aged 60-80 were in the first quantile: (N=80) out of (N=356). In addition, the highest number of people aged 40-60 were in the second quantile, (N=30) out of (N=143). Looking at the same table (Table 3.3), it was observed that 22% of people aged 60 to 80 showed HGS with the amount of 20 kg compared to the maximum of 122 kg of grip strength, while in the age range of 40 to 60, 21% of people showed a strength of 47kg. In addition, the highest percentage of people in the age range of 25 to 40 years were in the third quantile (36.8%) (Table 3.3).

Table 3.3: Five five quantiles (kg) according to age group of cancer survivors

Quantile HGS [kg]	25-40 (N=38)	40-60 (N=143)	60-80 (N=356)
Q_1 20(0%)	1 (2.6%)	13 (9.1%)	80 (22.5%)
Q_2 47.7 (25%)	8 (21.1%)	30 (21.0%)	56 (15.7%)
Q_3 60.2(50%)	14 (36.8%)	28 (19.6%)	52 (14.6%)
Q_4 75.3(75%)	3 (7.9%)	28 (19.6%)	63 (17.7%)
Q_5 122.3(100%)	10 (26.3%)	27 (18.9%)	57 (16.0%)

Abbreviations: HGS: hand grip strength, N: number

In terms of dominant hand, the highest percentage of right-handed individuals belonged to the third quantile with 60 kg of HGS (18.5%), but the highest percentage of left-handed individuals (25%) were observed in the fourth quantile with HGS of 75 kg (Table 3.4).

Table 3.4: Five quantiles of hand grip strength (kg) according to the dominant hand of cancer survivors

Quantile HGS [kg]	Equal (N=16)	Left handed (N=32)	Right handed (N=489)
Q_1 20(0%)	2 (12.5%)	7 (21.9%)	85 (17.4%)
Q_2 47.7 (25%)	4 (25.0%)	7 (21.9%)	83 (17.0%)
Q_3 60.2(50%)	0 (0%)	4 (12.5%)	90 (18.4%)
Q_4 75.3(75%)	4 (25.0%)	8 (25.0%)	82 (16.8%)
Q_5 122.3(100%)	6 (37.5%)	5 (15.6%)	83 (17.0%)

Abbreviations: HGS: hand grip strength, N: number

In addition, the HGS values for the entire sample classified by gender and age for cancer survivors is presented in Table 3-5. The average HGS was 68.2 kg at age 25 to 40, 66 kg at age 40 to 60 and 60.4 kg at age range of 60 to 80.

Table 3.5 : Handgrip strength according to age of cancer Survivors

Handgrip strength (kg)/Age	25-40	40-60	60-80
Mean	68.2 kg	66.0 kg	60.4 kg
[Min-Max]	[43.8,122]	[22.7,119]	[20.3,108]

As well, the overall average HGS of right hand grip strength was 79.2 kg compared to 76 kg for the left hand. On the other hand, women showed an equal average of 49.8 kg for both right and left hand grip strength.

Table 3.6 :Handgrip strength according to gender/dominant hand

HGS/Sex*Dominant hand	**Female**		**Male**	
	Left hand	Right hand	Left hand	Right hand

Mean HGS(kg)	49.8kg	49.8kg	79.2kg	76.0 kg
Standard Deviation	(8.09)	(12.7)	(14.4)	(17.6)

3.4 Summary of primary and final skewness

To examine whether the data have normal distribution, the skewness of numerical data was evaluated, as explained above in the Data analysis section. The data were then modified according to the value of skewness. For example, total protein had a skewness of -0.05, which means that the mean value is approximately equal to the median. In such cases the values of the variable were not changed. On the other hand, the inverse method was used for two variables with severe skewness. The initial skewness of alanine aminotransferase and aspartate aminotransferase were 7.5 and 6.8, respectively. After application of the inverse method, the final skewness of alanine aminotransferase and aspartate aminotransferase were 0.6 and 0.006, respectively. In addition, the square-root method was used for combined hand grip strength with moderate skewness=0.4, which reduced the skewness to - 0.02. The summary of skewness function for other variables is shown in Table 3.7.

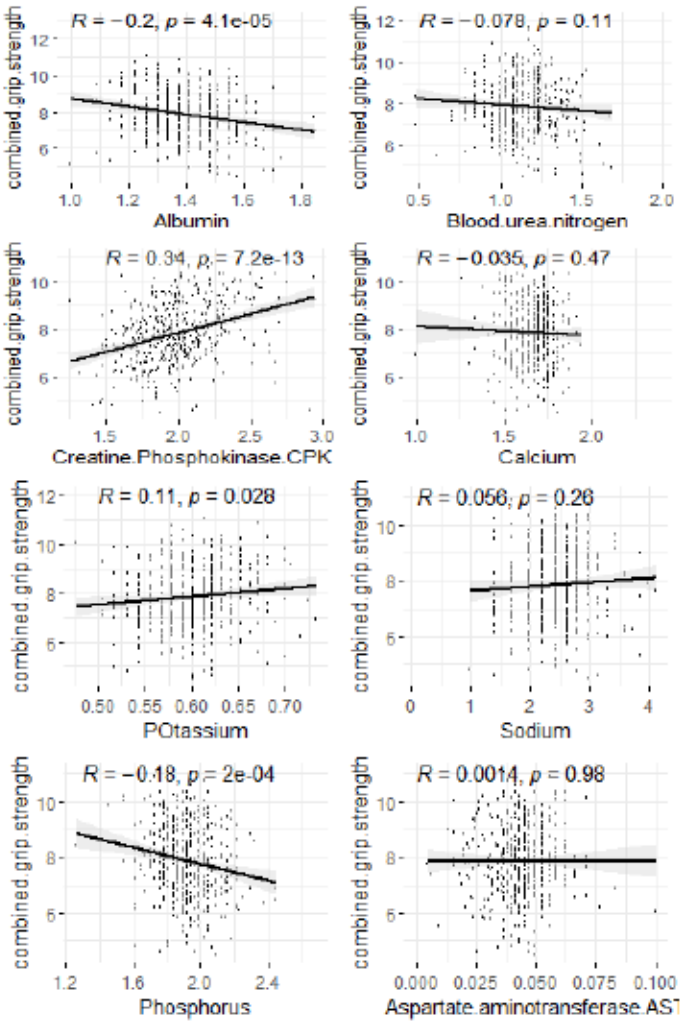
Table 3.7: A summary of primary and final skewness of different variables

Transformation methods: log10(x) for high skewness			Transformation methods: Sqrt(x) for moderate skewness		
Variables	Before	After	Variables	Before	After
BMI	0.9	0.2	Albumin	-0.3	-0.002
BUN	3.3	0.2	Calcium	-0.4	-0.2
CP	3	0.4	Sodium	-0.7	0.05
Potassium	0.4	0.09	Phosphorus	0.7	0.3

Abbreviations: BUN= Blood urea nitrogen, CP= Certain phosphokinase

3.5 Correlation analysis

After transforming the numerical variables to normal distribution, Pearson r correlation was estimated between HGS as dependent variable and other independent variables. In order to better visualize the correlation between variables, a scatter plot consisting of the correlation coefficients and *p* values between HGS and each of standard biochemical characteristics was plotted. It was observed that correlation between weight, creatine phosphokinase and HGS was $r = 0.3$ ($p < 0.001$) and the correlation between albumin and HGS was $r = 0.2$ ($p < 0.001$), which were the highest correlation values compared to other independent variables (Figure 3.2). In addition, the relationship between HGS and other independent variables changed in this order: phosphorus, alanine aminotransferase ($r = -0.1$, $p<0.001$), The amount of p values showed that among all biochemistry markers, the relationship between HGS and creatine phosphokinase, albumin, phosphatase and alanine aminotransferase was significant. Other variables such as BMI, blood urea nitrogen, total calcium, sodium and aspartate aminotransferase had non-significant correlations with HGS.


R = −0.2, p = 4.1e-05
combined.grip.strength
Albumin
R = −0.078, p = 0.11
Blood.urea.nitrogen
R = 0.34, p = 7.2e-13
Creatine.Phosphokinase.CPK
R = −0.035, p = 0.47
Calcium
R = 0.11, p = 0.028
POtassium
R = 0.056, p = 0.26
Sodium
R = −0.18, p = 2e-04
Phosphorus
R = 0.0014, p = 0.98
Aspartate.aminotransferase.AST

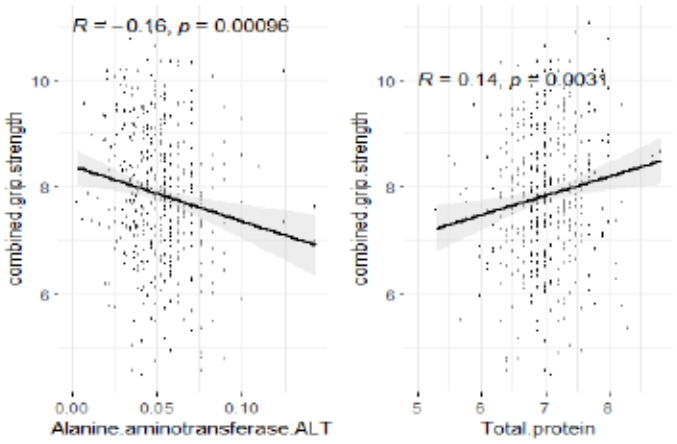


Figure 3.2: Scatterplot containing the correlation coefficients and p-values between each biochemistry marker and hand grip strength

3.6 Multivariate backward regression model

Eighteen different factors were included as independent variables for multiple regression analysis, namely age, sex, race, BMI, arm circumflexion, self-reported physical activity level, smoking status, dominant hand and 10 biochemical factors. On the other hand, HGS was regarded as dependent variable. The output of the multivariate backward regression model using AIC value for weighted data with NAs, gave us the variables that could be removed from the full model. In fact, removal of these variables leads to significant decrease in AIC compared to the whole model. These removed variables were sodium, albumin, total protein, physical activity, phosphorus and calcium. Finally, the final model showed an adjusted R^2 of 0.66 and an AIC of 987.78. The backward elimination procedure began with the elimination of the factor "sodium" associated with the smallest, non-significant reduction in R^2 and having an adjusted R^2 of 0.66. Fitting the model with the remaining 17 factors resulted in an increase in the AIC value to 894.03 with little effect on the high adjusted R^2 value, as indicated in Table 3.8. In Step 2, the albumin was eliminated with an adjusted R^2 value of 0.66

thereby further increasing the AIC value to 892.08. Another factor as independent variable like total protein having AIC value 890.19 was eliminated from the model in Step 3 without any negative impact on the R^2 value. In this manner, the other insignificant terms included physical activity, phosphorus and calcium were eliminated in steps 4 through 6, respectively, while sequentially increasing the AIC value to 887.80 with no effect on the adjusted R^2.

Table 3.8: The statistical analysis of each of the six steps used in multivariate backward regression model using AIC value for weighted data with NAs

Backward Elimination Summary

Variable	AIC	RSS	Sum Sq	R-Sq	Adj. R-Sq
Full Model	987.788	196.536	417.478	0.67992	0.66307
Sodium	894.039	196.541	417.474	0.67991	0.66395
Albumin	892.084	196.563	417.451	0.67987	0.66479
Total protein	890.195	196.617	417.397	0.67978	0.66557
Activity	888.426	196.730	417.284	0.67960	0.66625
Phosphorus	887.896	197.453	416.561	0.67842	0.66589
Calcium	887.809	198.397	415.617	0.67688	0.66517

The AIC plots (

Figure 3.3) show that the drop in AIC from the full model to the model without sodium was the most substantial. Therefore, sodium was the first parameter to be deleted from the full model. The next largest drop in AIC occurred by deleting albumin, total protein, physical activity, phosphorus and calcium, respectively.

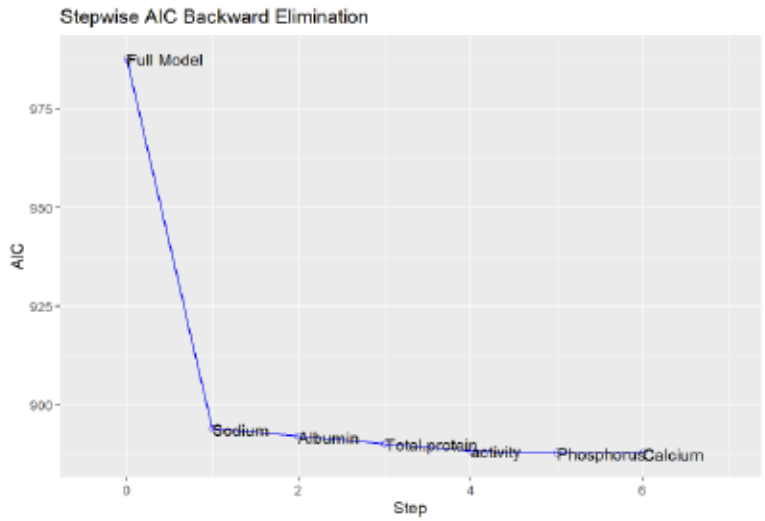


Figure 3.3: AIC plots in backward elimination for weighted data with NAs

The results of multiple backward regression for weighted data without NAs (imputed data) with the Mice package gave different results including four factors with an adjusted R^2 value of 0.63 and AIC of 1413.8. These factors included: sodium, albumin, physical activity, total protein (Table 3-9).

Table 3.9: The statistical analysis of the each of the four steps used in multivariate backward regression model using AIC value for weighted data without NAs

Backward Elimination Summary

Variable	AIC	RSS	Sum Sq	R-Sq	Adj. R-Sq
Full Model	1413.819	305.993	568.685	0.65016	0.63661
Sodium	1263.931	306.004	568.674	0.65015	0.63730
Albumin	1262.082	306.090	568.588	0.65005	0.63789
Activity	1260.252	306.187	568.491	0.64994	0.63848
Total protein	1259.037	306.635	568.043	0.64943	0.63864

4 DISCUSSION

To our knowledge, this is the first study to find the relationship between HGS and an extensive number of standard biochemical factors (10 factors) as well as several demographic parameters in cancer survivors. A cross-sectional analysis of NHANES data was performed to reach this objective.

In the present study, by categorizing patients into HGS percentiles, we determined the normative range of HGS in cancer survivors (for both male and female and dominant/ non-dominant hands) from two data release cycles in US population for individuals aged 25-80 years. We found that HGS showed variations across different age groups. The norm of grip strength for different age groups found in this study was different from the findings of Ying-Chih Wang et al [4], who compared grip strength data for all available participants, from 2011-2012 and 2013-2014 NHANES data. The first reason for this difference was that the effects of surgery, chemotherapy, and radiotherapy might worsen the physical function in older cancer survivors, consequently leading to lower grip strength in their study. Another reason is that 10% of body weight is lost during the cancer process in 45% of cancer patients [26], which might be a further source of variation in the ranges of HGS in their study compared to previous research. In addition, while previous research showed that the physical function would recover 6 months after chemotherapy, [8], we could not prove this point in our study.

Our study found that HGS was associated with demographic independent variables like sex, age, race, BMI, arm circumference, smoking status and dominant hand. Most of our samples (66.2%) were in the ages of 60-80 years. Most cancer survivors in the 60-80 years group were in the first quantile of HGS. Thus, our hypothesis was confirmed,

in which cancer survivors in the age group of 60-80 years had lower HGS than other age groups. The result of our study is in agreement with other studies that have shown the effect of sarcopenia and cachexia on reducing the amount of HGS [9, 10].
In terms of biochemical factors, the results of our study confirmed our hypothesis, while 50% of the biochemistry markers considered in this study were associated with HGS in cancer survivors in this particular population. The contributing biochemistry factors are presented in the following section.

Statistical analysis approach:

In the multivariate backward regression model using AIC values with missing data, we identified the following biochemical factors that were significantly associated with HGS: blood urea nitrogen, creatine phosphokinase, potassium, aspartate aminotransferase and alanine aminotransferase and also the other factors like: gender, age, BMI, arm circumference, smoking status and dominant hand ($R^2 = 0.66$). On the other hand, in the multiple backward regression for weighted data without NAs (imputed data) using the mice package, the following variables were associated with HGS: blood urea nitrogen, creatine phosphokinase, calcium, potassium, phosphorus, aspartate aminotransferase and alanine aminotransferase, gender, age, BMI, arm circumference, smoking status and dominant hand ($R^2 = 0.64$). The advantage of using backward regression in our study was that it helped us to know which parameters were more important in predicting HGS in cancer survivors. However, forward regression begins with a model that contains no variables (called the null model). Then, it starts adding the most significant variables one after the other. The backward stepwise model, on the other hand, starts with the full model that considers the effects of all variables at the same time.

The results of the backward regression models showed that the factors including blood urea nitrogen, creatinine phosphokinase, potassium, aspartate aminotransferase and alanine aminotransferase had significant relationship with HGS in both models [3, 13]. Our result is agreement with the findings of Joseph et al that showed that colon and lung adenocarcinomas presented lower creatine phosphokinase activity than the normal tissues. In contrast, lung carcinoids had higher creatine phosphokinase activity than normal lung tissue [49]. As well, in regards to aspartate aminotransferase, Xie et al showed increased aspartate aminotransferase was better than alanine aminotransferase in detecting and predicting liver cancer and the increased risk of mortality [31]. In addition, another study similarly reported that although the prevalence of alanine aminotransferase were 3 times higher than aspartate aminotransferase in liver cancer, the aspartate aminotransferase could better predict the risk of liver cancer survivors [31]. Our findings were in agreement with the results of these two previous investigations. Furthermore, albumin and protein were not significantly related to HGS in our study since they were excluded from our stepwise regression models. Our results differed from another study that showed physical function was associated with serum albumin levels [50, 51]. Regarding total protein, a previous study showed that cancer patients with cachexia had lower total protein compared to cancer patients without cachexia. In fact, the prevalence of malnutrition in cancer patients has been reported as 40% to 80%, which can lead to decreased muscle mass and impaired immune function, excess morbidity, and mortality and finally, increased muscle protein breakdown, while this relationship was not confirmed for the population in our study.

Iamartino et al discuss the clinical and experimental evidence for the extracellular calcium-sensing receptor (CaSR)'s role in colonic inflammation and colorectal cancer. Their review study showed that the calcium receptor acts as a tumor suppressor in colorectal, parathyroid, pancreatic and neuroblastoma cancers and as an oncogene in

gastric, prostate, breast and Renal carcinoma cancers. They proposed that activating the CaSR lowers the risk of both diseases. They showed with the strongest data that dietary Ca2+ lowers the risk of colorectal cancer. In addition, they found direct use of CaSR as a pharmacological target for reducing or preventing inflammation of the colon as well as preventing colon tumors for colorectal cancer [52].

Some common late effects of cancer treatment has been reported as heart problems, hypertension, lung problem, endocrine system problems, hormone problems for men, bone, joint, and soft tissue problems, brain, spinal cord, and nerve problems, secondary cancers and motional difficulties [53]. Long-term follow-up strategies are becoming more important due to improvements in cancer survival as well as great advances in treatment options [54]. For each cancer survivor, it is necessary to do their follow-up in long term, provide lifestyle recommendations and summarize the treatment with detailed recommendation. Therefore, in our study, we discussed the biochemistry factors contributing to cancer survivals. These associations will finally help us to provide some guidelines to clinicians about the consequences of treatment plans and improving them. Some similar studies have been pursued previously. For example, in a meta-analysis study, it was examined whether there is an increased risk of high-grade aspartate aminotransferase and alanine aminotransferase with immune checkpoint inhibitor-based treatment. This study concluded that using immune checkpoint inhibitors had a causal relationship to an increased risk of high-grade elevated aspartate aminotransferase and alanine aminotransferase [55]. Such negative consequences of this treatment approach might even lead to developing a second cancer in cancer survivors. In terms of other biochemistry factors, another study showed that the development of serum electrolyte abnormalities including hyponatremia and hypokalemia may be associated with symptoms that can negatively affect quality of life. Diagnosis of these disorders and corrective treatment of electrolyte abnormalities

are very important in the care of cancer patients. Rosner et al found a weak positive association between pre-diagnostic higher serum potassium (> 5 mEq/L) and overall death [HR: 1.26 (95% CI: 1.01-1.59)] as compared to conditions with low or normal levels of potassium. Management of restoring electrolyte levels in cancer patient is complex and electrolyte abnormality can affect the health status and may limit treatment approach. Therefore, chemical imbalance is an essential factor for the clinicians to establish proper and effective corrective measures [56]. A minor electrolyte imbalance may be treated by diet changes. For example, the Gerson regimen involves consuming fresh, raw fruits and vegetable juices, eliminating salt from the diet, taking supplements such as potassium, vitamin B12, thyroid hormone, pancreatic enzymes, and detoxifying liver with coffee enemas. This regimen can help to stimulate metabolism and might be used as an alternative for cancer treatment. In fact, Gerson therapy is based on electrolyte imbalances and emphasizes increasing potassium intake, minimizing sodium consumption [57]. A systematic review showed the evidence for the role of diet and physical activity on cancer incidence. This study suggested that a low-fat, high-fiber diet might be protective against cancer recurrence and progression [58]. This evidence was in agreement with the results of another systematic review and meta-analysis that showed performing exercise significantly reduced the risk of mortality in patients with cancer and in cancer survivors. As well, a recent publication shows that exercise significantly reduced the risk of recurrence in cancer survivors (RR = 0.52, 95% CI = 0.29-0.92, I2 = 25%, P = .030) [59].

Comparing regression model coefficients

The plot summary (Figure 4.1) showed a rapid review for the difference between the two backward regression models (data with NAs and imputed data (without NAs)). In fact, this plot made it easier to compare the models and coefficients. Coefficients were

between -1 to 1, and any parameter closer to zero had less correlation with HGS such as sodium, albumin, physical activity, and total protein. On the other hand, other parameters farther away from zero were better associated with HGS such as gender, age, BMI, arm circumference, blood urea nitrogen, creatinine phosphokinase, and aspartate aminotransferase.

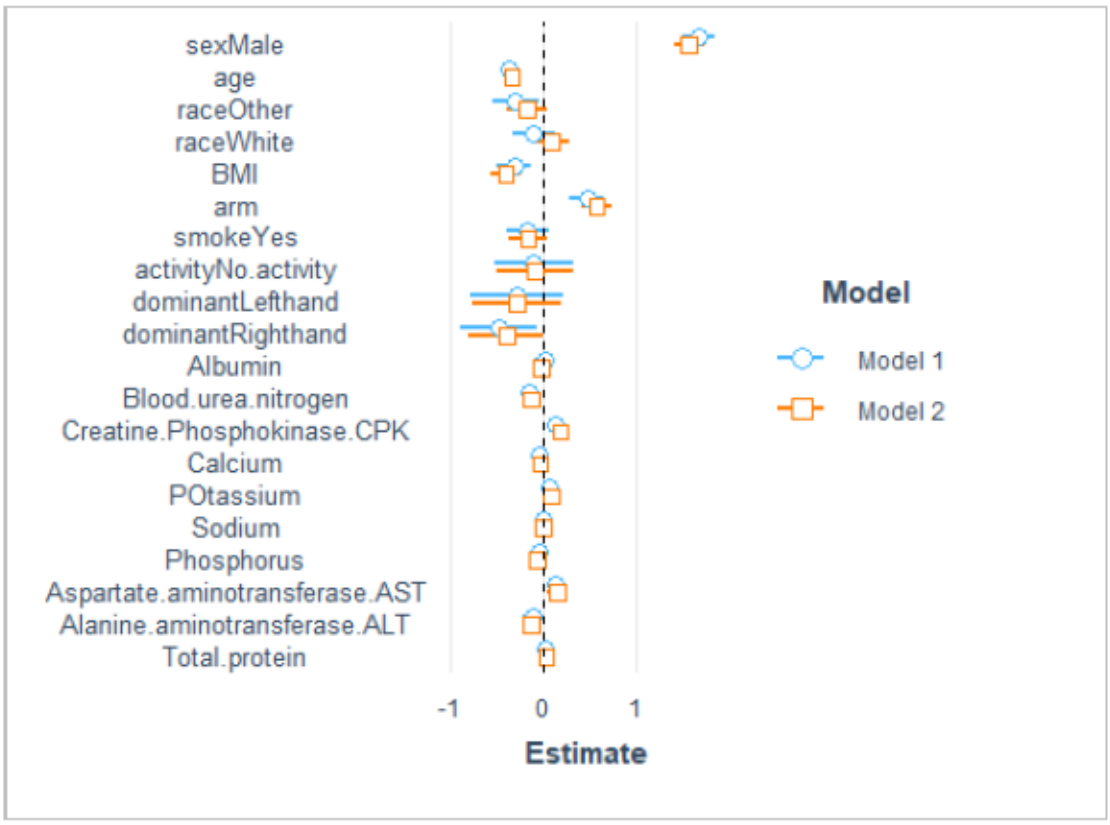


Figure 4.1: Comparing two reggression models and their coefficients visually

Comparing two regressions in table output

We compared two backward regression models including regression model with and without weighting data. Both models considered HGS as the dependent variable and

18 variables including albumin, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, total calcium, creatine phosphokinase, phosphorus, total protein, sodium and potassium as independent variables. The results for model without weighting data showed that HGS was significantly related to gender, age, BMI, arm circumference, blood urea nitrogen, creatinine phosphokinase, aspartate aminotransferase. Other parameters such as race, dominant hand (left) and alanine aminotransferase showed moderate association with HGS. On the other hand, the results for weighted model showed that HGS was significantly related to age, BMI, arm circumference, Blood urea nitrogen. Adjusted R^2 were exactly the same for two models (R^2=0.7, Adjusted R^2=0.7).

Table 4.1 : Comparison or the two backward regression models (with/without weights)

Coefficients of both models		
	Dependant variable	
Independent variable	Handgrip strength Model(1)	Handgrip strength Model(2)
Sex	1.7*** (0.1)	1.6*** (0.1)
Age	-0.03***(0.003)	-0.02*** (0.003)
Race other	-0.3** (0.1)	-0.3* (0.2)
Race white	-0.1 (0.1)	-0.1 (0.1)
BMI	-3.4*** (1.0)	-3.9*** (1.0)
Arm circumference	0.1*** (0.02)	0.1*** (0.02)
Smoking	-0.2 (0.1)	-0.04 (0.1)
Physical activity	-0.1 (0.2)	0.2 (0.2)
Dominant hand(Left)	-0.3 (0.3)	-0.5 (0.3)
Dominant hand(Right)	-0.5** (0.2)	-0.5* (0.3)
Albumin	0.1 (0.4)	-0.2 (0.4)
Blood urea nitrogen	-0.8*** (0.2)	-0.8*** (0.2)
Creatine Phosphokinase	0.5*** (0.2)	0.3** (0.2)
Total calcium	-0.5 (0.4)	-0.4 (0.4)
Potassium	1.5 (0.9)	2.0** (1.0)
Sodium	-0.01 (0.1)	0.02 (0.1)
Phosphorus	-0.3 (0.3)	-0.4* (0.2)
Aspartate Aminotransferase	11.7*** (4.5)	5.4 (4.6)
Alanine aminotransferase	-6.2** (2.7)	-4.0 (2.8)
Total protein	0.03 (0.1)	0.04 (0.1)
Constant	11.1*** (1.7)	11.8*** (1.8)
Observations	401	401
R^2	0.7	0.7
Adjusted R^2	0.7	0.7
Residual Std. Error (df = 380)	0.7	140.1
F Statistic (df = 20; 380)	40.4***	41.1***
Note:	*p<0.1; **p<0.05; ***p<0.01	

Thus, our proposal of a biochemistry based marker to predict HGS in cancers survivors is based on the significant coefficient factors presented in Table 3-10.

In this study, we did large cross-sectional analysis of NHANES data with detailed information which can add some knowledge about biochemistry marker in cancer survivors. Furthermore, we used a solid analysis that might enable physicians to have a better clarity of the biochemistry marker components in cancer survivors that are related to muscle strength. By knowing these biochemistry markers, a physician can focus on the factors that might lead to a better performance related to treating cancer patients wherever applicable. We used a coherent strategy for the analysis and went through all the steps, step by step, like quantiles based on handgrip strength, summary of primary and final skewness, correlation analysis, multivariate backward regression model and comparison of two regression models. This regular and comprehensive sequence has not been followed by previous studies. Therefore, the findings of this study might provide more robust evidence compared to similar previous studies.

LIMITATIONS

One of the limitations is related to the data provided in NHANES that was self-reported. It was not possible to determine the exact amount of physical activity of the participants. In addition, in this study, there was no difference between the individuals who were suffering from cancer and taking medication for cancer and those individuals who were

suffering from cancer and not taking cancer medication. Another limitation was the potential different types of cancer treatments or surgery used for cancer survivors, since the relevant information was not available. In addition, we did not know exactly at what age the cancer ended. These sources of variations might have impacted the results of our regression models.

CONCLUSION

In conclusion, HGS as a dependent variable was associated with some important biological factors and various other factors in cancer survivors from a cross-sectional analysis of NHANES data. Based on HGS and the three age groups, our results showed that cancer survivors in their 60s and 80s, who have a low percentiles of hand grip strength compared to the other two age groups, may need more care and support services. This is the first study that explored the relationship between HGS and biochemistry marker in a representative national sample of adults with self-reported diagnosed cancer survival. Finally, our results included some important clinical implications in various types of cancer survivors. These findings suggest that targeted interventions in cancer survivors could be effective in preventing a decrease in muscle strength.

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