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Research Article

Predictors of Cardiac Cachexia among Jordanian Chronic Heart Failure Patients

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Abstract

Background: Cardiac cachexia is considered as an ominous complication that possibly associated with the terminal stages of chronic heart failure (CHF) as it consumes the protein-calories reserves of the patients. Cardiac cachexia still poorly understood as a result of complex pathophysiology and its treatment modalities; even of the growing incidence and the devastating pathological consequences.

Aim: The aim of this study was to identify the most significant predictors of cardiac cachexia in Jordanian chronic heart failure patients.

Methods: A cross-sectional design was employed in the study. A convenient sample of 300 chronic heart failure patients was recruited from accessible chronic heart failure patients who regularly visit the cardiac care clinics at two different selected hospitals that represent two different major health sectors in Jordan. A self-developed instrument was used to collect the data for the purpose of this study.

Results: Stepwise regression analysis was conducted to determine whether the interaction of different sociodemographic variables of chronic heart failure patients contributed significantly to the total cardiac cachexia score. The most significant predictors of cardiac cachexia are: age, New York Heart Association (NYHA) classification of heart failure, hospital type, chronic diseases that the participating chronic heart failure patients suffer from, and level of education. These variables explained 65.8% of the variance in the total cachexia score.

Conclusion: Cardiac cachexia has not been widely measured and studied yet world widely. The findings of this study can be used as a baseline data about the predictors of cardiac cachexia and the roles of the sociodemographic characteristics among Jordanian chronic heart failure patients since this study is the first of its kind conducted to examine cardiac cachexia at the national and even regional level. In addition, this study can be useful for determining effective therapeutic modalities that can be employed on behalf of those patients among the health care team; particularly nurses.

Keywords: Cardiac cachexia; Chronic Heart Failure (CHF); Complication; Jordan

Introduction and Background

Cardiac cachexia is an old concept that was recognized from decades, but recently the investigations about it have grown effectively as a result of its growing incidence and its devastating pathological consequences [1]. Indeed, cardiac cachexia is an independent factor for reducing the survival rate of CHF [2,3]. Statistics show that mortality rate in cachectic heart failure patients may reach 50% within 18 months of initial weight loss compared to 5 years in non-cachectic heart failure patients [4].

Several definitions were adopted to identify cardiac cachexia; however most definitions agreed that it is a wasting, catabolic state that affects the bone, muscle, and fat tissues of the CHF patients, which eventually leads to terminal hemodynamic compromise after the body fails to compensate [5-7]. Cardiac cachexia is diagnosed when non-edematous weight loss of more than 5% of the pre-morbid normal patient's weight, without the presence of any other cachectic causes like: cancer, thyroid diseases and severe liver diseases that occurred over a period of at least 6 months [8-10].

In fact, the pathophysiology of cachexia that occurred with CHF patients is not fully understood; because the cardiac cachexia occurred as a result of many factors that contribute in complex imbalances in the catabolic and anabolic processes leading to the wasting and catabolic state [5,7,10]. Activation of complex series of metabolic, neurohormonal,and immunological processes by the development of CHF, are thought to have roles in the imbalances of the catabolic and anabolic processes [11].

According to the most recent statistics, approximately 15% of patients of advanced CHF developed cardiac cachexia [12,13]. However, in USA alone, the number of CHF patients currently is about 5 million and is growing annually with 500,000 new cases [4,14]. In Jordan and other developing Middle-East countries, heart diseases are emerging health problem with a proportion of deaths range from 25% to 45% due to increased risk factors with a lack of effective preventive measures [15]. In Jordan specifically, Coronary Heart Diseases (CHD) is responsible on 35% of the overall deaths [16].

Multiple research studies about heart disease including CHF and cardiac cachexia were reviewed to build the idea about the predictors of cardiac cachexia. Through these published studies, multiple risk factors were identified for developing heart failure including: Hypertension (HTN), Diabetes Mellitus (DM), smoking, stress, sedentary life style, dyslipidemia and obesity [17-19]. However, obesity was found to be as a protective factor from cachexia among CHF patients according to Shirley [20], review study; in which six studies from 1999 to 2006 were reviewed to examine the relationship between obesity and CHF patient's survival.

Advancing in the age of population is considered as one of the risk factors of heart failure. According to Lloyd-Jones and von Haehling

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[4,17], about 5.7 million Americans who are older than 65 years old were hospitalized with heart failure. Von Haehling [21] review study tried to explain the normal pathophysiology of aging among cardiac cachectic patients. The researchers provided evidences to support that the energy expenditure decreased with advancing of age in most of the CHF patients, but the resting energy expenditure in some patients increased as a result of increase cardiac ventilator work and resting peripheral oxygen consumption.

Diabetes association with low muscle mass was examined recently by a cross sectional observational study of Kim [22] and his colleagues as they studied 414 Korean adults whose age was 65 years and older. Results of the study revealed that type 2 DM and low muscle mass were closely correlated among the study sample of Korean older adults.

The Hypertension (HTN) was considered as a major contributor to the development of CHF and its complications like cachexia by many literature studies that tried to explain the association between CHF and HTN [23,24]. In Chen review study, the researcher found that either HTN or CHF had the ability to increase the stimulation of Cardiac Sympathetic Afferent Reflex (CSAR) which contributes to excessive sympathetic activation that greatly contributes in the pathogenesis of both CHF and HTN, and this increases the risk of their complications. As it is understood from Chen study, the combination of CHF and HTN diseases will increase the risk for developing complications like cardiac cachexia as the additive effects of CHF and HTN maximizes the sympathetic activation and its pathogenity.

The effect of chronic disease in general on psychological status of the patients who suffered from and the resulted high levels of anxiety, stress, and depression were discussed through many of the literature studies [25-28]. Lee [26] examined the stress level among 402 adults with different chronic diseases including: DM, HTN, and cardiovascular diseases. The researchers found a significant positive correlation between chronic diseases in general and the stress level.

Many literature studies discussed the effects of the level of education on the quality of the heart failure patients' life [29,30]. Barbareschi [29] and his colleagues found that highly educated patients showed better adaptation behaviours with emotional problems and better physical and social functioning when they compared with the low educational level patients. Moreover, pain, fatigue, and limitations in role functioning were significantly lower in highly educated patients. The researchers concluded that the educational level of the heart failure patients has effects on decreasing anxiety levels, and on improving physical and emotional functioning.

Majority of studies investigated cardiac cachexia among CHF patients were conducted in western countries, which necessitates the conduction of this subject in other countries in terms of its incidence and prevalence that could be different due to various social, environmental, and cultural variables that could have effects on cardiac cachexia among Jordanian CHF patients.

On the other hand, the extensive search in literature didn't reveal on a specialized cardiac cachexia instrument and some variations were found in the diagnosing of cardiac cachexia. The variations that existed in the diagnosing of cardiac cachexia encourage the researcher to dig more to search in the literature fora non-expensive, valid and reliable instrument which clearly diagnoses cardiac cachexia.

Consequently, the purposes of this study were to identify the most significant predictors of cardiac cachexia in Jordanian CHF patients.

Methodology

Design and Sample

A cross-sectional design was used to conduct this study. The target population and the interest of this study were all Jordanian CHF patients who were followed up in the Jordanian hospitals. The accessible population of the interest for this study was Jordanian CHF patients who were followed up in two hospitals represent two major health care settings in the central part of Jordan; military hospital while the other one is a governmental.

A convenient sampling technique was used to recruit CHF for the study. The sample size was determined by using power primer analysis based on the statistical tests that will be used to analyze the participant's data [31]. A sample size of 200 CHF patients was needed to obtain a power of 0.8, medium effect size, and an alpha of 0.05. To allow for 10% drop-out rate, there was a need to increase the sample by 10 % to reach 220 CHF patients. However, as a result of the availability of participants and to overcome the potential drop-out, the sample size was increased to 300CHF patients to increase the generalizability of the result and to increase the external validity of the study.

Eligibility criteria were adult Jordanian patients who had chronic heart failure and were able to understand Arabic. Those with known neoplastic, thyroid disorders, nutritional impairments, or any chronic inflammatory conditions were excluded from the study; to exclude other well-known types of cachexia, like cancer and pulmonary cachexia. Furthermore, during the first exposure visit, any patients with signs of fluid overload that may mask the detecting of weight loss were also excluded. Subjects were excluded on the basis of the data gathered from their medical records that show their eligibility to be recruited for the study. For example, if the records showed that the participant has known neoplastic or nutritional impairment with repetitive visits to nutritional clinic, the participant will be excluded from the study.

Instrument

A researcher-developed instrument based on the latest dimensions of cardiac cachexia identification was used in this study (Table 1). Using a combination of anthropometrics measures, biological markers, and clinical manifestations as reported in the available literature was used in this study to detect and diagnose cardiac cachexia among Jordanian CHF patients [8,9,32,33].

The instrument consisted mainly from two parts: patients' sociodemographic data sheet and cardiac cachexia instrument which divided to three main parts: anthropometrics, biomarkers, and clinical manifestation that associated with cardiac cachexia that were measured majorly as what it is followed in cancer cachexia assessment scale based on Common Terminology Criteria for Adverse events (CTCAE) version 4 that were developed by the American National Institute of Health and National Cancer Institute in 2010 [32,34].

In fact, after extensive search in the literature, no specific instruments were found to measure cardiac cachexia and the targeted variables. Different methods were used to detect cardiac cachexia incidence among CHF patients, which include mainly clinical manifestations, anthropometric measures, biochemical markers, imaging, and functional tests to quantify muscle mass. Unfortunately, there are variations existed in diagnosing cardiac cachexia, even with the use of different methods in detecting cardiac cachexia. However, Gabison and her colleagues built in 2010 a cachexia assessment scale to detect cachexia among cancer patients based on a combination of anthropometric measures, biological markers and clinical manifestations that occurred in cancer cachectic patients similar to the targeted variables for measuring through cardiac cachexia instrument [32]. The comprehensive approach and the applicability of assessment that only followed in cancer cachexia scale make the building blocks for the cardiac cachexia instrument.

Total cachexia score was calculated by summing up each answered item contained within the cardiac cachexia instrument. The classification of the severity of cardiac cachexia was calculated as per to what is adopted in the cancer cachexia assessment scale based on the

Table 1: Cardiac Cachexia Instrument.

	Item	0	1	2	3	4
Anthropometrics	% Weight loss during 6 months	<5%	5%-10%	10%-20%	≥20%	
	BMI	Normal (<19)	Moderate (17-19)		Severe weight loss (<17)	
	AMA (mm) According to age and gender	Average (>15th but ≤85th)	Below average (>5th but ≤ 15th)		Wasted (≤5th)	
Biomarkers	Albumin (g/l)	35-50	30-<35	20- <30	< 20	
	Createnine "ULN: Upper Limit of Normal"	Normal	>ULN - 1.5 X ULN	(>1.5 - 3.0) ULN	(>3.0 - 6.0) ULN	>6.0 X ULN
	Hemoglobin (g/dl)	Normal	10	8-9.9	6.5-7.9	<6.5
Clinical Manifestations	Decrease muscle strength According to age and gender	Average	Below average		Poor according	
	Fatigue	No fatigue	Fatigue relieved by rest	Fatigue not relieved by rest; limiting instrumental ADL	Fatigue not relieved by rest, limiting self-care ADL	
	Anorexia	No anorexia	Loss of appetite without alteration in eating habits	Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated	Associated with significant weight loss or malnutrition (e.g., inadequate oral caloric and/or fluid intake); tube feeding or TPN indicated	Life-threatening consequences; urgent intervention indicated

CTCAE version 4 [32,34]; where 0 to 2 score = no cachexia; 3 to 18 = mild cachexia; 19 to 24 = moderate cachexia; and 25 to 24 = severe cachexia.

The face and scale content validity of the researcher-developed instrument items was checked by panel of specialized experts in cardiac care nursing and nutrition. All selected experts were PhD-prepared faculty members in the nursing schools at various Jordanian universities. For the content validity, the experts evaluated the relevancy of the developed cardiac cachexia instrument items by using a scale of 1 to 4; where 1 = not relevant, 2 = somewhat relevant, 3 = quite relevant, and 4 = highly relevant. The Scale Content Validity Index (S-CVI) were calculated and found to be 0.93.

Pilot Study

A pilot study was carried out with a sample of 30 CHF patients who met the inclusion criteria at the military hospital to test the clarity, reliability and feasibility of the instrument. Cronbach's alpha that was calculated and found to be 0.92 indicated high internal consistency reliability when applying the instrument during the pilot study.

Data Collection Procedure

Before administering the instrument for CHF patients, an official approval of institutional Review Board (IRB) was attained. Then, administrative approval from the institutional review board of the selected hospitals and its administrations were obtained.

A convenient and eligible sample was used based on non-probability sampling technique, which recruits all accessible CHF patients until obtaining the specified targeted sample. The primary researcher was the only data collectors who contacted the participants and administered the instrument of the study. To ensure that all the participants are voluntarily involved in the study, consent forms were distributed to participants before applying the instruments to make sure that CHF patients participation has no influence on their quality of care that was provided for them. The primary researcher provided a short debriefing session for each patient to clarify the purpose, the research procedure and researcher's commitment of ensuring confidentiality and privacy of all potential participants.

The sociodemographic data were collected by direct questions to the participating CHF patients after brief description for the study researcher and his qualification. NYHA class for every participant was identified through asking direct questions by the researcher according to the known criteria of each class; while the cardiac cachexia instrument were filled according to the participants' measurements and verbal answers. Data collection from the participants started in the 12 of April 2016 and ended in 23 of June 2016.

Methods of Data Analysis

The statistical analysis was performed using Statistical Package for Social Science (SPSS) version 22. A descriptive statistical analysis was conducted to describe Jordanian CHF patients and their socio-demographics characteristics of the sample. Stepwise regression analysis was used to identify the most significant predictors of cardiac cachexia among Jordanian CHF patients. α- level of 0.05 was set as a level of significance for all statistical procedures executed in this study.

Ethical Considerations

Ethical approvals were taken appropriately; Jordan University of Science and Technology Institutional Review Board (IRB) approval was obtained before data collection process starts. In addition, administrative permissions were obtained from the institutional review board of the selected hospitals. Administrative permissions from each hospital administration were also obtained.

Participation in the study was voluntary and every effort was taken to ensure confidentiality of participants. Participants provided informed consent to ensure that they voluntarily participate in the study. Informed consents were signed by the participating CHF patients after the study debriefing that was provided by the researcher personally. This include: the study purpose, research procedures, and commitment to maintain privacy and confidentiality for all provided information. Moreover, the importance of early detection of cardiac cachexia to enhance its management and to decrease its high morbidity and mortality rates was also explained for each participant. Clarifications also provided about the participants' decision to participate in the study or not have no effect on their treatment or their follow up in all care clinics.

Results

Characteristics of the Sample

From the two different hospitals that belong to two different health

sectors inside Jordan, this study recruited three hundred Jordanian CHF patients who were conveniently selected according to the inclusion and exclusion criteria to apply the cardiac cachexia instrument on them. One hundred and sixty CHF patients (53.3% of the total study participants) were recruited from the military hospital, while the rest of the study sample, one hundred and forty CHF patients (46.7%) were recruited from the governmental hospital (Table 2).

Most Significant Predictors of Cardiac Cachexia among Jordanian CHF Patients

Stepwise regression analysis was conducted to determine whether the interaction of hospital type, age, gender, marital status, monthly income, level of education, employment status, medical insurance, number of years since firstly diagnosed as CHF, smoking status, number of daily smoked cigarettes, presence of chronic disease, and participants' NYHA classification contributed significantly to the total cardiac cachexia score. The model with age was a significant predictor of total cachexia scores among Jordanian CHF patients and contributed to 58.9% of the variance in total cachexia score. The model was statistically significant (F=308.12, P=0.001). In the second model, the addition of NYHA classification increased the explained variance in total cachexia score by 3.6%. In this model, age and NYHA classification significantly explained approximately 62.5% of the variance in total cachexia score among Jordanian CHF patients. Advanced age and NYHA classification predicted higher levels of cardiac cachexia (F=179.19, P=0.001). In the third model, the addition of hospital type significantly increased the explained variance in total cachexia score by 1.8%. In this model, age, NYHA classification, and hospital type significantly explained almost 64.3% of the variance in the total cachexia score (F= 129.54, P= 0.001). In the fourth model, the addition of chronic diseases that participants suffer from increased the explained variance in total cachexia score by 1%.In this model, age, NYHA classification, hospital type, and chronic diseases significantly explained almost 65.3% of the variance in the total cachexia score (F= 101.70, P= 0.001). Finally, the addition of the level of education in model five increased the explained variance in total cachexia score by 0.5%. In this model, age, NYHA classification, hospital type, chronic diseases, and level of education significantly explained 65.8% of the variance in the total cachexia score (F= 83.39, P= 0.001) (Table 3).

Table 2: Sample characteristics.

Variable	N	%
Hospital		
Military	160	53.3
Governmental	140	46.7
Gender		
Male	198	66
Female	102	34
Marital status		
Married	238	79.3
Single, widowed or divorced	62	20.7
Level of education		
Low educational level	173	57.7
High educational level	127	42.3
Employment status		
Employee	108	36
Retired	192	64
Medical insurance		
Yes	213	71
No	87	29
Chronic diseases		
No chronic diseases	91	30.3
DM	47	15.7
HTN	149	46.3
Both DM and HTN	23	7.7
NYHA classification		
I	58	19.3
II	130	43.3
III	86	28.7
IV	26	8.7
Smoking status		
Smoker	215	71.7
Non-smoker	85	28.3
Variable	**M (SD)**	**Actual Range**
Age	57.76 (10.66)	39-90
Monthly income	398.78 (168.92)	100-1000
Number of years since diagnosed as CHF	8.66 (5.77)	Feb-31
Number of smoked cigarettes	22.32 (8.39)	Mar-50

Table 3: Significant predictors of cardiac cachexia.

Model	Variable	Beta	Adjusted R	F	P
1	Age	0.769	0.589	308.119	0.001
2	Age NYHA classification	0.687 0.209	0.625	179.189	0.001
3	Age NYHA classification Hospital type	0.663 0.251 -0.146	0.643	129.535	0.001
4	Age NYHA classification Hospital type Chronic diseases	0.545 0.239 -0.131 0.165	0.653	101.701	0.001
5	Age NYHA classification Hospital type Chronic diseases Level of education	0.56 0.242 -0.119 0.146 0.083	0.658	83.391	0.001

The most significant predictors ranked accordingly to their variance contribution in the dependent variable as the following: the patient's age, NYHA classification, hospital type, and chronic diseases that CHF suffer from. Whereas, the participants' level of education was identified as the less significant predictor.

Discussion

Most Significant Predictors of Cardiac Cachexia among Jordanian CHF Patients

Stepwise regression analysis was employed to determine the most significant predictors from hospital type, age, gender, marital status, monthly income, level of education, employment status, medical insurance, number of years since firstly diagnosed of CHF, smoking status, number of daily smoked cigarettes, presence of chronic disease, and participants' NYHA classification in predicting the total cardiac cachexia score. Results showed that the most significant predictor were the participants' age, NYHA classification, hospital type, chronic diseases that the participants suffer from, and participants' level of education.

Participants' age alone was responsible on 58.9% of the variance in the total cachexia score. In general, the muscle mass loss increased with advancing in age as the levels of protein and fat synthesis inside the

body decreased, which resulted from the ongoing decline in the levels of testosterone and other many anabolic hormones with advancing in age [5,35-37].

The second significant predictor was NYHA classification of heart failure which was responsible on 3.6% of the variance in the total cachexia score. Progressing in the NYHA classes of the heart failure positively correlates with the CHF patient's morbidity and mortality as the levels of some of the anabolic hormones, cardiac index, and cardiac output decreased significantly with the increments in NYHA classes [1,35,38]. Jankowska and her colleagues found a significant inverse relationship between NYHA classes and the levels of some of the anabolic hormones like: DHEAS, total testosterone (TT), and free testosterone ($P<0.01$); in which the depletion of each of them considered as an independent factor for the poor prognosis of CHF and developing complications like cachexia. Also in Araujo study [1], a significant relationship were found between cardiac cachexia and NYHA class (III) or (IV) ($P<0.001$). Moreover, MacGowan and his colleagues [38] found a significant differences between the cachectic and non-cachectic patients in the cardiac output and the cardiac index ($P<0.05$) that could be attributed to advancing of CHF and progressing in NYHA classes.

The third significant predictor was the hospital type which explained about 1.8% of the variance in the total cachexia score. The two different health sectors that were represented through the selected study hospital have different follow-up and treatment protocols in dealing with CHF patients, which may contribute in being a predictor for cardiac cachexia. Moreover, considering the hospital type as a predictor for cardiac cachexia could be attributed to the higher percentage of measured chronic diseases and the higher percentage of participants in class (III) and class (IV) in military hospital when it is compared with the governmental hospital. The reviewed literature studies supported that the progressing in NYHA classes and having chronic disease like DM and HTN have significant correlations with CHF and cardiac cachexia [1,5,19,22].

The fourth predictor was the chronic diseases that the participants suffer from which explained about 1% of the variance in the total cachexia score. DM and HTN contribute in decreasing the muscle mass and several biomarkers fluctuations, leading to excessive sympathetic activation and increasing the pathogenity of CHF and cardiac cachexia [22-24]. The reviewed literature studies identified the significant correlation of DM and HTN with cardiac cachexia and considered them as risk factors for developing of the CHF and its complications like cardiac cachexia [22-24]. Kim [22] and his colleagues supported the ability of DM, specially type 2, to decrease muscle mass in adults when they found that the muscle mass was significantly lower ($P<0.001$) in 144 patients with type 2 diabetes mellitus compared with 270 healthy adults whose aged 65 years and more. Moreover, HTN was considered as a major contributor to the development of CHF and its complications like cachexia, as HTN leads to several biomarkers fluctuations which contribute in an excessive sympathetic activation [23,24].

The fifth predictor was participants' level of education that explained about 0.5% of the variance in the total cachexia score. High education levels' people were found to have higher physical and emotional functioning [29], while low level of education was associated with cardiac muscle dysfunctions [30]. In the study of Barbareschi and his colleagues [29] on 553 heart failure patients, a significant correlation ($p<0.05$) was found between the participants' level of education and their quality of life, as the higher education level group found to have significant higher physical and emotional functioning ($p<0.05$) and significant lower anxiety levels ($p<0.05$) when they compared to the lower educational group of heart patients. Moreover, Christensen et al. [30] found after they assessed by echocardiogram a random subset of their 18616 healthy adult sample that the low level of education was significantly associated with cardiac muscle dysfunctions ($p<0.05$) like: left ventricular hypertrophy, left ventricular dilation, reduced left ventricular ejection fraction, and with severe diastolic dysfunction.

Strengths and Limitations

The major strength of the study lies in the overall number of the sample (n= 300) in comparison with most of the reviewed studies that were conducted with a few number of participants. However, the convenient sampling technique was used to recruit the study participants from only two health sectors without including the private or university-affiliated health sector causes limitation in the external validity and limits the generalizability of the results.

Another major limitation of the current study was related to the main study instrument which developed by the researcher. In fact, after extensive search in the literature, no specific instruments were found to measure cardiac cachexia and the targeted variables. So, the study instrument was built after a thorough and extensive search in the literature to find the measured variables that contribute in cardiac cachexia incidence. However, further testing of psychometric properties is recommended to ensure accurate and valid measurement of the cardiac cachexia.

Conclusion

Cardiac cachexia has not been widely measured and studied yet world widely. Sociodemographic characteristics of the CHF patients and their chronic diseases have roles in developing cardiac cachexia and should be taken into consideration when dealing with CHF patients and when developing and implementing treatment plans of cardiac cachexia.

Relevance to Clinical Practice

The results of this study can be used as a baseline data about the cardiac cachexia predictors and the role of different sociodemographics in developing of cardiac cachexia among Jordanian CHF patients; since this study is the first of its kind conducted to examine cardiac cachexia at the national and even the regional level. Establishing baseline data about cardiac cachexia paved the way in front of future researches for it helps the researchers to conduct additional more controlled research studies in terms of their designs and methodologies. In addition, this study can be useful for determining effective therapeutic modalities that can be employed on behalf of cachectic patients among the health care team; particularly nurses.

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