The Egyptian Heart Journal 69 (2017) 209–213

HOSTED BY

Contents lists available at ScienceDirect

The Egyptian Heart Journal

journal homepage: www.elsevier.com/locate/ehj

Original Article

Obesity paradox in heart failure patients – Female gender characteristics-KAMC-single center experience

Sheeren Khaled [a,b,*], Rajaa Matahen [a]

[a] King Abdullah Medical City-Makkah, Muzdallfa Road, Saudi Arabia
[b] Banha University, Egypt

ARTICLE INFO

Article history:
Received 8 November 2016
Accepted 3 June 2017
Available online 22 June 2017

Keywords:
Obesity paradox
Heart failure
Female gender

ABSTRACT

Background/Introduction: The correlation between low body mass index (BMI) and congestive heart failure (obesity paradox) has been described in the literature; However, the association between BMI and clinical outcome measures is not well characterized. Little is known about CHF in the Middle Eastern female population; most of the gender-specific information on heart failure comes from higher income "Western" countries.

Objectives: We aimed to identify the correlation between heart failure patients especially those with low BMI and clinical/safety outcome measures with focusing on female patients subgroup characteristics.

Methods: We performed group comparisons of statistically relevant variables using prospectively collected data of HFrEF patients hospitalized over a 12 month period.

Results: The 167 patients (Group I) enrolled by this study with mean age of 59.64 ± 12.9 years, an EF score of 23.96 ± 10.14, 62.9% had ischemic etiology, 12.5% were smoker, 18% had AF, 31.1% had received ICD/CRT-D and an estimated 8.85 ± 9.5 days length of stay (LOS). The low BMI group of patients (Group II) had means age of 58.7 ± 14.5 years, a significant lower EF score of 20.32 ± 8.58, significantly higher 30, 90 days readmission rates and in-house mortality (22%, 36.6% and 17.1% vs 10.2%, 20.4% and 6.6% respectively) and higher rates of CVA, TIA and unexplained syncope (19.5% vs 7.2%). Similarly, female patients with low BMI (Group IV) had lower EF score of 22.0 ± 53, higher 30,90 days readmission rates and in-house mortality (34.4%,43.8% and 25% vs 13.5%,21.6% and 5.4% respectively) and higher rates of CVA, TIA and unexplained syncope(10% vs 0%).

Conclusion: Our findings showed that heart failure patients with low BMI had poor adverse clinical outcome measures (poor EF, recurrent readmission, mortality and composite rates of CVA, TIA and unexplained syncope) which reflect the effect of obesity paradox in those patients with HFrEF. Female patient subgroup showed similar characteristic findings which also might reflect the value of gender-specific BMI related clinical outcomes.

1. Introduction

The obesity paradox is a phenomenon that describes positive association with obesity, as measured by a high body mass index (BMI) and survival observed in certain patient categories.[1] Thus, advanced heart failure (HF) patients with a higher BMI had inversely or not associated risk of mortality and morbidity outcomes.[2] The hemodynamic alterations of overweight/obesity and its pathological effects on arterial blood pressure (BP) and cardiac structure and function, thus contributing role in HF was described in a previous study.[3] Horwich et al. conducted one of the first studies that demonstrated obesity paradox in HF and concluded that HF prognosis was better among overweight patients followed closely by obese patients, and the worst prognosis occurred in underweight HF patients, followed closely by patients with "normal" BMI.[4] The correlation between low body mass index (BMI) and congestive heart failure (obesity paradox) has been described in the literature.

In the Western literature, female patients with congestive heart failure (CHF) are typically older and have a higher incidence of obesity, hypertensive etiology, urinary tract infections, and atrial fibrillation compared with male patients. They are also more likely to suffer from anemia, depression, complications, and underutiliza-

Peer review under responsibility of Egyptian Society of Cardiology.

* Corresponding author at: King Abdullah Medical City-Makkah, Muzdallfa Road, Saudi Arabia.

E-mail addresses: sheeren.khaled@gmail.com (S. Khaled), m_riri@hotmail.com (R. Matahen).

http://dx.doi.org/10.1016/j.ehj.2017.06.002
1110-2608/

tion of resources than their male counterparts; however, they show less incidence of ischemic etiology in comparison. Moreover, a low body mass index (BMI) of <25 kg/m^2, valvular heart disease, dementia, pulmonary hypertension, malignancy, and aortic stenosis were found to predict poor outcome and mortality of hospitalized females.[5–8] Despite most of the gender-specific information on heart failure comes from higher income "Western" countries, little is known about CHF in the Middle Eastern female population.

In this study, we aim to determine the impact of obesity paradox on clinical and safety indicators of heart failure patients with consideration of female gender subgroup characteristics description which may add benefit on clinical practice to the treating physicians and guideline makers. Male-to-female comparison was not a primary objective of this study.

2. Methods and statistical analysis

The King Abdullah Medical City-heart failure (KAMC-HF) registry is an observational single-center prospective registry of hospitalized patients with congestive heart failure (CHF), comprising patients initially hospitalized with increased BNP levels, evidence of pulmonary congestion upon chest X-ray, an ejection fraction of <40% on echocardiogram, and New York Heart Association (NYHA) class II-IV symptoms. A total of 167 patients with HFrEF (37 (22%) female patients) were enrolled in our study and followed up for one year. We retrospectively analyzed the epidemiological, clinical, and safety characteristics of each patient and calculated the American Heart Association (AHA)-advocated readmission and the Get With the Guidelines (GWTG) inhouse mortality scores of all patients enrolled.[9,10] Patients with HFpEF and those who lost during the 1 year follow-up were excluded from our study.

Clinical indicators of the patients were monitored and detected. Length of stay (LOS) was calculated during the initial hospitalization, and 30- and 90-day readmission rates were calculated during any one of the relevant hospitalizations. In house mortality was identified as death occurred due to any cause at home. Many safety indicators were also assessed. Device related complications (infection, thrombosis, lead dislodgment and malfunctions), serious bleeding mandated blood transfusion or evidence of orthostatic hypotension, whereas serious infections with positive blood cultures and hemodynamic instability, compared with non-serious ones all were assessed. Acute kidney injury (AKI) was defined as rapid loss of renal function, resulting in a number of complications including fluid imbalance, metabolic acidosis, and uremia and that might be related to angiotensin converting enzyme inhibitors (ACI). Evidence of thromboembolic complications (TIAs and CVAs) was also detected.

We used a standard cutoff value for BMI < 25 kg/m^2 to define the low BMI class. Also, we compared the clinical and safety indicators between low BMI's group and all patient's group (including all normal, overweight and high BMI) to demonstrate the features and specific disease's pattern in those subgroup of patients with referral to the characteristics of female gender in the same way. Low BMI-high BMI comparison was not a primary objective of our study.

The KAMC heart failure observational registry is designed to be the part of the standard of patient care, to measure and improve quality of CHF disease management program, and has received approval of the organization ethics committee/institutional review board.

The collected data were tabulated and analyzed using SPSS version 16 software (Spss Inc, Chicago, ILL Company) and Microstate W software (India, CNET Download.com). Categorical data were presented as number and percentages while quantitative data were expressed as mean ± standard deviation. "*Z*" test was used to analyze categorical variables. Quantitative data were analyzed using Student "*t*". The accepted level of significance in this work was stated at 0.05 ($P < 0.05$ was considered significant).

3. Results

We categorized our data into two categories: patient's baseline characteristics and safety and clinical indicators and compared between the all patient's group (Group I) and low BMI's group (Group II) regarding those data. Also, we discussed female gender subgroup's characteristics in the same way.

3.1. Baseline characteristics

The 167 patients (Group I) enrolled by this study were of Arab descent and had a mean age of 59.64 ± 12.9 years, an EF score of 23.96 ± 10.14, 62.9% had ischemic etiology, 12.5% were smoker, 18% had AF, 31.1% had received ICD/CRT-D and an estimated 8.85 ± 9.5 days length of stay (LOS). However, the low BMI group of patients (Group II) means age of 58.7 ± 14.5 years, a significant observed lower EF score of 20.32 ± 8.58, 63.4% had ischemic etiology, 9.7% were smoker, 26.8% had AF, 26.8% had received ICD/CRT-D during 1 year of follow up and an estimated 8.69 ± 7.83 days (LOS) Table 1.

3.2. Clinical and safety indicators

The main clinical indicators such as 30 days and 90 days readmission rates and inhouse mortality were higher among patients of group II (Low BMI group) (22%, 36.6% and 17.1% vs 10.2%, 20.4% and 6.6% respectively). The safety indicators were either direct CHF or CHF co morbidity-related events and mostly were observed to be higher in low BMI group of patients (Group II). The indication for abdominal or thoracic interventional drainage performance was higher among group II (14.6% vs 6%). CVA, TIA and unexplained syncope were occurred significantly higher among patients of group II (19.5% vs 7.2%). Also, device related complications and under-or over-anticoagulation adverse events were observed more in patients of group II (14.6 and 14.6% vs 6%

Table 1
Comparison between all patients and those with low BMI subgroup regarding clinical characteristic.

Variable	All patients, *n*: 167 (100%)	All patients low BMI, *n*: 41 (24.5%)	Test	*P*
Age (mean ± SD)	59.64 ± 12.9	58.7 ± 14.5	St. "*t*" = 0.39	0.69 (NS)
EF (mean ± SD)	23.96 ± 10.14	20.32 ± 8.58	2.12	0.035 (S)
LOS (mean ± SD)	8.85 ± 9.5	8.69 ± 7.83	0.099	0.92 (NS)
Ischemic etiology	62.9%	63.4%	*Z* = 0.06	0.95 (NS)
Smoking rate	12.5%	9.7%	0.49	0.62 (NS)
AF rate	18%	26.8%	1.27	0.2 (NS)
ICD/CRT-D rate	31.1%	26.8%	0.54	0.59 (NS)
Furosemide average dose in mg (mean ± SD)	(59.42 ± 27.02)	57.5 ± 28.6	St. "*t*" = 0.4	0.68 (NS)

AF: Atrial fibrillation, CRT-D: Cardiac Resynchronization Therapy-Device, EF: Ejection fraction, ICD: Intra Cardiac Device, LOS: length of stay.

Table 2
Comparison between all patients and those with low BMI subgroup regarding to clinical outcome and safety measures.

Variable	All patients, *n*: 167 (100%)	All patients with low BMI, *n*: 41 (24.5%)	*Z*	*P*-value
30 days readmission rate	10.2%	22.0%	2.05	0.04 (S)
90 days readmission rate	20.4%	36.6%	2.19	0.028 (S)
In house mortality	6.6%	17.1%	2.14	0.032 (S)
Drainage rate	6%	14.6%	1.85	0.064 (NS)
AKI suspected ACEi-related	3.6%	2.4%	0.38	0.7 (NS)
Device related complication	6%	14.6%	1.85	0.064 (NS)
Total infection/bleeding rate	18%	12.2%	0.89	0.37 (NS)
CVA, TIA and unexplained syncope	7.2%	19.5%	2.39	0.002 (S)
Anticoagulation and thrombotic event rates	10.7%	14.6%	0.7	0.48 (NS)

ACEi: angiotensin converting enzyme inhibitor, AKI: acute kidney injury, CVA: cerebrovascular accidents, TIA: transient ischemic attack.

Table 3
Comparison between all female patients and those with low BMI subgroup regarding clinical characteristics.

Variable	All female, *n*: 37 (22%)	Female with low BMI, *n*: 32 (19%)	St. "*t*"	*P*
Age	65.5 ± 8.64	63.8 ± 7.86	0.85	0.39 (NS)
EF	27.3 ± 12.52	22.0 ± 5.3	2.20	0.031 (S)
LOS (mean ± SD)	9.6 ± 15.1	3.57 ± 2.44	2.23	0.029 (S)
Ischemic etiology	65%	71%	*Z* = 0.53	0.59 (NS)
Smoking rate	0%	0%	–	–
AF rate	11%	14%	0.38	0.71 (NS)
ICD/CRT-D rate	14%	0%	2.2	0.027 (S)
Furosemide average dose in mg (mean ± SD)	(65.16 ± 30.5)	50.0 ± 25.8	St. "*t*" = 2.21	0.031 (S)

AF: Atrial fibrillation, CRT-D: Cardiac Resynchronization Therapy-Device, EF: Ejection fraction, ICD: Intra Cardiac Device, LOS: length of stay.

Table 4
Comparison between all female patients and those with low BMI subgroup regarding to clinical outcome and safety measures.

Variable	All female, *n*: 37 (22%)	Female with low BMI, *n*: 32 (19%)	*Z*	*P*
30 days readmission rate	13.5%	34.4%	2.05	0.04 (S)
90 days readmission rate	21.6%	43.8%	1.97	0.048 (S)
In house mortality	5.4%	25%	2.31	0.02 (S)
Drainage rate	11%	0%	1.94	0.053 (NS)
AKI suspected ACEi-related	8.1%	14%	0.78	0.43 (NS)
Device related complication	2.7%	14%	1.73	0.08 (NS)
Total infection/bleeding rate	22%	0%	2.83	0.005 (S)
CVA, TIA and unexplained syncope	0%	10%	1.97	0.048 (S)
Anticoagulation and thrombotic event rates	5.4%	0%	1.33	0.18 (NS)

ACEi: angiotensin converting enzyme inhibitor, AKI: acute kidney injury, CVA: cerebrovascular accidents, TIA: transient ischemic attack.

and 10.7% respectively). While the composite total infection and bleeding event rate, and AKI suspected ACEi-related were higher among patients of group I with no significant differences (18% and 3.6% vs 12.2% and 2.4% respectively) Table 2.

3.3. Female subgroup characteristics

The mean age of female patients with low BMI (Group IV) was 63.8 ± 7.86 years with 71% had ischemic etiology and EF score of 22.0 ± 53. While they had significantly shorter LOS in comparison with all female patients (3.57 ± 2.44 vs 9.6 ± 15.1 days), they had higher 30 days and 90 days of readmission rates and inhouse mortality (34.4%,43.8% and 25% vs 13.5%, 21.6% and 5.4% respectively). Also, AKI suspected ACEi-related, device related complications, and CVA, TIA and unexplained syncope were observed to be higher in low BMI female patients (Group IV) (14%,14% and 10% vs 8.1%, 2.7% and 0% respectively). However, drainage rate and composite total infection/bleeding event rate were higher in all female patients group (Group III) in comparison with low BMI female patients (Group IV) (11% and 22% vs 0% and 0% respectively) Table 3 and 4.

4. Discussion

In this study, the mean age of around 65 years is consistent with the findings reported from European nations.[11] Although the BMI-based obesity paradox concept may ignore the impact of some confounding factors, such as the degree of cardio respiratory fitness, wasted muscle volume, cachexia status, and waist circumference measurement, there is currently strong evidence that supports a high BMI, especially in females, confers an added survival benefit.[3,8,12,13] In our study, around 24.5% of patients had a BMI value of <25 kg/m^2, and consequently, a higher mortality risk than the all patients group (17.1% vs 6.6%). The low BMI group (Group II) patients had a significant lower EF score and higher CVA/TIA or unexplained syncope rate compared to the all patients group (20.32 ± 8.58 and 19.5% vs 23.96 ± 10.14 and 7.2% respectively). Heart failure co-morbidity-related events were observed to occur significantly higher in patients with low BMI such as 30-days and 90-days readmission rates. However, percutaneous drainage requirements and device related complications also occur higher in low BMI group, and they were not significantly different.

Our findings consistent with Sharma and colleagues who recently reported a meta-analysis of 6 studies that assessed adverse events, including CV mortality, all-cause mortality, and re-hospitalization, during a 2.9 year mean follow-up, prognosis was the worst with low BMI group of patients.[14] Similarly, it was reported that the presence of overweight and obese, at least mild obesity in those with HF, appears to confer a better short-and intermediate-term prognosis than in their leaner counterparts who have similar degrees of HF.[3,15]

Obesity paradox in HF patients can be explained by multiple mechanisms. The catabolic state occurs in HF patients with overweight and obesity represents the metabolic reserve while patients with low BMI levels may suffer from unintentional weight loss resulting in "cardiac cachexia," known to be associated with a poor prognosis. The increased levels of serum lipoproteins associated with increased body fat may play an anti-inflammatory role, neutralizing circulating bacterial endotoxins or cytokines.

4.1. Heart failure, BMI and stroke

It is known that obesity can increase the risk of stroke due to inflammation caused by excess fatty tissue. This can lead to difficulty in blood flow and an increased risk of blockage, both of which can cause stroke.[16,17] However, in a recent study, risk of stroke recurrence was not increased in obese stroke patients (BMI > 30) when compared with lean stroke patients (BMI < 25) in a multivariate analysis.[18] In patients with CHF, the most frequently recognized reasons for cardio embolic stroke are thrombus formation due to A Fib or left ventricular (LV) hypokinesia.[19] However, the association between heart failure patients with high or low BMI and stroke is not well characterized and examined well before. Most of studies demonstrated that increased BMI was associated with steady increase in the total risk but not the severity of the stroke. However, some data suggested that BMI might be inversely associated with severity of fatal hemorrhagic stroke.[18] Interestingly, in our study there was significant correlation between heart failure patients with low BMI and CVA/stroke events. So, more complete understanding of this relative correlation needs to be studied well in further researches.

4.2. Female subgroup characteristics

Female patients represented about 22% of our study population with 19% of them having low BMI. This is similar to that reported in recent HF clinical trials as systolic HF is known to be more common in men, and women make up only 28% of subjects.[20,21] This selection extends into studies of the obesity paradox in HF, where women may be as little as 13% of a study population.[22] The mean age of female patients with low BMI (Group IV) was 63.8 ± 7.86 years with 71% having ischemic etiology and EF score of 22.0 ± 53. In comparison with 5539 patients in a European setting, enrolled in a multicenter female-data registry from 2002 to 2012, females in our study had a higher female to male ratio (22% vs. 15.1%), lower non-ischemic etiology (35% vs. 60.2%), and less prevalence of atrial fibrillation (11% vs. 18.7%).[23] In our study, the in house mortality reach up to 5.4%, 30 days re-hospitalization rate is ~13.5%, the mean length of stay (LOS) is 9.6 ± 15.1 days. In comparison, in developed countries, CHF in-hospital mortality rates range from 2% to 7% and reach 20% in patients with kidney failure and low systolic blood pressure (SBP). The 30-day re-hospitalization rate is ~27%, the mean length of stay (LOS) is 6.4 ± 85.2 days, worsening of heart failure symptoms caused ~80% of the admissions, and a LOS of >7 days may predict re-hospitalization, worse prognosis, and high mortality.[24–26]

Safety indicator values might offer important, future benchmarking benefits for CHF-related organizational quality improvement projects. In this study, the highest complication rates were related to combined infection and bleeding incidences (22%), followed by the need for ultrasound-guided abdominal and thoracic drainage (11%) and acute kidney injury suspected to be a secondary complication of ACEI uses (8.1%). Lastly, these were followed by a thrombotic or under-and over-anticoagulation rate of 5.4%, and an implantable device complication rate of 2.7%. Having an insight into the prevalence and impact of such non-cardiac complications is vital, as non-cardiac mortality in CHF patients claims 30% of the total CHF mortality rate. Furthermore, 45% of re-hospitalizations are caused by non-cardiac comorbid conditions.[26,27]

On focusing female subgroup with low BMI, in spite they had shorter length of stay; they had lower EF score, higher ischemic burden, and higher hospital readmission and mortality rates. Regarding to safety indicators, they also showed higher rates of device related complications, CVA, TIA and unexplained syncope. These findings were interesting, as obesity paradox was described in HF patients while gender characteristics are not well discussed and need to be studied in further researches.

4.3. Study limitation

Our study had some limitations. First, the study data are derived from an observational registry; therefore, causality cannot be determined. Second, the number of study population was relatively small as it was a single center study and many patients were lost during the follow-up period and hence excluded. Also, our center is a tertiary center and many patients after providing appropriate diagnosis and management strategies were referred to their primary hospitals, completing their treatment and follow up there, and that limited our patient population. Moreover, the number in the selected female-only subgroup is small due to the nature of the single center study, and the low female gender prevalence of CHF disease. In addition, the study enrolled patients with a reduced ejection fraction of <40%, hence, the results exclude a subgroup of CHF patients having preserved ejection fractions.

5. Conclusion

Heart failure patients with low BMI had high incidence of hospital readmission/mortality and composite rates of CVA/TIA/unexplained syncope. Similarly, low BMI female patients with HF had increased incidence of readmission/mortality and composite rate of CVA/TIA/unexplained syncope in spite of shorter length of stay and lower incidence of total infection and bleeding. This study may open the door for future intra-gender, female-specific outlooks on the male-dominated prevalence of CHF disease. Further evaluation using larger cohorts and longitudinal studies is recommended.

Conflict of interest

The authors declare that there is no conflict of interest.

References

1. van Dis I, Kromhout D, Geleijnse JM, Boer JM, Verschuren WM. Body mass index and waist circumference predict both 10-year nonfatal and fatal cardiovascular disease risk: study conducted in 20,000 Dutch men and women aged 20–65 years. *Eur J Cardiovasc Prev Rehabil.* 2009;16:729–734.
2. Clark AL, Chyu J, Horwich TB. The obesity paradox in men versus women with systolic heart failure. *Am J Cardiol.* 2012;110:77–82.
3. Lavie Carl J et al.. Impact of obesity and the obesity paradox on prevalence and prognosis in heart failure. *JACC Heart Fail.* 2013;93–102.
4. Horwich TB, Fonarow GC, Hamilton MA. The relationship between obesity and mortality in patients with heart failure. *J Am Coll Cardiol.* 2001;38:789–795.
5. Parissis JT, Mantziari L, Kaldoglou N, Ikonomidis I, Nikolaou M, Mebazaa A, et al.. Gender-related differences in patients with acute heart failure: management and predictors of in-hospital mortality. *Int J Cardiol.* 2013;168:185–189.
6. Myftiu S, Sulo E, Burazeri G, Sharka I, Shkoza A, Sulo G. A higher burden of metabolic risk factors and underutilization of therapy among women compared to men might influence a poorer prognosis: a study among acute myocardial patients in Albania, a transitional country in Southeastern Europe. *Croatian Medical Journal.* 2015;56:542–549.
7. Stein GY, Ben-Gal T, Kremer A, Bental T, Alon D, Korenfeld R, et al.. Gender-related differences in hospitalized heart failure patients. *Eur J Heart Fail.* 2013;15:734–741.

8. Vest AR, Wu Y, Hachamovitch R, Young JB, Cho L. The heart failure overweight/obesity survival paradox: the missing sex link. *JACC Heart Fail*. 2015;3:917–926.
9. Peterson PN, Rumsfeld JS, Liang L, Albert NM, Hernandez AF, Peterson ED, et al.. A validated risk score for in-hospital mortality in patients with heart failure from the American Heart Association get with the guidelines program. *Circ Cardiovasc Qual Outcomes*. 2010;3:25–32.
10. Keenan PS, Normand S-LT, Lin Z, Drye EE, Bhat KR, Ross JS, et al.. An administrative claims measure suitable for profiling hospital performance on the basis of 30-day all-cause readmission rates among patients with heart failure. *Circ Cardiovasc Qual Outcomes*. 2008;1:29–37.
11. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, et al.. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the task force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur J Heart Fail*. 2008;10:933–939.
12. Davos CH, Doehner W, Rauchhaus M, Cicoira M, Francis DP, Coats AJ, et al.. Body mass and survival in patients with chronic heart failure without cachexia: the importance of obesity. *J Card Fail*. 2003;9:29–35.
13. Clark AL, Fonarow GC, Horwich TB. Impact of cardiorespiratory fitness on the obesity paradox in patients with systolic heart failure. *Am J Cardiol*. 2015;115:209–213.
14. Sharma A, Lavie CJ, Borer JS, et al.. Meta-analysis of the relation of body mass index to all-cause and cardiovascular mortality and hospitalization in patients with chronic heart failure. *Am J Cardiol*. 2015;115:1428–1434.
15. Clark AL, Fonarow GC, Horwich TB. Obesity and obesity paradox in heart failure. *Prog Cardiovasc Dis*. 2014;56:409–414.
16. Sriram K, Benkovic SA, Miller DB, O'Callaghan JP. Obesity exacerbates chemically induced neurodegeneration. *Neuroscience*. 2002;115:1335–1346.
17. Daniels et al.. American Heart Association childhood obesity research summit report. *Circulation*. 2009;119:e489–e517.
18. Ovbiagele B, Bath PM, Cotton D, Vinisko R, Diener H-C. Obesity and recurrent vascular event after recent ischemic stroke. *Stroke*. 2011;42:3397–3402.
19. Pullicino PM, Halperin JL, Thompson JL. Stroke in patients with heart failure and reduced left ventricular ejection fraction. *Neurology*. 2000;54:288–294.
20. Lloyd-Jones D, Adams RJ, Brown TM, Carnethon M, Dai S, De Simone G, et al.. Heart disease and stroke statistics–2010 update: a report from the American Heart Association. *Circulation*. 2010;121:e46–e215.
21. Hsich EM, Pina IL. Heart failure in women: a need for prospective data. *J Am Coll Cardiol*. 2009;54:491–498.
22. Hall JA, French TK, Rasmusson KD, Vesty JC, Roberts CA, Rimmasch HL, et al.. The paradox of obesity in patients with heart failure. *J Am Acad Nurse Pract*. 2005;17:542–546.
23. Providência R, Marijon E, Lambiase PD, Bouzeman A, Defaye P, Klug D, et al.. Primary prevention Implantable Cardioverter Defibrillator (ICD) Therapy in women-data from a multicenter French registry. *J Am Heart Assoc*. 2016;5:1–2.
24. Gheorghiade M, Pang PS. Acute heart failure syndromes. *J Am Coll Cardiol*. 2009;53:557–573.
25. Jencks SF, Williams MV, Coleman EA. Rehospitalizations among patients in the Medicare fee-for-service program. *N Engl J Med*. 2009;360:1418–1428.
26. Zaya M, Phan A, Schwarz ER. Predictors of re-hospitalization in patients with chronic heart failure. *World J Cardiol*. 2012;4:23.
27. Wakabayashi K, Sato N, Kajimoto K, Minami Y, Mizuno M, Keida T, et al.. Incidence and predictors of in-hospital non-cardiac death in patients with acute heart failure. *Eur Heart J Acute Cardiovasc Care*. 2015.