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ORIGINAL REPORT

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DIFFUSE IDIOPATHIC SKELETAL HYPEROSTOSIS IN SUBJECTS WITH CONGESTIVE HEART FAILURE UNDERGOING CARDIAC REHABILITATION: A DECISION TREE ANALYSIS

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Objective: **To assess the prevalence of diffuse idiopathic skeletal hyperostosis and its relationship with vascular risk factors among patients with congestive heart failure.**

Design: **Population-based cross-sectional study.**

Participants: **A total of 584 consecutive patients admitted to a Rehabilitative Cardiology Unit.**

Methods: **Chi-square Automatic Interaction Detector (CHAID) decision tree analysis was used to build a predictive model.**

Results: **The mean age (standard deviation) of the study population was 68.1 years (standard deviation 12.3), and 77.7% of the subjects were men. The overall prevalence of diffuse idiopathic skeletal hyperostosis in the cohort was 49.8%. Logistic regression analysis showed that age was a predictor of diffuse idiopathic skeletal hyperostosis (odds ratio 1.034; 95% confidence interval: 1.021–1.047, $p<0.001$), with increasing odds ratios for increasing age tertiles. The CHAID prediction model identified 2 age "buckets": ≤69 and >69 years. Patients >69 years had a diffuse idiopathic skeletal hyperostosis prevalence of 60.1%, compared with 39.2% among those ≤69 years. Notably, body mass index was a predictor of diffuse idiopathic skeletal hyperostosis in this younger subset of patients ($p=0.028$), with 2 body mass index buckets, ≤23.3 and >23.3 kg/m^2, the latter showing more than twice the prevalence of diffuse idiopathic skeletal hyperostosis (43.2% vs 20%).**

Conclusion: **Diffuse idiopathic skeletal hyperostosis is extremely frequent among patients with congestive heart failure, with age and body mass index being the strongest predictors.**

Key words: diffuse idiopathic skeletal hyperostosis; spine; congestive heart failure; disability; rehabilitation; exercise; chi-square automatic interaction detector.

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LAY ABSTRACT

Diffuse idiopathic skeletal hyperostosis (also known as Forestier's disease) is a systemic condition with a wide spectrum of clinical manifestations. Patients with diffuse idiopathic skeletal hyperostosis often experience pain, stiffness, loss of range of motion, and even difficulty breathing or swallowing. As a consequence, the presence of such disabling symptoms may interfere with activities of daily living and significantly reduce perceived quality of life. Moreover, the ankylosed spine in patients with diffuse idiopathic skeletal hyperostosis is prone to unstable fractures, thus exposing patients to a considerable risk of secondary spinal cord injury. This study found an exceptionally high prevalence of diffuse idiopathic skeletal hyperostosis among patients with congestive heart failure who were undergoing cardiac rehabilitation, particularly in obese and older individuals. Given the risk of spinal fractures, even after low impact trauma, and of severe disability, the presence of diffuse idiopathic skeletal hyperostosis should always be investigated in patients with congestive heart failure who report stiffness of the spine or chronic back pain, especially in those undergoing exercise-based activities.

Diffuse idiopathic skeletal hyperostosis (DISH) is a common, but often unrecognized, systemic disorder, observed mainly in elderly people. DISH is characterized by calcification and ossification of entheseal sites, especially in the axial skeleton, but also in peripheral joints (1). A diagnosis of DISH is made when large bridging osteophytes in at least 4 adjacent thoracic vertebrae are present on conventional radiographs (2).

Despite these significant structural changes, DISH can be an asymptomatic condition. Thus DISH has been poorly investigated and its clinical relevance has been acknowledged only in recent years (3). DISH can produce incarceration syndromes, spinal immobility, radiculopathy and myelopathy, with the possibility of para- and tetraparesis, dysphagia and dysphonia, rhinolalia by irritation of the recurrent laryngeal nerve, reduced lung capacity and airway obstruction (4). Furthermore, individuals with DISH have a significantly higher risk of spinal fractures after low impact trauma compared with individuals with a non-ankylotic spine (5). Thus, although DISH is often asymptomatic, its high prevalence in the general population, and the possibility of severe and disabling complications, justify the increasing interest in this condition in recent years.

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Research into the mechanisms that contribute to new bone growth in patients with DISH (6, 7) reports a strong association with individual components of the metabolic syndrome (e.g. diabetes mellitus, obesity, hypercholesterolaemia) (8) and an increased risk of cardiovascular comorbidity (9). In keeping with this, a prevalence of DISH of 30.3% has been reported recently among patients with severe atherosclerotic cardiovascular diseases (CVDs) (10), with an even higher prevalence (42.2%) in a small subgroup of patients diagnosed with congestive heart failure (CHF) (10).

To better address this issue, this study evaluated the prevalence of such potentially disabling condition in a larger cohort of subjects diagnosed with CHF who were undergoing exercise-based cardiac rehabilitation. Moreover, this study used decision tree analysis to build a predictive model for development of DISH in this clinical setting.

MATERIAL AND METHODS

Study design

This is a single-centre, population-based, observational study.

Setting and participants

From July 2016 to January 2019, 608 consecutive patients diagnosed with CHF admitted to the heart disease rehabilitation programme in our Rehabilitative Cardiology Unit were screened for enrollment in the study. The protocol was approved by the Institutional Review Board of ICS Maugeri – Institute of Cassano Murge, Bari, Italy on April 13, 2016.

Inclusion and exclusion criteria

The target study population consisted of inhospital patients of either sex and any race, with a known diagnosis of CHF (International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes 428.0, 428.1 and 428.9). Exclusion criteria were: any clinical condition that could alter the radiographic aspect of the spine: e.g. ankylosing spondylitis or any seronegative spondyloarthritis; rheumatic diseases; severe spine deformities; previous vertebral fractures; active metastatic cancer.

Variables and measurements

At admission, all patients underwent a complete cardiological examination by a trained staff member. The following information was collected from the whole population: sex, age, New York Heart Association (NYHA) class, ejection fraction, personal history of ischaemic heart disease, atrial fibrillation, chronic obstructive pulmonary disease (COPD), liver disease, thyroid disease, and cancer. Subsequently, all patients underwent measurements of systolic and diastolic blood pressure, weight, height, and body mass index (BMI) calculation. Blood samples were also collected to evaluate total cholesterol, high-density lipoprotein cholesterol (HDLc), serum fasting glucose, creatinin, and b-type natriuretic peptide (BNP) levels. According to validated criteria (11), hypercholesterolaemia with low HDLc was defined as total cholesterol $\geq$200 mg/dl with HDLc $\leq$40 mg/dl for men and $\leq$50 mg/dl for women, hypertension as blood pressure $\geq$130/85 mmHg, impaired fasting glucose as a fasting glucose level $\leq$100 mg/dl, and obesity as BMI values $\geq$30 kg/m^2. The presence of end-stage renal disease (ESRD) was defined as an estimated glomerular filtration rate (eGFR) $\leq$15 ml/min (12).

Chest radiographs were performed for formal assessment of thoracic diseases. Images were acquired with computed radiography equipment (Prestige SI, GE Healthcare, Little Chalfont, United Kingdom) using a standardized technique (125 kV with 2 lateral fields; 200-cm focus-to-film distance). Images were examined by a radiologist and a rheumatologist, both blinded to rheumatological and metabolic evaluations. DISH was established when the radiological criteria of Resnick & Niwayama were fulfilled on the posteroanterior or lateral view or both (2). These criteria require the involvement of at least 4 contiguous thoracic vertebral segments, preservation of intervertebral disc spaces, and the absence of apophyseal joint degeneration or sacroiliac inflammatory changes. Individuals with inconclusive radiographs were scored as non-DISH subjects.

Statistical analysis

Statistical analysis was performed with the IBM SPSS 25 system (SPSS Inc., Chicago, IL, USA). Continuous data are expressed as mean (standard deviation; SD), whilst categorical data are expressed as percentage. Preliminarily, the *t*-test was performed to compare continuous variables, while the χ^2 test was employed to analyse categorical data (using the Montecarlo approach to compute the *p*-values in order to cope with small sample size).

In order to evaluate the impact of different covariates on the evaluated outcome and calculate the odds ratio (OR) for the presence of DISH, a multivariate logistic regression analysis (stepwise method) was adopted, with the presence of DISH as the dependent variable and the following demographic (age, male sex) and clinical covariates related to disease severity and aetiology (NYHA class, BNP levels, ejection fraction, ischaemic CHF aetiology), presence of traditional vascular risk factors (obesity, hypertension, hypercholesterolaemia, diabetes), and comorbidities (cancer, ESRD, liver disease, thyroid disease, COPD, atrial fibrillation) as independent variables. A supplementary logistic regression analysis was performed, also including continuous data (age, BMI, ejection fraction, and BNP levels) categorized into tertiles as independent variables to account for possible marginal non-linearity. Finally, in order to identify possible variable interactions at different levels, a Chi-square Automatic Interaction Detector (CHAID) classification and regression tree was fitted onto the sample using a hierarchical approach (13, 14). The significance level for node splitting in the CHAID model was $p<0.05$.

The area under the curve of receiver operating characteristic (AUC-ROC) was estimated in order to quantify the discriminating ability of both CHAID and logistic regression methods.

All the results are shown as 2-tailed with the confidence interval for statistical significance set at 95% (95% CI).

RESULTS

Among the 608 patients evaluated, 24 were excluded (18 vertebral fractures, 6 diagnosed with rheumatic or spine diseases other than DISH). Therefore, 584

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Table I. Demographic and clinical features of the study population and stratification according to diffuse idiopathic skeletal hyperostosis (DISH) and non-DISH criteria achievement

	Overall 584	DISH 291 (49.8%)	No-DISH 293 (50.2%)	*p*-value
Age, years, mean (SD)	68.1 (12.3)	70.5 (11.0)	65.6 (13.0)	**< 0.001**
Male, sex, *n* (%)	454 (77.7)	225 (49.6)	229 (50.4)	0.443
Ischaemic CHF aetiology, *n* (%)	283 (48.5)	145 (51.2)	138 (48.8)	0.282
NYHA class, mean (SD	3.4 (0.6)	3.4 (0.6)	3.4 (0.6)	0.349
BNP (pg/ml), mean (SD	6,111.7 (8,957.5)	5,666.1 (7,796.8)	6,560.4 (9,984.5)	0.228
Ejection fraction, %, mean (SD	30.1 (11.4)	31.4 (11.5)	28.8 (11.2)	**0.006**
Obesity, mean (SD)	153 (26.7)	73 (26)	80 (27.5)	0.377
Height, cm	162.8 (9.0)	162.5 (8.6)	163.0 (9.4)	0.508
Weight, kg	75.0 (16.6)	76.0 (16.0)	74.0 (17.2)	0.172
BMI, kg/m^2	27.9 (5.7)	28.2 (5.5)	27.5 (5.8)	0.112
Hypertension, *n* (%)	335 (57.4)	178 (61.2)	157 (53.6)	**0.038**
Hypercholesterolaemia, *n* (%)	72 (12.4)	36 (12.4)	36 (12.4)	0.544
Diabetes mellitus/IFG, *n* (%)	203 (34.8)	101 (37.8)	93 (31.7)	0.073
COPD, *n* (%)	166 (28.4)	95 (32.6)	71 (24.2)	**0.015**
Atrial fibrillation, *n* (%)	214 (37.7)	118 (41.7)	96 (33.7)	**0.030**

DISH: diffuse idiopathic skeletal hyperostosis; CHF: congestive heart failure; NYHA: New York Heart Association; BNP: b-type natriuretic peptide; BMI: body mass index; IFG: impaired fasting glucose; COPD: chronic obstructive pulmonary disease. Continuous variables with normal distribution are presented as mean (standard deviation; SD). Significant values are shown in bold.

subjects entered the study. Clinical and demographic features of the study population are shown in Table I.

The mean (SD) age of the study population was 68.1 years (SD 12.3), and 77.7% of the subjects were men. The overall prevalence of DISH in the cohort was 49.8%. Patients with DISH showed an older age, an increased prevalence of hypertension, COPD, and atrial fibrillation, and a significantly higher ejection fraction. However, after adjusting for all the other clinical and demographic variables by means of multivariate analyses, only age was an independent predictor of the presence of DISH (OR 1.034; 95% CI 1.021–1.047, $p<0.001$). It is notable that a second logistic regression analysis, also including continuous data categorized into tertiles, showed that both age and BMI impacted significantly on the presence of DISH. The risk of development of DISH according to increasing tertiles of age and BMI is shown in Fig. 1.

Accordingly, CHAID analysis identified 2 variables significantly affecting the presence of DISH: age and BMI. The other variables did not reach significance, thus only age and BMI were used to build the CHAID decision tree. The model included a total of 5 nodes, with 3 terminal nodes (numbers 2, 3 and 4). In detail, 2 age "buckets" were identified: ≤69 years (node 1), with a DISH prevalence of 39.2%, and >69 years (node 2), in which DISH diagnostic criteria were achieved by 60.1% of subjects. Of interest, BMI was significantly correlated with the presence of DISH in the younger subset of patients ($p=0.028$), since 2 BMI buckets were identified, ≤23.3 kg/m^2 (node 3) and >23.3 kg/m^2 (node 4), the latter showing more than twice the rate of DISH prevalence (43.2% vs 20%) (Fig. 2).

Using a default 50% classification threshold, the overall estimated accuracy was 60.4% for the CHAID model and 62.8% for the logistic regression model.

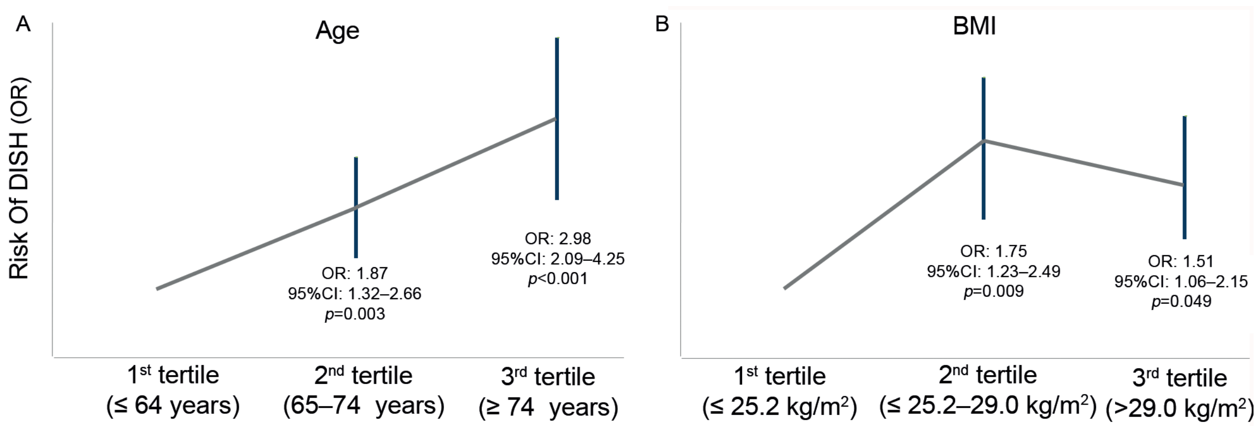

Fig. 1. Risk of development of diffuse idiopathic skeletal hyperostosis (DISH) according to increasing tertiles of (A) age and (B) body mass index (BMI). OR: odds ratio; 95% CI: 95% confidence interval; BMI: body mass index.

When the 2 models were compared they were found to be statistically equivalent in terms of predictive power, since similar AUC-ROC with similar confidence intervals were found (Fig. 3).

DISCUSSION

To our knowledge, this is the first population-based study specifically designed to report on the prevalence of DISH in patients with CHF who are undergoing cardiac rehabilitation. In addition, it is the first time that the CHAID decision tree analysis has been used to identify potential risk factors for the presence of DISH. The study documented a 49.8% overall prevalence of DISH in patients with CHF. This prevalence is higher than that reported in other clinical settings (15–17), but it is in line with the results of a previous study, showing a prevalence of DISH of 30.3% in subjects with severe atherosclerotic CVDs and a prevalence of 42.2% in the small subgroup of patients with CHF (n=45) (10). One of the largest population-based studies on DISH documented a prevalence of only 25% in men and 15% in women (15). Thus, our group previously reported a similar prevalence (15.1%) in 93 Italian women (17). In contrast, only 3.8% of men and 2.6% of women achieved DISH diagnostic criteria in the Finnish general population (18). These apparently contrasting results are probably due to the different populations evaluated in each study, and it can be hypothesized that the cardiometabolic status of the patients enrolled in our study may account for the ≈50% reported prevalence of DISH. The association of DISH with metabolic syndrome and its individual components (e.g. diabetes mellitus, obesity, hypertension) has been documented previously (7–9). Increasing evidence is emerging about the presence of a common pathogenic substrate for metabolic syndrome-associated disorders (including atherosclerosis) and the process of new bone formation in patients with DISH (6, 10, 19). In fact, approximately half of the patients in the current study had a history of ischaemic cardiovascular events, with a high prevalence of hypertension (57.4%) and diabetes mellitus (34.8%) and a mean BMI of 27.9 kg/m^2.

However, most individual components of metabolic syndrome did not impact on the prevalence of DISH in our study, nor did the aetiology or disease severity of CHF (NYHA class, BNP levels, ejection fraction). In addition, the high prevalence of traditional cardiovascular risk factors, one of the main differences between our study population and those of previous studies reporting lower percentages of DISH is older age. Our patients had a mean age of 68.1 years, and the results of our multivariate analyses consistently confirmed the impact of age on the presence of DISH, with an

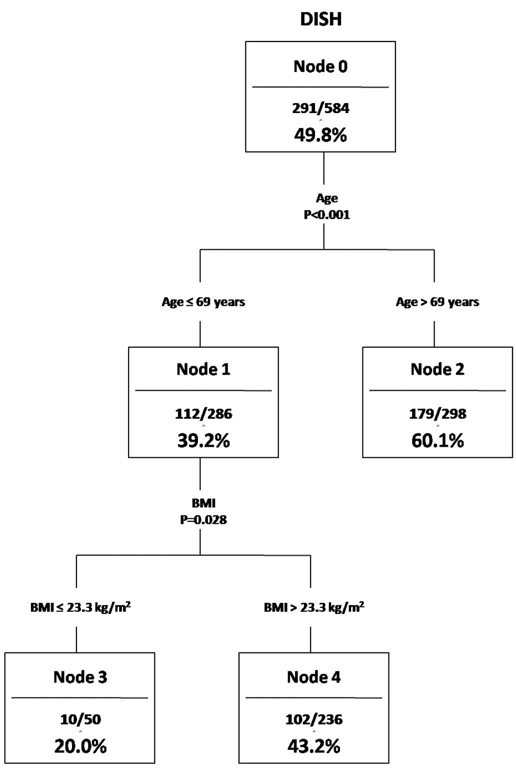

Fig. 2. Prevalence of diffuse idiopathic skeletal hyperostosis (DISH) among 584 patients with congestive heart failure (CHF): a CHAID (Chi-square Automatic Interaction Detector) classification tree. The tree shows the impact of age and body mass index (BMI) on the prevalence of DISH by splitting the original sample according to these variables and corresponding thresholds (nodes).

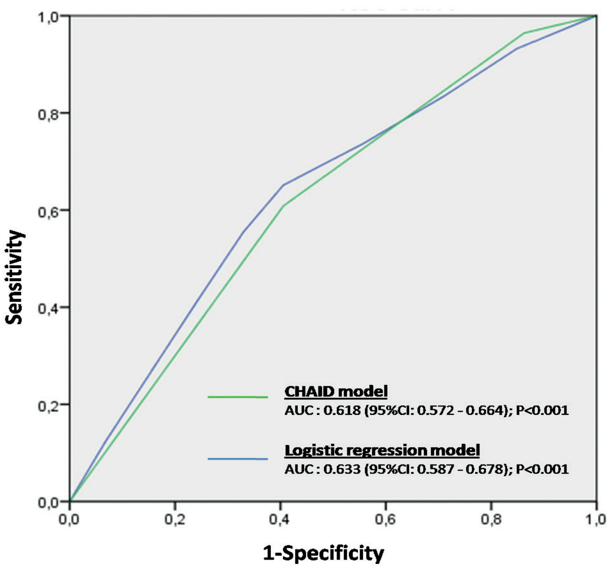

Fig. 3. Receiver operating characteristic (ROC) curves of CHAID (Chi-square Automatic Interaction Detector) model and logistic regression model for prediction of the presence of diffuse idiopathic skeletal hyperostosis (DISH) in patients with congestive heart failure. AUC: area under the curve; 95% CI: 95% confidence interval.

increasing OR for increasing age tertiles. The other variable significantly impacting on the prevalence of DISH was BMI. The role of age and BMI as predictors of DISH was better described by CHAID decision tree analysis. CHAID is a frequently used data-mining approach, which has been developed as a useful tool for epidemiological investigations. Compared with conventional logistic regression analysis, CHAID reveals possible partitions of the data-set, by using the predictor that, at that precise stage, most significantly explains the outcome. In the current study, the CHAID prediction model identified 2 age buckets: ≤69 and >69 years. Patients >69 years had a prevalence of DISH of 60.1%, compared with a prevalence of 39.2% among those ≤69 years. It is notable that, in this younger subset of patients, BMI was the only predictor of the presence of DISH, since 2 BMI buckets were identified, ≤23.3 and >23.3 kg/m^2, the latter showing more than twice the rate of prevalence of DISH (43.2% vs 20%).

Although this predictive model showed only moderate accuracy, it substantially confirmed the results of logistic regression analysis. Overall, these findings suggest that age and BMI are the strongest predictors of the presence of DISH among patients with established cardiovascular disorders, in line with our previous report on a different subset of patients (10). While ageing is inevitable, body weight is a modifiable risk factor, in which both patients and clinicians may intervene. In our study population, a BMI ≤23.3 kg/m^2 was associated with significantly lower percentages of DISH among younger patients with CHF. Whether a BMI lower than this cut-off value could also be a reasonable "target" in other clinical settings is unknown. Moreover, it is not known whether a reduction in body weight could be able to slow down, stop or even reverse the progression of DISH. Overall, our results suggest the need for larger population-based studies with appropriate prediction models to better address these issues, also taking into account that no comparable study has been found in current literature that could be used as a "benchmark" for predictive accuracy.

Despite these unresolved queries, the results of this study may have some relevant clinical implications. DISH is a systemic condition with a wide spectrum of clinical manifestations, ranging from complete absence of symptoms to severe disability (6). Patients with DISH often report pain, stiffness, loss of range of motion, and even difficulty breathing or swallowing (9). Involvement of the axial skeleton, with postural abnormalities and severe limitations of spinal mobility, may be such as to be differentiated from the manifestations of ankylosing spondylitis (20, 21). As a consequence, the presence of such disabling symptoms may interfere with activities of daily living and significantly reduce the patient's perceived quality of life (22). Moreover, it is well known that the ankylosed spine in patients with DISH is prone to unstable fractures due to long lever arms and consecutive stress concentration (23), thus exposing patients to a considerable risk of secondary spinal cord injury (24, 25) and increased mortality (26). A recent multicentre study on 285 patients with DISH showed that trivial trauma accounts for 77.2% of spinal fractures in this clinical setting, with delayed diagnosis being significantly associated with neurological deterioration and subsequent disability (27). Our population-based study was conducted in a rehabilitation centre, where subjects with CHF underwent a comprehensive intervention, based on a thorough patient assessment followed by patient-tailored therapies, which include, but are not limited to, exercise training, education, and behaviour changes. However, exercise remains the cornerstone of a rehabilitation programme for patients with heart disease (28–32). The results of the current study showed an exceptionally high prevalence of DISH among patients with CHF undergoing a programme of in-hospital rehabilitation, particularly in obese and older individuals. Given the risk of spinal fractures even after low impact trauma and of severe disability, we believe that the presence of DISH should always be investigated in patients with CHF who report spine stiffness or chronic back pain, especially in those undergoing exercise-based activities. Thus, more tailored rehabilitation programmes should be administered to patients with CHF with concomitant symptoms or a diagnosis of DISH. In this regard, physiatrists might be particularly suited to take a leadership role in the design phase of a cardiac rehabilitation programme for patients with such comorbidity, since cardiologists may have limited experience of the needs of physically disabled patients. Thus, a strict collaboration between cardiologists and physiatrists could be exhorted in order to identify the best rehabilitative approach for patients with CHF and concomitant DISH.

The translational relevance of our results can be better understood if we consider that different subsets of patients undergoing other forms of exercise-based rehabilitation (e.g. rheumatological, orthopaedic, pulmonary, neurological) often have several comorbidities (33–35), including an increased cardiovascular risk (36–38). Thus, the presence of DISH may represent a concern, not only for cardiologists, but also for other health professionals working in the field of rehabilitation. Further, population-based, studies with appropriate prediction models are needed in order to assess the prevalence of DISH in different settings and the impact that this condition may have on the effectiveness of rehabilitation programmes.

Study limitations

This study has a number of limitations. First, no healthy control group was enrolled, and an observational analysis of the setting was performed. Overall, characteristics of our study population reflect the heterogeneity of the population that is referred to a cardiac rehabilitative programme.

Secondly, although no significant association was found between the ischaemic CHF aetiology and the presence of DISH, we are aware that other aetiologies (valvular, arrhythmic, etc.) accounted for the remaining 51.5% of patients with CHF in our study population. Unfortunately, no information about the isolated prevalence of each non-ischaemic condition related to insurgence of CHF was recorded in our database. Thus, we could not assess the impact of the different non-ischaemic aetiologies on the evaluated outcome.

A further consideration is the ≈60% estimated accuracy of our predictive models. Although the accuracy of both CHAID and logistic regression may appear to be low, 2 main aspects should be taken into account. First, more sophisticated models (e.g. machine-learning models) could be tested, but a much larger sample size would be necessary. This would eventually allow us to assess the predictive performance of the presented models on a separate validation set. Secondly, the residual variability of our models could be due to predictors that have not been considered in this study (e.g. hypertriglyceridaemia, presence/absence of metabolic syndrome). However, to the best of our knowledge, no study is currently available in the existing literature reporting on the predictive ability of estimating the risk of DISH in this specific clinical setting. Therefore, our study would serve as an initial "benchmark" for future research.

Conclusion

The results of this study consistently show that DISH is extremely frequent among patients with CHF, and that age and BMI are the strongest predictors of the presence of DISH in this clinical setting. Given the risk of spinal fractures and the presence of DISH-related disabling symptoms, a strict collaboration between cardiologists and physiatrists should be exhorted in order to identify the best rehabilitative approach for patients with such comorbidity. Larger controlled studies are needed to delineate the entire spectrum of this condition in patients with cardiovascular diseases.

Authors' contribution. Ambrosino P and Pappone N conceived and designed the study, performed statistical analysis, interpreted results and drafted the manuscript. Scrutinio D, De Campi M, Miniero E, Formisano R and Iannuzzi GL acquired clinical data and drafted the manuscript. Spedicato GA performed statistical analyses and critical revisions. All Authors read and approved the final version of the manuscript. Pappone N had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of data analysis.

The authors have no conflicts of interest to declare.

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