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Cluster analysis of heart failure patients based on their psychological and physical symptoms and predictive analysis of cluster membership

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Abstract

Aim: Patients with heart failure experience multiple co-occurring symptoms that lower their quality of life and increase hospitalization and mortality rates. So far, no heart failure symptom cluster study recruited patients from community settings or focused on symptoms predicting most clinical outcomes. Considering physical and psychological symptoms together allows understanding how they burden patients in different combinations. Moreover, studies predicting symptom cluster membership using variables other than symptoms are lacking. We aimed to (a) cluster heart failure patients based on physical and psychological symptoms and (b) predict symptom cluster membership using sociodemographic/clinical variables.

Design: Secondary analysis of MOTIVATE-HF trial, which recruited 510 heart failure patients from a hospital, an outpatient and a community setting in Italy.

Methods: Cluster analysis was performed based on the two scores of the Hospital Anxiety-Depression scale and two scores of the Heart-Failure Somatic Perception Scale predicting most clinical outcomes. ANOVA and chi-square test were used to compare patients' characteristics among clusters. For the predictive analysis, we split the data into a training set and a test set and trained three classification models on the former to predict patients' symptom cluster membership based on 11 clinical/sociodemographic variables. Permutation analysis investigated which variables best predicted cluster membership.

Results: Four clusters were identified based on the intensity and combination of psychological and physical symptoms: mixed distress (high psychological, low physical symptoms), high distress, low distress and moderate distress. Clinical and sociodemographic differences were found among clusters. NYHA-class (New York Heart Association) and sleep quality were the most important variables in predicting symptom cluster membership.

Conclusions: These results can support the development of tailored symptom management intervention and the investigation of symptom clusters' effect on patient

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outcomes. The promising results of the predictive analysis suggest that such benefits may be obtained even when direct access to symptoms-related data is absent.

Implications: These results may be particularly useful to clinicians, patients and researchers because they highlight the importance of addressing clusters of symptoms, instead of individual symptoms, to facilitate symptom detection and management. Knowing which variables best predict symptom cluster membership can allow to obtain such benefits even when direct access to symptoms-data is absent.

Impact: Four clusters of heart failure patients characterized by different intensity and combination of psychological and physical symptoms were identified. NYHA class and sleep quality appeared important variables in predicting symptom cluster membership.

Reporting Method: The authors have adhered to the EQUATOR guidelines STROBE to report observational cross-sectional studies.

Patient or Public Contribution: Patients were included only for collecting their data.

KEYWORDS

cluster analysis, heart failure, machine learning, symptom

1 | INTRODUCTION

Heart failure (HF) is a global clinical syndrome affecting 1%–2% of the adult population in developed countries (Ponikowski et al., 2016) and 26 million people worldwide (Sethares & Chin, 2021). Despite improvements in prevention, diagnosis and treatments, outcomes in HF patients remain poor (Bekelman et al., 2009). Indeed, HF patients experience multiple physical symptoms, such as dyspnoea and oedema (Jeon & Redeker, 2016; McDonagh et al., 2021), which contribute to lowered quality of life (Heo et al., 2020; Mozaffarian et al., 2016), high hospitalization (McDonagh et al., 2021) and mortality rates (Benjamin et al., 2019; Gathright et al., 2017). Even after heart transplantation or implantation of ventricular assist devices, HF symptoms often persist (Casida & Parker, 2012; Kugler et al., 2011). In addition, HF patients often experience psychological symptoms such as anxiety and depression, (DeVon et al., 2017) which can intensify the perception of physical symptoms (Vongmany et al., 2016). Ultimately, HF patients report levels of symptom burden as high as patients with advanced malignancies (Bekelman et al., 2009; Solano et al., 2006), which often increase as the disease progresses (Walke et al., 2007).

Symptoms are defined as 'subjective physical or mental experiences, appraised and defined by the patient, and reflective of an altered health state or change therein' (p. 209) (Barbara Riegel et al., 2019). In HF, multiple physical and psychological often occur simultaneously, (Lee et al., 2014; Moser et al., 2014; Sethares & Chin, 2021) and their co-existence in clusters may increase the perceived severity of each symptom (Song et al., 2010). A symptom cluster consists of two or more co-occurring symptoms, (Miaskowski et al., 2007) and increasing evidence suggests that symptom clusters may be more predictive of clinical outcomes than single symptoms (Ferreira et al., 2008; Moser et al., 2014). Identifying symptom clusters could allow healthcare professionals and advanced nurses to better understand the symptom experience of HF patients (Moser et al., 2014) and deliver tailored assistance. Second, it could make HF patients aware of symptom clusters, recognize impending exacerbations, (Song et al., 2010) and adopt timely symptom management strategies (Jurgens et al., 2009b). Third, it could foster future investigations assessing the effect of symptom clusters on patient outcomes (Miaskowski et al., 2004).

1.1 | Background

Most studies performing cluster analysis, also within HF research, tended to cluster symptoms (Hu et al., 2021; Jurgens et al., 2009b; Moser et al., 2014; Salyer et al., 2019; Sethares & Chin, 2021; Song et al., 2010) (i.e. different symptoms occurring together forming a cluster, e.g. gastrointestinal cluster, fatigue cluster), instead of patients based on different levels of the same subset of symptoms (i.e. different distributions of the same number/type of symptoms forming different clusters, e.g. high physical-low psychological symptoms cluster; low physical-high psychological symptoms cluster). The first approach, clustering symptoms, allows understanding how symptoms are grouped into mutually exclusive clusters, while the second one, clustering patients based on their symptoms, allows understanding how the same symptoms are differently distributed in a population and how burdensome they are in different combinations.

Some studies (Denfeld et al., 2020; Hertzog et al., 2010; Huang et al., 2018; Lee et al., 2014; Park et al., 2019) clustered HF patients based on their symptoms: Some of them only considered physical

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symptoms, (Huang et al., 2018; Sethares & Chin, 2021) while others also included psychological ones (Denfeld et al., 2020; Lee et al., 2014; Park et al., 2019). However, the existing studies that included both physical and psychological symptoms had some limitations. First, few of them adopted the HF Somatic Perception Scale (HFSPS) (Jurgens et al., 2017) to assess physical symptoms, as many adopted the Kansas City Cardiomyopathy Questionnaire (Green et al., 2000) or the Minnesota Living with HF Questionnaire (Rector & Cohn, 1992). Compared to the HFSPS, the other two only include a narrow set of symptoms as they are not specifically intended to solely measure HF physical symptoms. Second, previous cluster analyses of HF-symptoms recruited patients from either hospital wards or outpatients, but not from community settings, which could have allowed a broader generalization of results. Third, previous studies have rarely given equal weight to physical and psychological symptoms when identifying the clusters.

Previous research showed that symptom clusters are associated with specific clinical and sociodemographic characteristics. For instance, higher psychological distress is associated with lower quality of life and younger age (Lee et al., 2010; Zambroski et al., 2005); higher physical distress is associated with NYHA class III-IV and female gender (Lee et al., 2010). Other authors also found symptom severity to be associated with other variables such as mutuality levels (Zhou et al., 2022) and sleep quality (Conley et al., 2023; He & Pan, 2022). Specific symptom data may not always be collected, contrary to other sociodemographic or basic clinical information such as NYHA-class. In cases where no data on symptoms are available, but other clinical and sociodemographic information is collected, it may be helpful to understand how the latter could still be used to predict symptom cluster membership. Indeed, this could facilitate addressing symptoms even when direct access to patients' symptoms is impossible.

1.2 | The study

In this study, we aimed to (a) cluster HF patients based on their psychological and physical symptoms; and (b) predict cluster membership using variables other than symptoms.

2 | METHODS

2.1 | Design, study setting and sampling

This is a cross-sectional secondary analysis of baseline data from the MOTIVATE-HF RCT, (Vellone et al., 2020) which aimed to improve self-care in HF patients through motivational interviewing. Adult patients ($n = 510$) were recruited from three Italian healthcare centres (hospital, outpatient, community). Inclusion criteria were a HF diagnosis with NYHA class II-III-IV; poor self-care (scored 0–2 on ≥2 items of the Self-Care of HF Index v.6.2) (Vellone et al., 2013); willingness to participate in the study and sign the informed consent form. Exclusion criteria were severe cognitive impairment (scored 0–4 on the Six-item Screener [Callahan et al., 2002]), myocardial infarction in the previous 3 months; living in residential facilities.

2.2 | Data collection and data sources

After the study protocol (Vellone et al., 2017) received ethical approval, patients were recruited. Research assistants screened them with the SCHFI v.6.2 and the Six-item Screener. If meeting the inclusion criteria and willing to sign the informed consent form, patients were provided with the questionnaires to complete.

To identify the clusters, the HF Somatic Perception Scale (HFSPS) and the Hospital Anxiety and Depression Scale (HADS) were used. Both scales have been validated in an Italian population (Iani et al., 2014; Pucciarelli et al., 2019). The HFSPS (Jurgens et al., 2017) is a valid and reliable instrument measuring HF physical symptom burden and consisting of 18 items grouped into four dimensions: chest discomfort, dyspnoea, early and subtle, oedema. Each item can be rated from 0 to 5. Higher scores indicate higher symptom burden. The HADS (Roberts et al., 2001; Zigmond & Snaith, 1983) is a valid and reliable instrument measuring anxiety and depression and consisting of two scales, one for anxiety and one for depression, with seven items each. Scores of both scales range between 0 and 21, with higher scores indicating higher anxiety or depression.

To describe patients' sociodemographic and clinical characteristics, the following instruments were adopted. The Montreal Cognitive Assessment (Nasreddine et al., 2005) was used to measure cognitive function (scores 0–30, cut-off for normal cognition ≥26). The Mutuality Scale (Dellafiore et al., 2018) was used to measure mutuality (scores 0–4, higher scores indicate greater mutuality). The 12-item Short Form was used to measure generic physical and mental quality of life (Ware et al., 1996) (standardized scores 0–100, higher scores indicate better quality of life). The Self-care of HF Index v.6.2 (Riegel et al., 2019) was used to measure self-care (composed of three scales measuring self-care maintenance, self-care management, self-care self-efficacy. Scores 0–100, higher scores indicate better self-care). To describe patients' characteristics, we did not used the management scale both because poor interoception could artificially deflate self-care management scores and because of the high missing values for this scale. The Pittsburgh Sleep Quality Index (Buysse et al., 1989) was used to measure sleep quality (scores 0–21, cut-off for poor sleep quality ≥5). The Kansas City Cardiomyopathy Questionnaire (Green et al., 2000) was used to measure the perceived HF-specific health status (scores 0–100, higher scores indicate higher health status). The Charlson Comorbidity Index (Charlson et al., 1987) was used to measure the presence and severity of comorbidity and the related long-term mortality risk (scores 1–2: mild, 3–4: moderate, ≥5: severe risk). All the instruments have been validated in an Italian population, (Curcio et al., 2013; Dellafiore et al., 2018; Kodraliu et al., 2001; Miani et al., 2003; Pirrotta et al., 2015; Vellone et al., 2013) except for the Charlson Comorbidity Index.

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2.3 | Data analysis

Data analysis was performed with SPSS v.25 (George & Mallery, 2018) and SLEIPNER v.2.1 (Bergman & El-Khouri, 2002) by implementing four sequential steps. First, we described patients' sociodemographic and clinical characteristics. Second, we conducted a missing values analysis and tested for multivariate outliers using the SLEIPNER-RESIDUE module and confirmed if the Average Squared Euclidean Distance was <0.5. Third, we performed cluster analysis on the scores of the HADS subscales (anxiety, depression) and two HFSPS dimensions (dyspnoea, early and subtle) and then derived the optimal number of clusters. We decided to include only dyspnoea and early and subtle symptoms because (a) the inclusion of two psychological and two physical dimensions allows a more balanced cluster analysis, equally distributed between psychological and physical symptoms; and (b) they have been shown to predict most clinical outcomes in HF patients (Jurgens et al., 2017). Finally, we investigated differences among clusters with one-way analysis of variance (ANOVA).

For the cluster analysis, (Bergman, 1998) we initially implemented Ward's hierarchical method (SLEIPNER-CLUSTER-module) to evaluate different cluster solutions based on the decrease of the explained error sum of squares (Bergman, 1998). Then, we further relocated individuals by k-means nonhierarchical analysis to increase cluster homogeneity (McLachlan, 1992) (SLEIPNER-RELOCATE-module). Finally, we evaluated the optimal number of clusters based on four indices: C-index, (Hubert LJ, 1976) G (+), (Rohlf, 1974) Gamma, (Baker & Hubert, 1975) and point-biserial correlation (Milligan, 1981) (SLEIPNER-EVALUATE-module). ANOVA was conducted to investigate differences in patients' characteristics among clusters. Post hoc tests were based on Bonferroni correction unless Levene's homogeneity test was not tenable; in this case, Games–Howell post hoc test was chosen. To compare frequency distributions, we implemented chi-square tests of independence.

The predictive analysis was performed in Python, using the scikit-learn library (Pedregosa et al., 2011). Three classification models were trained to predict the cluster membership of the patients based on 11 selected clinical and sociodemographic variables: age, gender, marital status, Charlson Comorbidity Index, Montreal Cognitive Assessment, NYHA class, HF duration, number of medications, SCHFI maintenance, SCHFI self-efficacy and Pittsburg Sleep Quality Index. We selected such variables based on the existing literature suggesting their symptom-related relevance. Plus, we excluded variables with numerous missing values (i.e. SCHFI self-care management $n=156$, haemoglobin $n=50$). The data were split into a training set (80%) and a test set (20%). The three classification models were as follows: multinomial logistic regression with cross-validated regularization, support vector classification with cross-validated hyperparameter tuning, and random forest model with cross-validated hyperparameter tuning. The optimal set of hyperparameters for the models was found via nested cross-validation, and the models were trained on the training set. The models were subsequently evaluated on the test set based on three metrics (Accuracy, Balanced accuracy, and AUROC score). Finally, we investigated the importance of the 11 variables in predicting cluster membership by computing the decrease in accuracy of the classifier after randomly shuffling the values of a feature (permutation importance analysis).

3 | RESULTS

3.1 | Characteristics of the sample

Patients ($n=510$) were typically older adults (72.4 ± 12.3 years), predominantly men (58%) and partnered (62%). Most patients were in NYHA classes II-III (92.8%), with mild cognitive impairment (22.8 ± 6.7), mild anxiety (7.8 ± 4.4) and depression (7.9 ± 4.4), poor physical (35.4 ± 9.5) and mental (44.7 ± 10.1) quality of life and poor sleep (12.3 ± 3.6). On average, self-care behaviours were inadequate (<70). No multivariate outliers and no missing values were detected neither in the HFSPS nor in the HADS (Table 1).

3.2 | Results of the cluster analysis

The 5, 4 and 3-cluster solutions were explored because of the steeper decline in the error sum of squares (Table S1). The G+ and Gamma indexes suggested the 5-cluster solution, C-index suggested the 3-cluster solution, and the point-biserial correlation suggested the 4-cluster solution. However, the 5-cluster solution did not seem theoretically meaningful and, although having the highest ESS, it included one small cluster of 49 patients (9.61% of the total sample). The 3-cluster solution explained a relatively low variance. These considerations highlighted the 4-cluster solution as optimal.

Figure 1 and Table 2 show the mean scores of HADS (Anxiety and Depression subscales) and HFSPS (Dyspnea and Early and Subtle subscales) for each of the four clusters, which were labelled based on the intensity and combination of psychological and physical symptoms. Cluster 1 has high psychological symptoms scores and low physical symptoms scores; therefore, it was labelled as 'Mixed distress'. Cluster 2 has high psychological and physical symptoms scores; therefore, it was labelled as 'High distress'. Cluster 3 has low psychological and physical symptoms scores; therefore, it was labelled as 'Low distress'. Cluster 4 has average psychological and physical symptoms scores; therefore, it was labelled as 'Moderate distress'.

3.3 | Clusters description and comparison

The ANOVA showed that the HADS and HFSPS subscales were statistically different across the clusters. The only exception was a non-significant difference in anxiety between Clusters 1 and 2 ($p=1.00$) (Table 2).

Individuals in Cluster 1 (Mixed distress) had an equal distribution of gender, a mean age of 72.4 years, and were mainly in NYHA class

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TABLE 1 Sociodemographic and clinical characteristics of the sample ($N = 510$).

Sample characteristics	M (SD) or *n* (%)
Age (years)	72.37 (12.28)
Gender (female)	214 (42.0)
Marital status	
Single/never married	24 (4.7)
Married/partnered	316 (62.0)
Divorced/separated	20 (3.9)
Widowed	150 (29.4)
Occupation	
Unemployed/retired	428 (83.9)
Active worker	82 (16.1)
Education (≥middle school)	168 (33.0)
Charlson Comorbidity Index	2.91 (1.98)
Haemoglobin ($n = 50$ missing)	12.74 (2.25)
MoCA ($n = 7$ missing)	22.84 (6.36)
NYHA class	
II	313 (61.4)
III	160 (31.4)
IV	33 (6.5)
Illness duration (months)	66.7 (76.66)
Number of medications	6.64 (2.90)
Mutuality scale (total score)	2.94 (0.62)
SF-12	
Physical component summary	35.46 (9.57)
Mental component summary	44.74 (10.17)
SCHFI	
Maintenance	45.44 (15.39)
Management ($n = 156$ missing)	39.73 (17.64)
Self-efficacy	51.42 (21.59)
PSQI	
Total score	12.31 (3.68)
Duration	0.91 (0.99)
Disturbances	2.36 (0.61)
Latency	1.87 (0.80)
Daytime dysfunction	1.93 (0.81)
Efficiency	1.55 (1.26)
Quality	2.18 (062)
Medications	1.51 (0.78)
KCCQ	
Total score	57.09 (22.03)
Physical limitation	46.18 (24.26)
Symptom stability	67.55 (32.43)
Symptom frequency	47.04 (18.95)
Symptom burden	67.15 (28.90)
Self-efficacy	53.65 (22.72)
Quality of life	45.17 (25.55)
Social limitation	49.53 (29.21)
Clinical summary	51.64 (21.66)
HADS	
Anxiety	7.81 (4.40)
Depression	7.96 (4.42)
HFSPS	
Total score	27.78 (16.61)
Dyspnoea	10.13 (7.60)
Chest discomfort	2.73 (2.35)
Early subtle	10.78 (6.11)
Oedema	4.13 (3.54)

Abbreviations: HADS, Hospital Anxiety and Depression Scale; HFSPS, Heart Failure Somatic Perception Scale; KCCQ, Kansas City Cardiomyopathy Questionnaire; MoCA, Montreal Cognitive Assessment Scale; NYHA, New York Heart Association; PSQI, Pittsburgh Sleep Quality Index; SCHFI, Self-care of Heart Failure Index.

II (Table S2). Patients in this cluster reported the lowest levels of mental quality of life (but not significantly different to Cluster 2). Sleep quality (PSQI) and HF-related health status (KCCQ) scores reported by patients in this cluster laid in between those reported by patients in the other clusters, meaning they had more average PSQI and KCCQ scores compared to the other clusters (although not significantly different to Cluster 4). Patients in this cluster reported the highest anxiety and depression levels compared to the other clusters (except Cluster 2).

Patients in Cluster 2 (high distress) were mostly female, with a mean age of 74.2 years, mainly in NYHA classes III-IV. Compared to the other clusters, they had less favourable sociodemographic and clinical characteristics. In fact, they exhibited the highest comorbidity, the lowest haemoglobin level, the poorest cognitive function, the poorest physical (together with Cluster 4) and mental (together with Cluster 1) quality of life, self-care self-efficacy, sleep quality and HF-related health status. Patients in Cluster 2 reported the highest levels of anxiety and depression (except compared to Cluster 1).

Patients in Cluster 3 (low distress) were mostly male, with a mean age of 69.2 years, mainly in NYHA classes I-II. Compared to the other clusters, they exhibited the most favourable sociodemographic and clinical characteristics: they were the youngest patients, they were the most partnered, had the lower comorbidity, the highest haemoglobin, cognitive function, physical and mental quality of life, self-care behaviours (especially self-care maintenance), sleep quality and HF-related health status. Patients in this cluster reported the lowest levels of both psychological and physical symptoms.

Patients in Cluster 4 (moderate distress) were mostly male, with a mean age of 75.3, and equally distributed between NYHA classes. Compared to patients in the other clusters, they were the oldest and those with the poorest physical quality of life (not significantly different to Cluster 2). Patients in this cluster reported mental quality of life scores laying in between those reported by patients in the other clusters. Sleep quality scores and HF-related health status of patients in this cluster laid in between those reported by patients in the other clusters (except to Cluster 1), meaning this group of

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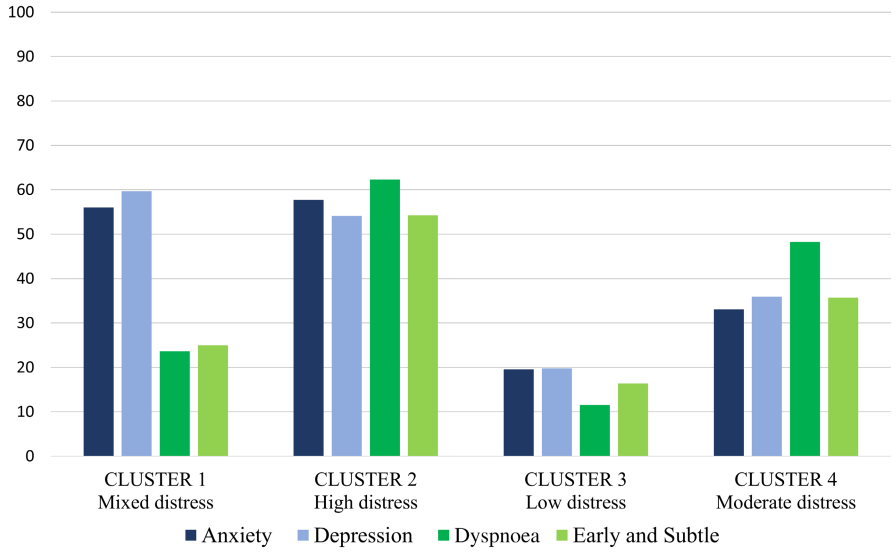


FIGURE 1 Graphical representation of the Heart Failure Somatic Perception subscales (dyspnoea, early and subtle) scores and the Hospital Anxiety and Depression subscales' (anxiety and depression) scores per each cluster. Each subscale has a standardized score from 0 to 100, with higher scores meaning higher physical symptom burden and higher anxiety and depression, respectively.

TABLE 2 Comparisons of the clusters according to the main scales' scores ($n = 510$).

	Cluster 1 mixed distress ($n = 86$, 16.87%)	Cluster 2 high distress ($n = 106$, 20.78%)	Cluster 3 low distress ($n = 184$, 36.08%)	Cluster 4 moderate distress ($n = 134$, 26.27%)	F or X^2	*p*	Post hoc test
Anxiety	11.77 (3.18)	12.12 (2.87)	4.11 (2.59)	6.95 (2.70)	207.03	**<.001**	1 ≠ 3; 1 ≠ 4; 2 ≠ 3; 2 ≠ 4; 3 ≠ 4
Depression	12.53 (3.30)	11.37 (2.90)	4.16 (2.75)	7.55 (2.81)	227.08	**<.001**	1 ≠ 2; 1 ≠ 3; 1 ≠ 4; 2 ≠ 3; 2 ≠ 4; 3 ≠ 4
Dyspnoea	23.64 (16.12)	62.30 (16.77)	11.54 (12.03)	48.26 (16.18)	319.90	**<.001**	1 ≠ 2; 1 ≠ 3; 1 ≠ 4; 2 ≠ 3; 2 ≠ 4; 3 ≠ 4[a]
Early and subtle	25.02 (11.02)	54.29 (9.25)	16.40 (9.77)	35.76 (10.77)	332.26	**<.001**	1 ≠ 2; 1 ≠ 3; 1 ≠ 4; 2 ≠ 3; 2 ≠ 4; 3 ≠ 4

Note: Comparisons in the post hoc test section refer to cluster numbers. Bonferroni post hoc test was performed unless otherwise specified. Data are displayed as mean (SD). Anxiety and depression scores are not standardized.

[a]Games and Howell test; significant *p*-values are in bold.

patients had average levels in the PSQI and KCCQ scales. Patients in this cluster also reported average levels of both psychological and physical symptoms, which fell between those reported by patients in all the other clusters.

3.4 | Results of the predictive analysis

Three classifiers were trained to predict the symptom cluster membership based on 11 selected clinical and sociodemographic variables. When evaluating the classifiers on three metrics (Table S3), the random forest model with cross-validated hyperparameter tuning had the best performance, resulting in an accuracy = 0.54, a balanced accuracy = 0.49 and an AUROC = 0.73.

By inspecting the performance of the random forest model (Figure 2), it can be noted that the classifier has a greater ability to classify patients belonging to Clusters 2 and 3 (AUROC = 0.84, 0.88, respectively), than patients belonging to Clusters 1 and 4 (AUROC = 0.57, 0.63, respectively). The importance of the 11 clinical and sociodemographic variables was computed (Figure 3) and showed that NYHA class (mean accuracy decrease = 0.098, SD = 0.029) and sleep quality (PSQI) (mean accuracy decrease = 0.089, SD = 0.033) were the most important variables in predicting cluster membership.

4 | DISCUSSION

The aim of this study was to cluster HF patients based on their psychological and physical symptoms. We found four clusters characterized by different levels and combinations of psychological and physical symptoms. We also found that NYHA class and sleep quality mostly predicted symptom cluster membership. These results may be particularly useful to clinicians, patients and researchers within symptoms science. Indeed, they highlight the importance of addressing clusters of symptoms, instead of individual symptoms, to facilitate symptoms detection and to develop tailored strategies for symptom management.

We found four clusters characterized by either consistently high or consistently low psychological and physical symptoms (similarly to previous studies [Denfeld et al., 2020; Lee et al., 2014; Park et al., 2019]), consistently moderate psychological and physical symptoms (similarly to Lee et al., 2014) and high psychological combined with low physical symptoms (similarly to Denfeld et al., 2020 and Park et al., 2019). We did not observe HF patients suffering from low psychological and high physical symptoms, as few other studies reported (Lee et al., 2010; Park et al., 2019). Increasing evidence highlights how somatic alterations are associated with psychological functions and cognition (Pollatos et al., 2009), suggesting that an

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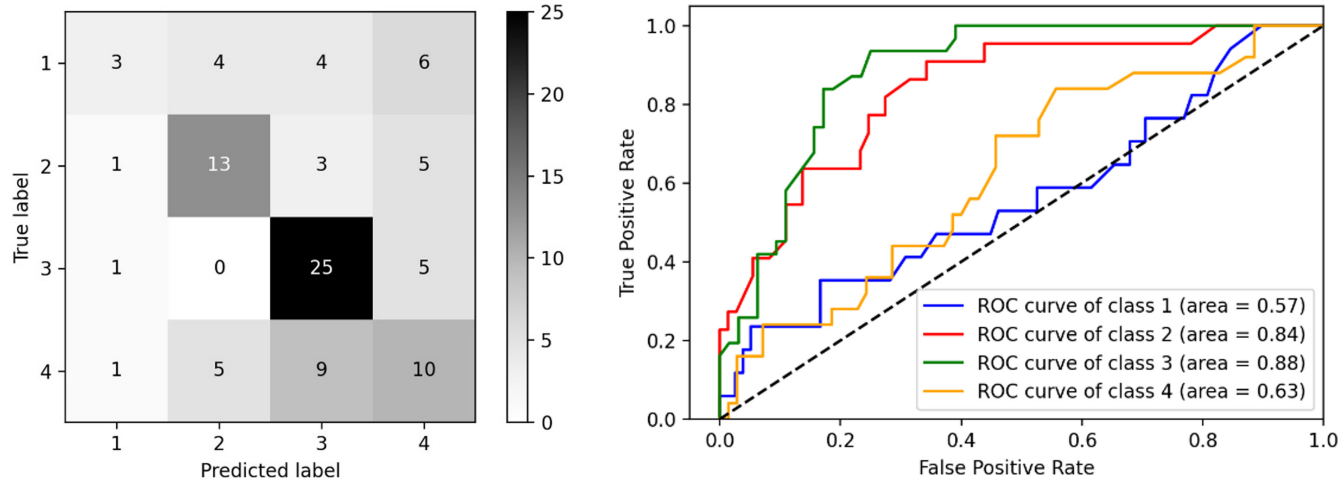


FIGURE 2 Performance of the random forest on test data. On the left, a confusion matrix shows the symptom cluster prediction (x-axis, 'Predicted label') for the patients belonging to the four clusters (y-axis, 'True label') (e.g. the model made a correct prediction for 25 out of the 31 patients actually belonging to Cluster 3). On the right, a ROC plot illustrates the diagnostic ability of the classifier as its discrimination threshold varies. In this multiclass scenario, the individual classes are binarized (e.g. Class 1 vs not Class 1), and individual scores are computed for each cluster.

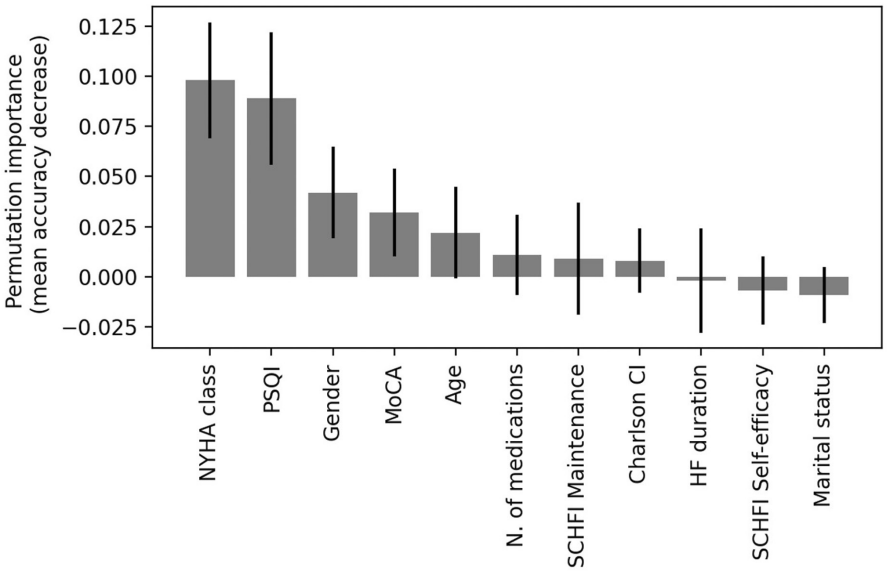


FIGURE 3 Importance of the 11 clinical and sociodemographic variables, measured as mean decrease in accuracy (±SD) when a specific variable is randomly shuffled. CI, Comorbidity Index; MoCA, Montreal Cognitive Assessment; NYHA, New York Heart Association; PSQI, Pittsburgh Sleep Quality Index; SCHFI, Self-care of HF Index.

increase in physical symptoms may lead to an increase in psychological symptoms. Our results support such assumption. Indeed, when physical symptoms were high also psychological symptoms were high too, and the opposite tendency did not occur in our clusters. This indicates that physical symptoms should be closely monitored as they seem to exert a leading role compared to the psychological ones. Some studies (Ramasamy et al., 2006; Vongmany et al., 2016) found that psychological symptoms can also influence physical symptoms. However, consistent with prior research, (Denfeld et al., 2020; Park et al., 2019) our 'mixed distress' cluster showed that psychological symptoms may be very high without affecting physical symptoms.

We found four clusters characterized by either consistently high or consistently low psychological and physical symptoms (similarly to previous studies [Denfeld et al., 2020; Lee et al., 2014; Park et al., 2019]), consistently moderate psychological and physical symptoms (similarly to Lee et al., 2014) and high psychological combined with low physical symptoms (similarly to Denfeld et al., 2020 and Park et al., 2019). We did not observe HF patients suffering from low psychological and high physical symptoms, as few other studies reported (Lee et al., 2010; Park et al., 2019). Increasing evidence highlights how somatic alterations are associated with psychological functions and cognition (Pollatos et al., 2009), suggesting that an increase in physical symptoms may lead to an increase in psychological symptoms. Our results support such assumption. Indeed, when physical symptoms were high also psychological symptoms were high too, and the opposite tendency did not occur in our clusters. This indicates that physical symptoms should be closely monitored as they seem to exert a leading role compared to the psychological ones.

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Some studies (Ramasamy et al., 2006; Vongmany et al., 2016) found that psychological symptoms can also influence physical symptoms. However, consistent with prior research, (Denfeld et al., 2020; Park et al., 2019) our 'mixed distress' cluster showed that psychological symptoms may be very high without affecting physical symptoms.

Similar to previous studies, (Friedman, 2003; Lee et al., 2010; Vongmany et al., 2016) we found that women experienced higher symptom burden (cluster 'High distress') than men, and patients with higher psychological symptoms experienced lower quality of life (Zambroski et al., 2005). Vongmany et al., (2016) suggested that psychological symptoms (e.g. anxiety) may contribute to poorer self-management behaviours. However, we did not observe any significant difference in self-care management among clusters. Therefore, our results suggest that anxiety alone may not be sufficient to reduce self-care management behaviours, as other variables like self-care self-efficacy may prevent worsening by counterbalancing its detrimental effect. It could also be that missing data for self-management might have tended towards those with better self-management potentially finishing that scale and being more motivated.

Previous studies in HF reported that younger patients experience either equal (Denfeld et al., 2020; Hertzog et al., 2010; Huang et al., 2018) or higher symptom burden, (Jurgens et al., 2009a) especially psychological, (Lee et al., 2010; Park et al., 2019) compared to older patients. Contrarily, we found that younger patients were less burdened from both physical and psychological symptoms. The authors of the above-mentioned studies argued that one possible reason for the lower symptom burden experienced by older patients could be due to declines in interoception (i.e. the ability to sense, elaborate and respond to symptoms), which, in the elderly, occur due to changes in adrenergic function (Cameron, 2001; Khalsa et al., 2009). However, we also know from the literature that older age is positively associated with an increased tendency to distract from body sensations, which, in turn, is negatively associated with interoceptive abilities and positively associated with symptom burden (Eng et al., 2020; Hayes et al., 1996; Huffziger & Kuehner, 2009; Prins et al., 2014). Thus, our results seem to confirm that older patients may suffer from greater interoceptive impairments, but in a way that such impairment might have led to distorted and exaggerated reported symptom patterns, resulting in a more burdensome experience of symptoms.

In HF patients, anxiety and depression are common comorbid conditions (Yohannes et al., 2010) that affect cardiovascular processes by altering neurohormonal function (Chapa et al., 2014). Thus, HF patients with anxiety or depression may exhibit a continued cycle of HF progression and increased anxiety and depression (Chapa et al., 2014). This seems to be confirmed by the consistence between the levels of physical and psychological symptoms in our clusters. However, our 'mixed distress' cluster represents an exception that could be due to impaired interoceptive levels discussed above. Since other studies (Denfeld et al., 2020; Park et al., 2019) also reported clusters with mixed levels of physical and psychological symptoms in HF, it would be relevant to further investigate the reasons for such discordance.

Finally, to the best of our knowledge, this is the first study predicting symptom cluster membership. We found that the random forest model had a greater ability to classify patients belonging to Clusters 2 and 3. Indeed, patients belonging to these two clusters reported very high or very low symptom distress. Instead, patients in Clusters 1 and 4 reported more average or mixed distress, logically more difficult for a model to predict as being less 'extreme'. Future research should further replicate this type of predictive analysis on larger samples and considering even more variables that could potentially allow a more precise prediction of symptom cluster membership. We also found that NYHA class and sleep quality, variables easily available in the clinic, were the most useful in predicting symptom cluster membership. These results are supported by the literature reporting significant association between sleep disturbances and physical symptom like dyspnoea and oedema, as well as psychological symptoms of anxiety and depression (He & Pan, 2022; Jaarsma et al., 2020; Pearse & Cowie, 2016). NYHA class has been found associated with psychological symptoms, especially depressive symptoms, (Celik et al., 2016; Yin et al., 2019) and, as per definition, higher NYHA class implies higher physical symptom severity (Heidenreich et al., 2022). Relying on variables other than symptoms to predict symptom cluster membership has potential to allow healthcare professionals, as well as researchers, to know the symptom cluster membership of patients, without necessarily asking or having access to any symptom-specific information, and therefore facilitate the process of addressing and managing symptoms.

4.1 | Strengths and limitations

Our sample included patients with poor self-care, which could reduce the generalizability of the results. In addition, patients in our sample were mainly in NYHA class II and III which could also reduce the generalizability of these results. However, we innovatively recruited patients from three different settings, which may compensate for that limitation and enhance generalizability of results across different settings. Furthermore, it is desirable that predictive analyses performed by splitting the sample into test and training sets are computed on large samples to increase the validity of the results. Our sample size was moderately small, as we ended up with 102 patients in the test set. However, our predictive analysis represents a first attempt to predict symptom cluster membership based on variables other than symptoms, and thus provide an exploratory starting point never done before.

4.2 | Recommendations for future research

The results of this study further expand the existent literature investigating clusters of symptoms in patients with heart failure. Our results highlight the need to further investigate the effect of clusters of symptoms, instead individual symptoms, on patient outcomes. The predictive analysis of symptom cluster membership should be

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further replicated on bigger samples and considering other potential clinical and sociodemographic variables.

4.3 | Implications for policy and practice

Knowing symptom cluster membership of HF patients could be useful for healthcare professionals and researchers to develop and implement interventions that target patients' needs based on their specific symptom profile. Furthermore, knowing which variables best predict symptom cluster membership (i.e. NYHA class and sleep quality) can allow to address symptom-related issues even when direct access to symptoms-data is absent.

5 | CONCLUSIONS

Our results indicate that, within an Italian HF population, it was possible to detect distinct clusters of HF patients based on different combinations and degree of physical and psychological symptoms. This may be particularly useful to support healthcare professionals and advanced nurses in develop and implement interventions tailored to a specific symptom profile, to assist patients in adopting appropriate symptom management strategies, and to spur future investigations assessing the effect of clusters of symptoms on patient outcomes. The promising results of the predictive analysis show that such benefits may be obtained even when access to symptoms-related data is absent.

AUTHOR CONTRIBUTIONS

Giulia Locatelli, Paolo Iovino, Alessandro Pasta, Corrine Y. Jurgens, Ercole Vellone, Barbara Riegel; Made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; Giulia Locatelli, Paolo Iovino, Alessandro Pasta, Corrine Y. Jurgens, Ercole Vellone, Barbara Riegel: Involved in drafting the manuscript or revising it critically for important intellectual content; Giulia Locatelli, Paolo Iovino, Alessandro Pasta, Corrine Y. Jurgens, Ercole Vellone, Barbara Riegel: Given final approval of the version to be published. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content; Giulia Locatelli, Paolo Iovino, Alessandro Pasta, Corrine Y. Jurgens, Ercole Vellone, Barbara Riegel: Agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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CONFLICT OF INTEREST STATEMENT

None.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/jan.15890.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to confidentiality reasons.

TRIAL AND PROTOCOL REGISTRATION

The study protocol was registered on ClinicalTrials.gov (Identifier: NCT02894502) https://beta.clinicaltrials.gov/study/NCT02894502

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