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RESEARCH ARTICLE

Comparing survival rates for clusters of depressive symptoms found by Network analysis' community detection algorithms: Results from a prospective population-based study among 9774 cancer survivors from the PROFILES-registry

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Abstract

Objectives: Previous studies have shown that depression is associated with mortality in patients with cancer. Depression is however a heterogeneous construct and it may be more helpful to look at different (clusters) of depressive symptoms than to look at depression as a discrete condition. The aim of the present study is to investigate whether clusters of depressive symptoms can be identified using advanced statistics and to investigate how these symptom clusters are associated with all-cause mortality in a large group of patients with cancer.

Method: Data from a large population-based cohort study (PROFILES) including various cancer types were used. Eligible patients completed self-report questionnaires (i.e. Fatigue assessment scale, Hospital anxiety and depression scale, EORTC QOL-C30) after diagnosis. Survival status was determined on 31 January 2022.

Results: In total, 9744 patients were included. Network analyses combining different community detection algorithms showed that clusters of depressive symptoms could be detected that correspond with motivational anhedonia, consummatory anhedonia and negative affect. Survival analyses using the variables that represented these clusters best showed that motivational and consummatory anhedonia were associated with survival. Even after controlling for clinical and sociodemographic variables items assessing motivational anhedonia were significantly associated with mortality over time.

Conclusion: Separate clusters of symptoms that correspond with motivational and consummatory anhedonia and negative affect can be distinguished and anhedonia may be associated with mortality more than negative affect. Looking at particular (clusters of) depressive symptoms may be more informative and clinically relevant than using depression as a single construct (i.e. syndrome).

KEYWORDS
anhedonia, cancer, depression, mortality, negative affect

INTRODUCTION

Previous studies have shown that depressive symptoms might be a risk factor for all-cause mortality among cancer survivors (Mols et al., 2013; Pinquart & Duberstein, 2010; Wang et al., 2020). These studies are limited, however, as they tend to treat depression as a homogenous concept. In reality, depression is a heterogenous concept with a broad range of distinguishable symptoms (Fried et al., 2016; Fried & Nesse, 2015).

According to DSM-V criteria, the core symptoms of a depressive disorder are anhedonia and depressed mood. Anhedonia is defined as 'markedly diminished interest *or* pleasure in all, or almost all, activities of the day' (*Diagnostic and statistical manual of mental disorders: DSM-5™, 5th ed*, 2013). Thereby, it is important to distinguish between *motivational* (lack of interest) and *consummatory* (lack of pleasure) *anhedonia* (Thomsen, 2015; Treadway & Zald, 2011). Besides anhedonia, negative affect is a core symptom of depression. It entails more than sadness and despair but also other negative emotions such as anxiety, worry and irritability (Beard et al., 2016; Kalin, 2020; Solms, 2012). This can be understood as these negative emotions are all reactions reflecting ancient brain mechanisms triggered by social loss and separation (Solms, 2012; Watt & Panksepp, 2009).

Studies investigating depressive symptoms in oncology tend to use self-report questionnaires such as the Hospital Anxiety and Depression Scale (HADS; Spinhoven et al., 1997), Centre for Epidemiologic Studies Depression scale (CES-D; Radloff, 1977) or the Beck Depression Inventory (BDI; Hubley, 2020). These questionnaires either focus on one aspect of depression (e.g. consummatory anhedonia) or a mixture of symptoms. That is, the HADS assess consummatory anhedonia (i.e. lack of pleasure) and anxiety and worry, the CES-D assesses both positive (i.e. consummatory anhedonia) as negative affect (Schroevers et al., 2000) and the BDI consist of items assessing a mixture of symptoms such as motivational anhedonia (i.e. item 12; loss of interest in others), consummatory anhedonia (i.e. item 4; loss of enjoyment), negative affect (e.g. sadness, crying, hopelessness) and other depressive symptoms such as insomnia, appetite and sexual interest. It is important, however, to distinguish between the core depressive symptoms of motivational anhedonia, consummatory anhedonia and negative affect as they have different aetiology and neurobiological underpinnings (Borsini et al., 2020; Solms, 2012; Treadway & Zald, 2011; van Roekel et al., 2019) and have distinct biological correlates (Argyropoulos & Nutt, 2013; Szczypiński & Gola, 2018). Consequently, the distinct core symptoms may be differently related to mortality in patients with cancer.

The aim of the present study is twofold. First to investigate whether clusters of depressive symptoms that correspond with motivational and consummatory anhedonia and negative affect, can be identified using Network Analyses. Second, to investigate how these symptom clusters are associated with all-cause mortality in a large group of patients with cancer.

METHODS

Setting and participants

Data from the PROFILES registry were used. PROs are collected within the sampling frame of the Netherlands Cancer Registry (NCR) and can, therefore, be linked with clinical data of all individuals newly diagnosed with cancer in the Netherlands (van de Poll-Franse et al., 2011). The PROFILES registry started data collection of the first cohort of cancer survivors in 2008 and is still ongoing, including studies on various cancer types.

Data collection

A detailed description of the data collection has been described previously (Bonhof et al., 2021; van de Poll-Franse et al., 2011). In brief, cancer patients were informed about the study via a letter by their (ex)attending specialist. This letter contained either an informed consent form and a paper questionnaire, or a secured link to a web-based informed consent form and online questionnaire. In study samples where the secured link was provided, patients that preferred a paper-and-pencil questionnaire could return a postcard to request one. Data from the PROFILES registry are freely available for non-commercial scientific research, subject to study question, privacy and confidentiality restrictions and registration (http://www.profilesregistry.nl). The current study made use of data from 12 study samples in which similar PRO questionnaires were used. Survivors were included between 2008 and 2015 with a primary cancer diagnosis between 1990 and 2015. Time between diagnosis and completion of the questionnaires differed between studies but was at least 6 months and always after ending primary treatment.

Depressive symptoms

A total of 21 items assessing the core depressive symptoms (motivational anhedonia, consummatory anhedonia, negative affect) from different self-report questionnaires were included. That is, three items from the Fatigue assessment scale (FAS; Hendriks et al., 2018; Michielsen et al., 2003), 14 items from the Hospital Anxiety and Depression Scale (Spinhoven et al., 1997; Zigmond & Snaith, 1983) and 4 items from the emotional functioning subscale of the EORTC QLQ-C30 (version 3.0; Aaronson et al., 1993).

The FAS consist of 10 items assessing chronic fatigue. Three items refer to lack of interest/motivation (i.e. I do not do much during the day, I have problems starting things, I feel no desire to do anything) and were included in this study. Each item is scored on a 5-point Rating-scale ranging from Never (1) to Always (5). The HADS is a much-used questionnaire with two subscales (Spinhoven et al., 1997; Zigmond & Snaith, 1983). The main construct assessed by the depression subscale (e.g. I still enjoy the things I used to enjoy, I can enjoy a good book or radio/TV program) is consummatory anhedonia (Langvik et al., 2016; Smith et al., 2002) while the anxiety subscale assess worry, tension and panic. The questions can be answered on a four-point Rating-scale. The EORTC QLQ-C30 is a self-report questionnaire assessing quality of life of patients with cancer. It contains five functional scales, a global quality of life scale, three symptom scales and six single items. Each item is scored on a four-point Rating-scale. Scores were linear transformed to a 0–100 scale. The 4-item emotional functioning subscale (Aaronson et al., 1993) assess feeling tense, worrying, feeling depressed and being irritable. A lower score on the emotional functional scale means a higher negative affect (Calderon et al., 2019; Lidington et al., 2022).

Survival status

The start of follow-up was defined as the time of completion of the questionnaire. Vital status was determined on 31 January 2022 by merging data from the Central Bureau for Genealogy with our dataset. Survival duration was defined as the time in days between completing the questionnaire until either death or censoring date (31 January 2022).

Sociodemographic and clinical characteristics

Sociodemographic characteristics were available from the NCR. Other relevant sociodemographic and clinical factors were collected through questionnaires.

Statistical analyses

The analysis methodology is based on the approach described by Tissier et al. (2018). A three-step approach is applied, which starts with network construction, followed by node (i.e. items) clustering to empirically derive modules or pathways and concludes with building of a prediction model using the identified modules. R version 4.0.0 was used for all analyses.

In the first step, a network model was constructed based on the 21 items included. Given the cross-sectional nature of our data, regularized partial correlation networks were used with the LASSO method as the regularization technique (graphical LASSO; Friedman et al., 2008). We optimized the network by choosing the LASSO penalty parameter to minimize the Extended Bayesian Information Criterion (EBIC). To identify which items are important to the network centrality indices (betweenness, closeness and strength) are calculated.

Subsequently (second step), multiple algorithms were employed on the generated network to detect communities within the network. The Spinglass, Walktrap and Louvain algorithm were used, in addition to the Clique Percolation Method (CPM). The first three methods generate non-overlapping communities, such that nodes (i.e. items) are assigned to a unique community for each node. To improve the performance of the Spinglass algorithm, which may show different results every time it is run, the algorithm was run a thousand times to estimate the median number of communities obtained. We selected the networks consisting of the median estimated number of communities. In the optimization of the weighted CPM, we selected the optimization parameters *'I' (strength of average relation within a community)* and *'k' (minimum clique size) such that the* ratio of largest to second largest community is closest to 2, as suggested by Farkas et al. (2007).

To derive a consensus definition of the communities across algorithms, we studied which items are loaded in which community for every algorithm. If an item loads in the same community in 3 out of 4 algorithms, the item was assigned to that community. Other items were designated as 'isolated' items, without assignment to a shared community.

In the final (third) step, the Sparse Group Lasso method was applied on the constructed communities to identify the most important variables in each community for the prediction of the survival outcome. Those items that represent a community best, were added to a Cox proportional hazard model with age as a covariate. Kaplan–Meier survival curves and log-rank tests were applied to quantify the association. Finally, a Cox proportion hazard model was computed for all depressive items that were assigned to a community, with sociodemographic (i.e. sex, age, education, marital status) and clinical variables (i.e. stadium at diagnosis, type of treatment) as covariates, in order to see which depressive items were most predictive taking other relevant variables into account. Missing data were handled differently for the different analyses. For the Network Analysis and Community Detection Algorithms, we used pairwise deletion of the missing values. For the Sparse Group Lasso, we do not have the option to pairwise delete the missing values. Therefore, we did a complete case analysis, which only includes

participants for whom we have no missing data on any variable of interest. Also for survival analysis, we used complete cases only.

RESULTS

Table 1 shows the sociodemographic and clinical characteristics. A total of 9774 patients were included of whom 3815 (39%) were deceased. The average follow-up in days was 3.114 (approximately 8.5 years) and the maximum follow-up time is 5.085 days (approximately 14 years).

Network estimation

We estimated a regularized partial correlation network where the edges between nodes are akin to partial correlations (see Figure 1). Centrality indices (betweenness, closeness and strength) are available in supplementary materials (Figure S1).

Community detection

We use the non-overlapping Spinglass, Walktrap and Louvain algorithms and the overlapping Clique Percolation Method to detect communities within the network. In a graph of a network model, nodes (circles) represent variables and edges (lines) represent the partial correlations between variables. Partial correlations are unique associations (i.e. associations that remain after the contribution of other variables in the network are taken out). Thicker lines represent stronger partial associations with positive associations in green and negative in orange/red. Graphs with all lines are hard to interpret so we estimated a regularized partial correlation network to show only significant edges. The penalty used is the Lasso (penalty = λ), and its parameter is chosen based on the Extended Bayesian Information Criterion (EBIC). Eventually, we chose the network which minimizes the EBIC value and its corresponding λ penalty ($\lambda = .016$, EBIC = 72,927).

The *Spinglass* algorithm was run a thousand times. In 98.2% of the cases, we found 4 communities. We can therefore see four communities as a stable result. Seven nodes belong to communities 1, 5 nodes belong to communities 2, 4 nodes belong to community 3 and 5 nodes belong to community 4 (see Table 2).

The *Walktrap* algorithm is much more stable than the Spinglass. If we repeat the algorithm we are much more likely to find the exact same solution. In the graph below we can see the communities found by the Walktrap algorithm. We see that, again, four communities are found (See Figure 2).

The *Louvain* algorithm finds, contrary to the above-used methods, five communities. In Figure 3 there can be seen which nodes belong to which community according to this algorithm.

In Figure 4 the communities determined by the Clique Percolation Method are presented. In the CPM, it is possible for nodes to belong to several communities at the same time (*HADS*8) or not belong to any community at all (*HADS*6, *HADS*9, *HADS*10).

Summarizing community detection results

The first aim of the study is to investigate whether clusters of depressive symptoms that correspond with motivational and consummatory anhedonia and negative affect, emerge from a large preexisting oncological dataset. Therefore, the results of all community detection algorithms were combined. In supplementary materials, an overview of the items belonging to each community according to the different community detection algorithms are presented (Table S1). If an item belongs to the same

TABLE 1 Sociodemographic and clinical characteristics.

	Survivors $N = 5959$ (61%)	Deceased $N = 3815$ (39%)	p-value
Sex			
Male	2924 (57.2%)	2190 (42.8%)	<.001
Female	3024 (65%)	1625 (35%)	
Age, mean (SD)	59.6 (11.8)	68.7 (9.4)	<.001
Education			
Lower education (or less)	853 (51.7%)	798 (48.3%)	<.001
Secondary education (high school)	1762 (63.1%)	1030 (36.9%)	
Secondary (vocational) education	1940 (63.4%)	1119 (36.6%)	
University, higher (vocational) education	1295 (63.4%)	749 (36.6%)	
Marital status			
Married/cohabiting	4697 (64.1%)	2636 (35.9%)	<.001
Divorced/separated	356 (66.8%)	177 (33.2%)	
Widowed	581 (43.8%)	744 (56.2%)	
Never married/never cohabited	251 (62.7%)	149 (37.3%)	
Tumour type			
Colon cancer	1355 (54.6%)	1126 (45.4%)	<.001
Rectum cancer	691 (56.2%)	538 (43.8%)	
Prostate cancer	776 (64.9%)	420 (35.1%)	
Endometrium carcinoma	634 (66%)	326 (34%)	
Basal cell carcinomas	500 (81.7%)	112 (18.3%)	
Diffuse large B-cell lymphoma and variants	336 (56.5%)	259 (43.5%)	
Thyroid gland	237 (80.9%)	56 (19.1%)	
Melanoma	220 (90.5%)	23 (9.5%)	
Ovarian carcinoma	174 (53.2%)	153 (46.7%)	
Hodgkin lymphoma	169 (83.3%)	34 (16.7%)	
Follicular lymphoma	147 (69.7%)	64 (30.3%)	
Rectosigmoid carcinoma	136 (55.3%)	110 (44.7%)	
B-CLL	114 (50.9%)	110 (49.1%)	
Other	470 (49.3%)	484 (50.7%)	
Stage			
I	2070 (67.7%)	986 (32.3%)	<.001
II	1632 (60.0%)	1088 (40.0%)	
III	1068 (57.9%)	775 (42.1%)	
IV	303 (40.9%)	437 (59.1%)	
Unknown/inapplicable	875 (62.3%)	529 (37.7%)	
Treatment type			
Surgery, yes/no	3981/1967	2462/1353 (	.015
Chemotherapy, yes/no	1519/4429	1214/2575	<.001
Radiation therapy, yes/no	1519/4429	950/2865	.48
Targeted therapy, yes/no	304/5644	309/3506	<.001
Immunotherapy, yes/no	18/5930	10/3805	.72
Follow-up in days	3834 (750)	1902 (1225)	<.001

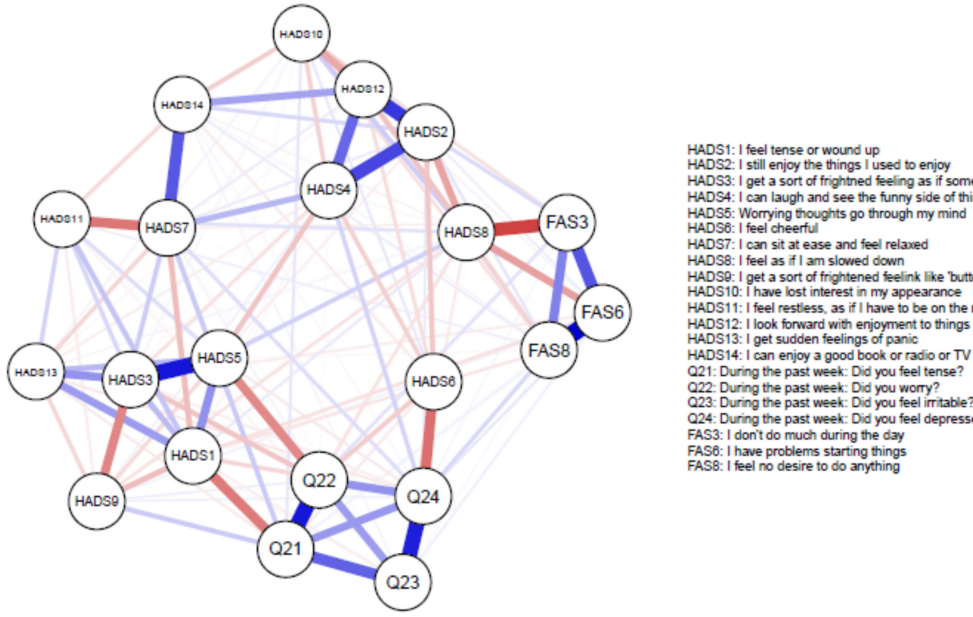

FIGURE 1 Network estimate (Lamda = .016, EBIC = 772,927).

TABLE 2 Communities detection with Spinglass algorithm.

Group 1	Group 2	Group 3	Group 4
HADS1	HADS9	HADS6	HADS2
HADS3	Q21	FAS3	HADS4
HADS5	Q22	FAS6	HADS7
HADS8	Q23	FAS8	HADS12
HADS10	Q24		HADS14
HADS11			
HADS13			

community in 3/4 of the community detection algorithms, it was assigned to this community. Based on this rule, the following communities were constructed (see Table 3).

Based on theory, we can label these communities. Community 1 comprises nodes (items) that correspond to a diminished motivation to pursue rewards (i.e. motivational anhedonia) as assessed by three items from the FAS and 1 from the HADS. Community 2 comprises nodes that correspond to a diminished pleasure in rewards (i.e. consummatory anhedonia) assessed with three items from the HADS depression subscale. Community 3 comprises nodes that involve the experience of negative emotions such as worry and panic as assessed with four items from the HADS. Community 4 also comprises nodes that involve the experience of negative emotions but are assessed by the five items of the EORTC emotional functioning subscale. While separable, communities 3 and 4 are closely linked. A summarized result can be found in Figure 5.

Variable selection

The second aim of the study was to investigate how these symptom clusters (i.e. communities) are associated with all-cause mortality. Therefore, those variables that represent the community best were

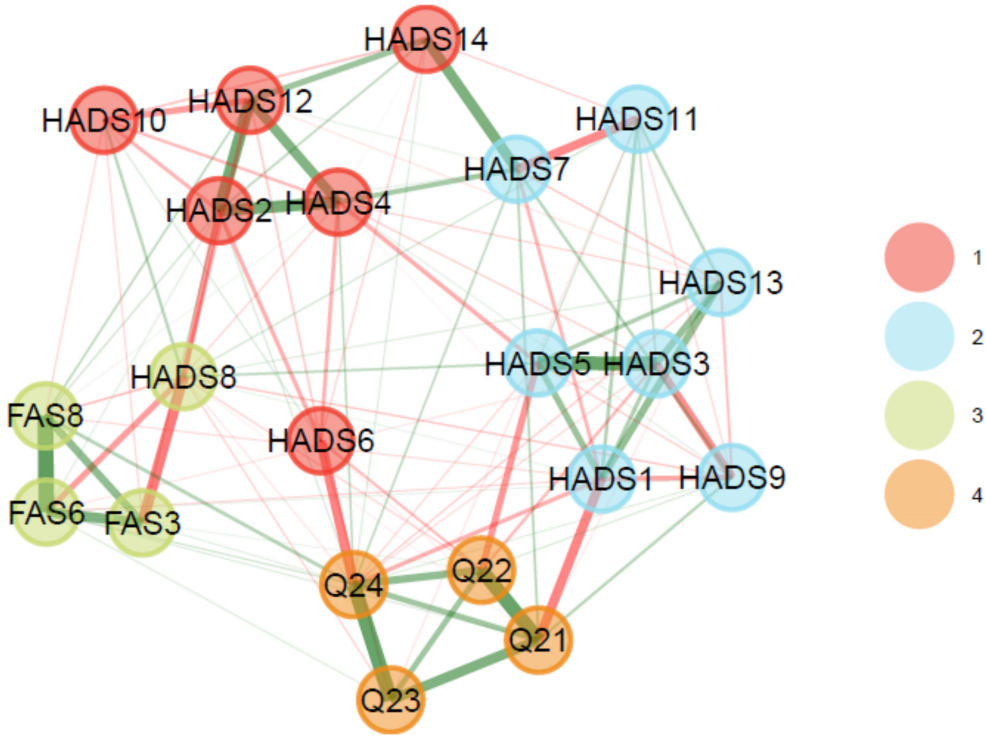

FIGURE 2 Walktrap network.

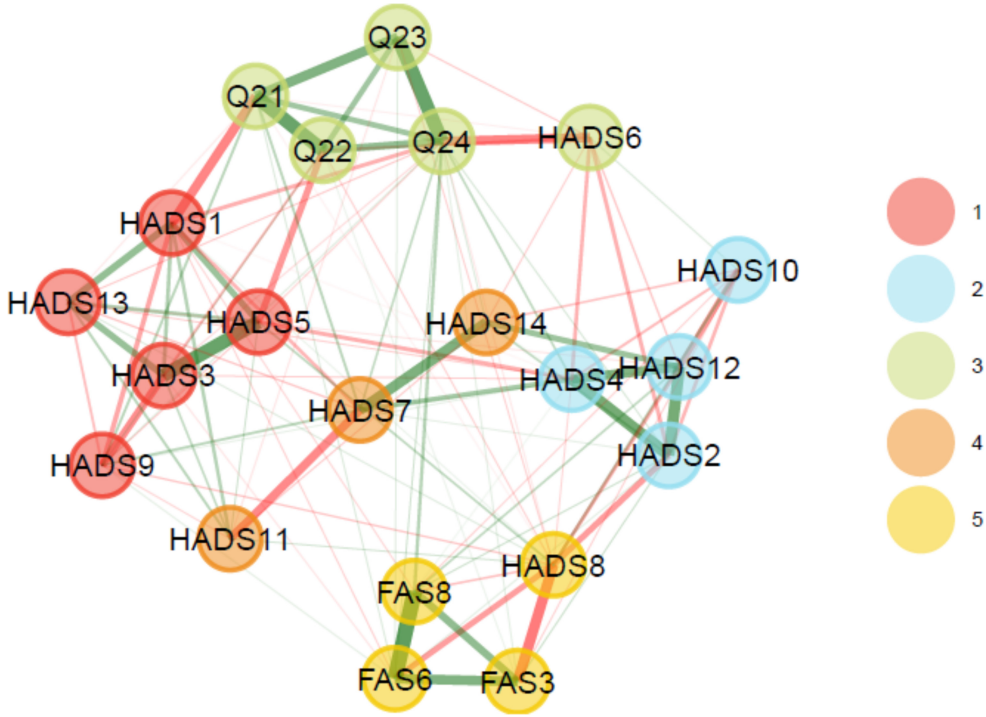

FIGURE 3 Louvain network.

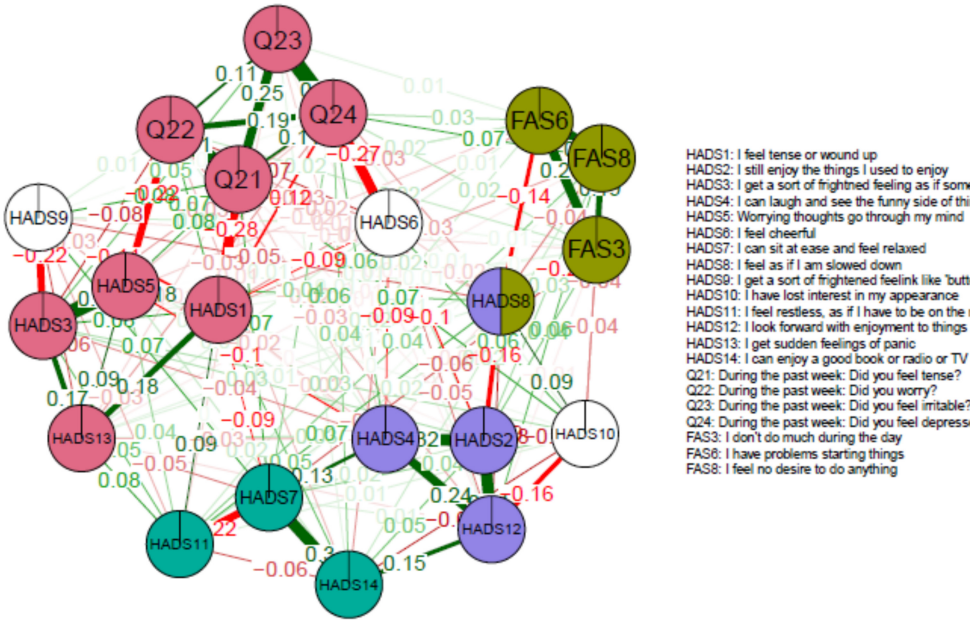

FIGURE 4 Clique percolation method network.

TABLE 3 Items per community.

Community 1	Community 2	Community 3	Community 4	No community
FAS3	HADS2	HADS1	Q21	HADS6
FAS6	HADS4	HADS3	Q22	HADS7
FAS8	HADS12	HADS5	Q23	HADS9
HADS8		HADS13	Q24	HADS10
				HADS11
				HADS14

selected using Lasso and Group Lasso Regularization (see Table S2). The parameters best representing each community were *FAS*3 (motivational anhedonia), *HADS*2 (consummatory anhedonia), *HADS*1 (negative affect) and *Q*23 (emotional functioning).

Survival analyses

A Cox Proportional Hazards Model with age as covariate and the representing variables of the communities as predictors found that the hazard ratios of *FAS*3 ('I don't do much during the day') and *HADS*2 ('I still enjoy the things I used to enjoy') were significant (exp(coef) = 1.25, $p < .001$; exp (coef) = 1.20, $p < .001$, respectively), the other two items (HADS1 and Q23) were not. We can interpret the strength of effect as measured by the hazard ratio as a risk ratio, whereby a hazard ratio of 1 indicates no difference in survival between the groups. Both *FAS*3 and *HADS*2 had a hazard ratio above 1, meaning that if these items increase (a respondent answers higher on the answer scale of these items) the chance of survival decreases. Note that answer categories of the FAS3 range from 1, 'never' till 5, 'always' and of the HADS3 from 0, 'definitely as much' till 3, 'hardly at all'.

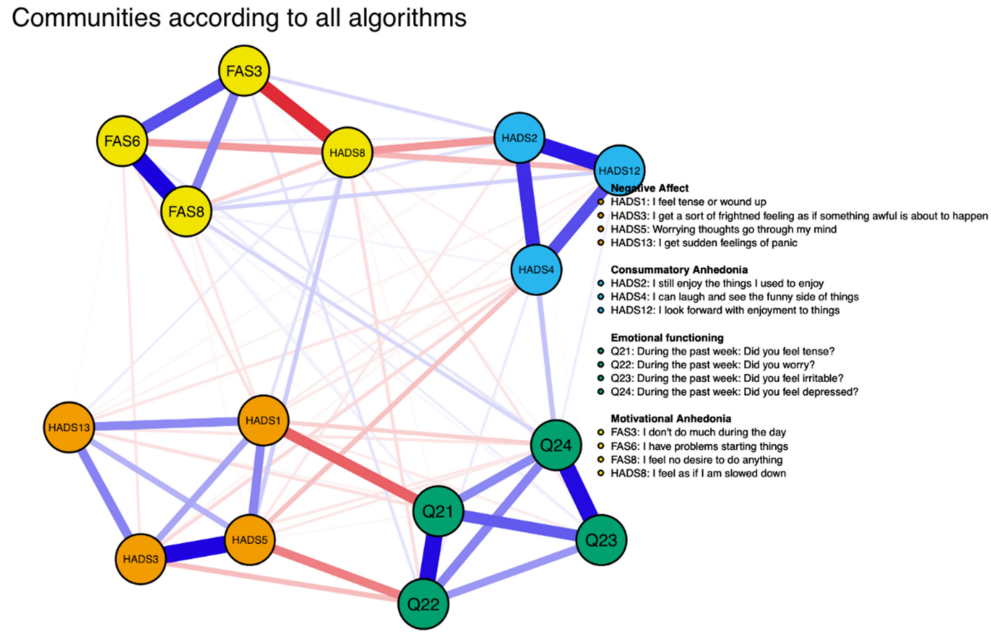

FIGURE 5 Summary network.

Next, we studied the association between the FAS3 and HADS2 and survival with survival plots and the log-rank test. Figure 6 represents the survival curves for the *FAS*3 ('I don't do much during the day'). The *y* axis shows the probability to survive, and the *x* axis shows the time in months.

The survival curves for especially the answer 'regularly', 'often' and 'always' drop faster than the other curves. Therefore, the probability to survive seems to decrease faster for patients in these groups. This is supported by the large differences between observed and expected number of deaths in these groups (see Table S3) with more observed than expected deaths. The survival curves for HADS2 ('I still enjoy the things I used to enjoy') are presented in Figure 7 with time in months. The number of observed and expected deaths are presented in Table S4 and shows that in the group of patients who answer HADS2 with definitely as much (0), the number of observed deaths was lower than could be expected while in the groups of patients who are less able to enjoy the things they used to enjoy (1, 2, 3) observed deaths was higher than could be expected.

Finally, the multivariate model with all depressive symptoms that were found to belong to a community and sociodemographic and clinical variables included, showed that *FAS*3 ('I don't do much during the day') was still associated with mortality over time ($p < .001$). Moreover, also HADS8 ('I feel as if I am slowed down') which just as the FAS3 is part of the community that comprises nodes (items) that correspond to motivational anhedonia, was associated with mortality. Lastly, Q22 (In the last week, did you worry?) was also found to be associated with mortality over time (see Table 4).

DISCUSSION

In the present study, we found support for the distinction between motivational anhedonia, consummatory anhedonia and negative affect by combining different community detection algorithms. This is in line with previous studies showing the importance of focusing on different (cluster) of symptoms rather than viewing depression as a single construct (Fried & Nesse, 2015; Hinnen & Mols, 2022).

While the relationship between depression and mortality in patients with cancer has been investigated before, this is the first study that separated the different core symptoms that defines a depressive

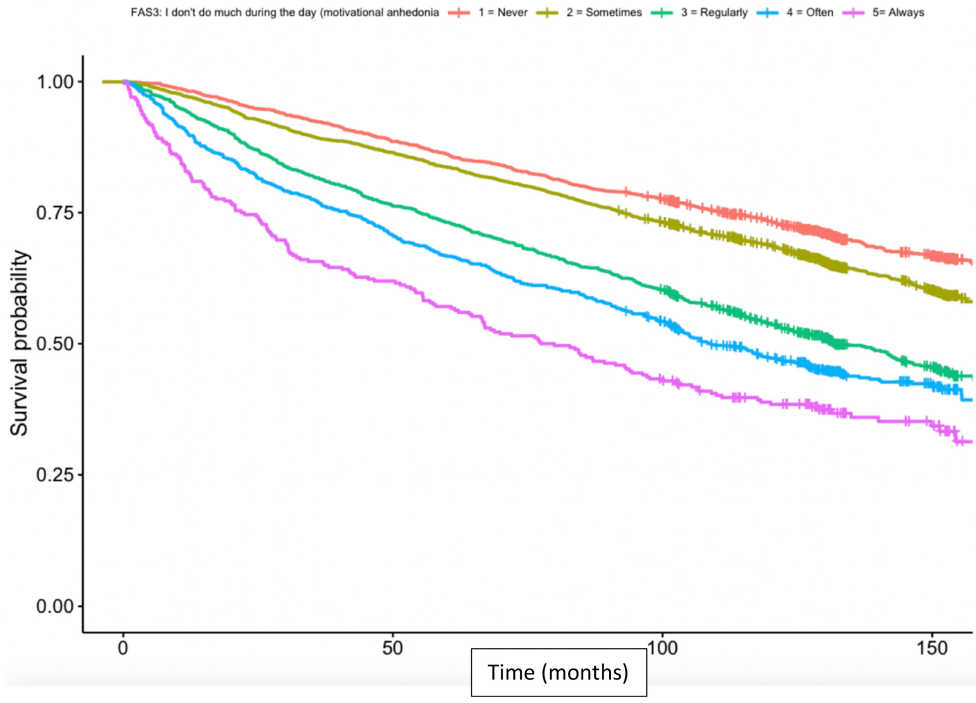

FIGURE 6 Survival curves for FAS3.

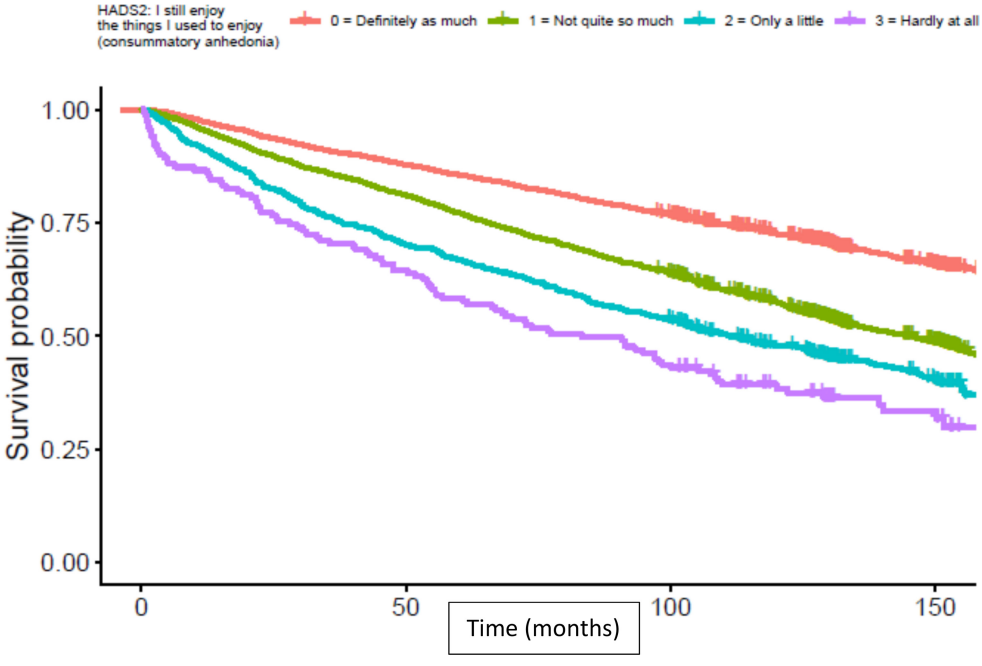

FIGURE 7 Survival curves for HADS2.

TABLE 4 Association between sociodemographic and clinical variables, depressive symptoms and mortality.

	B	Exp (*B*)	SE (*B*)	*Z* score	*p*-value
Age	.07	1.07	.00	23.76	<.001
Gender	−.36	.70	.06	−6.45	<.001
Education	−.05	.95	.03	−191	.06
Marital status	−.02	.98	.03	−.59	.56
Stadium II	.04	1.04	.07	.57	.57
Stadium III	.00	1.00	.08	.02	.98
Stadium IV	.48	1.62	.10	4.96	<.001
Unknown/not applicable	.66	1.96	.09	7.51	<.001
Surgery	−.03	.97	.07	−.44	.66
Chemotherapy	.27	1.31	.06	4.30	<.001
Radiation therapy	.09	1.10	.06	1.61	.11
Targeted therapy	.28	1.33	.08	3.43	<.001
Immunotherapy	−.21	.81	.34	−.61	.54
HADS1	.07	1.07	.05	1.41	.16
HADS2	.06	1.06	.04	1.38	.17
HADS3	−.07	.94	.04	−1.63	.10
HADS4	.05	1.05	.05	1.12	.26
HADS5	−.03	.97	.05	−.66	.51
HADS8[a]	−.12	.89	.04	−3.03	.002
HADS12	.03	1.03	.04	.77	.44
HADS13	.08	1.08	.05	1.67	.10
FAS3	.14	1.15	.03	5.06	<.001
FAS6	.01	1.01	.04	.17	.87
FAS8	.01	1.01	.04	.20	.84
Q21	−.08	.92	.05	−1.44	.15
Q22	.17	1.19	.05	3.46	<.001
Q23	−.07	.93	.05	−1.32	.19
Q24	.09	1.09	.06	1.57	.12

[a]A higher score means not feeling slowed down.

disorder and investigated their relationship with all-cause mortality. In the present study items assessing motivational anhedonia (i.e. I do not do much during the day, I feel as if I am slowed down) were found to be associated with mortality. This remained so when controlling for clinical and sociodemographic variables. This is in line with a study among patients with acute coronary syndrome in which Davidson et al. (2010) looked at the unique association between anhedonia and negative affect on the one hand, and clinical outcome and mortality on the other hand. Davidson also found that anhedonia and not negative affect predicted clinical outcomes and mortality (Davidson et al., 2010). In that study anhedonia was, however, not broken down in motivational anhedonia and consummatory anhedonia. Also, Doyle et al. (2012) found that consummatory anhedonia measured with the HADS-D was associated with mortality in patients with acute coronary syndrome while anxiety (HADS-A) and a mixture of depressive symptoms measured with the BDI was not (Doyle et al., 2012). Interestingly, in the meta-analyses by Pinquart and Duberstein (2010) the BDI was also not found to be associated with mortality in patients with cancer. This supports the notion that it is important to dissociate between the different clusters of depressive symptoms.

Several mechanisms have been suggested to explain why anhedonia may be especially deleterious for health and survival. First, behaviour may mediate this relationship. Motivational and consummatory anhedonia correspond, respectively, to impaired interest to be active, explore new things and obtain rewards ('wanting') and diminished satisfaction from (social) activities ('liking'; Zellner et al., 2011). Consequently, patients with anhedonia may be less inclined to change their lifestyle and take part in healthy behaviours such as physical activities (Leventhal, 2012) or perceive the benefits when doing so. This in turn may impact the changes of survival when confronted with cancer (Liu et al., 2022; Vijayvergia & Denlinger, 2015).

Second, anhedonia may impact social support and connectedness as it is associated with social engagement, motivation and enjoyment (Barkus, 2021; Tan et al., 2020). In turn, social support and connectedness have been found to be associated with clinical outcomes and survival in patients with cancer (Chou et al., 2012; Maunsell et al., 1995; Wu et al., 2020).

Third, inflammation may underly both anhedonia and cancer progression and mortality. That is, a growing body of evidence shows that inflammatory markers are more prevalent in patients with depressive symptoms (Miller & Raison, 2016) and may be especially associated with symptoms related to anhedonia (i.e. lack of interest and/or pleasure; Bekhbat et al., 2022; Mehta et al., 2020; van Eeden et al., 2020). It has been argued that inflammation and associated sickness behaviour (i.e. making the world smaller) may have adaptive values as it may preserve energy and, from an evolutionary perspective, promote survival for the individual (e.g. by preventing encounters with predators while being sick) and the group (e.g. by preventing the transmission of infectious agents; Miller & Raison, 2016). However, while inflammation may have adaptive values (e.g. wound healing) it may also have deleterious effects as it can promote tumour growth and has been found to be associated with tumour progression and mortality (Greten & Grivennikov, 2019; Zhao et al., 2021).

Moreover, in the Cox proportion hazard model item Q22 which asks people whether they worried in the last week was also found to be independently associated with mortality over time. High levels of worry may be a proxy for stress which may impact mortality by influencing both biological and behavioural processes (Collin et al., 2022; Tian et al., 2022).

The present study has some clear strengths such as large sample size and advanced statistics to determine clusters of depressive symptoms and identify those variables that represent these clusters best. Since our study is based upon a convenience sample, it is, therefore, not fully representative of all cancer types and overrepresents rare cancer types. Moreover, despite the longitudinal design of the present study, causality cannot be determined. For example, higher levels of anhedonia may signal a more advanced illness or a more unhealthy lifestyle (e.g. obesity) which may have impacted survival. Furthermore, depressive symptoms may impact people's willingness to participate in studies which may also have impacted the results of this study. Moreover, the time between inclusion (i.e. completing the questionnaire) and diagnosis varied considerably between patients and given the long period of follow-up the clinical importance of the association between depressive symptoms and mortality may be limited. Instead, it may generate hypotheses about the mechanisms of how biological and psychological factors (e.g. anhedonia) may impact clinical outcomes. Moreover, separate items were individually and in combination investigated in relation to survival and not clusters of symptoms. An advantage of using separate item is that the association is then based on a directly measurable/observable item. However, other options would have been possible (e.g. cluster-based association summary). Also, a mixture of self-report questionnaires that were available are used and reanalysed in the present study. Network analysis showed that the communities detected depend on the algorithm used and were largely but not completely in line with the self-report instrument used. Thereby, negative affect consisted of items from the HADS anxiety subscale and items from the emotional functioning subscale of the EORTC. The items within the different questionnaires clustered together but were also highly related, which suggests a single underlying construct (i.e. negative affect). This is in line with previous studies showing that anxiety, worry, feeling depressed and irritation often coexist (Beard et al., 2016; Kalin, 2020). Future studies may want to make use of a prospective design and of questionnaires specifically designed to assess the different core depressive symptoms. However, much-used measures assessing depressive symptoms in

oncology do not dissociate between pleasure and motivational aspects of anhedonia or between anhedonia and negative affect (Treadway & Zald, 2011).

Implications

The finding that separate clusters of symptoms that correspond with anhedonia and negative affect can be distinguished and that especially anhedonia may be associated with mortality is important as it suggests that looking at particular (clusters of) depressive symptoms may be more informative than using depression as a single construct (i.e. syndrome). If and why especially motivational anhedonia may impact clinical outcomes should be further investigated. Future studies investigating depression in oncology may want to dissociate between the core depressive symptoms as merging these symptoms may obfuscate the results.

AUTHOR CONTRIBUTIONS

C. Hinnen: Conceptualization; writing – original draft; writing – review and editing. **Hochstenbach, S:** Methodology; formal analysis. **F. Mols:** Supervision; writing – review and editing. **B.J.A. Mertens:** Supervision; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

The data is *freely available* for non-commercial scientific research, subject to study question, privacy and confidentiality restrictions and registration (www.profilesregistry.nl).

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was conducted according to the Declaration of Helsinki guidelines and ethical approval was obtained for all study samples separately, from a local certified medical ethics committee of the participating hospitals.

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