Prognostic value of a brief loneliness questionnaire for patients with coronary heart disease
Proposal for a prediction model
Blakoe, Mitti; Christensen, Anne Vinggaard; Palm, Pernille; Højskov, Ida Elisabeth; Thrysoee, Lars; Thorup, Charlotte Brun; Borregaard, Britt; Mols, Rikke Elmose; Rasmussen, Trine Bernholdt; Berg, Selina Kikkenborg

Published in:
Journal of Clinical Nursing

DOI:
10.1111/jocn.16023

Publication date:
2022

Document version:
Accepted manuscript

Citation for published version (APA):

Go to publication entry in University of Southern Denmark's Research Portal

Terms of use
This work is brought to you by the University of Southern Denmark. Unless otherwise specified it has been shared according to the terms for self-archiving. If no other license is stated, these terms apply:

• You may download this work for personal use only.
• You may not further distribute the material or use it for any profit-making activity or commercial gain
• You may freely distribute the URL identifying this open access version

If you believe that this document breaches copyright please contact us providing details and we will investigate your claim. Please direct all enquiries to puresupport@bib.sdu.dk
Prognostic value of a brief loneliness questionnaire for patients with coronary heart disease; proposal for a prediction model.

Mitti Blakoe a,b, MSc, mitti.blakoe@regionh.dk
Anne Vinggaard Christensen a, PhD, anne.vinggaard.christensen@regionh.dk
Pernille Palm a, PhD, pernille.palm@regionh.dk
Ida Elisabeth Hojskov c, PhD, ida.elisabeth.hoejskov@regionh.dk
Lars Thrysoe c, PhD, lars.thrysoe@rsyd.dk
Charlotte Brun Thorup c, PhD, cbt@rn.dk
Britt Borregaard f,g, PhD, britt.borregaard@rsyd.dk
Rikke Elmove Mols h, PhD, rikkmols@rm.dk
Trine Bernholdt Rasmussen i, PhD, trine.bernholdt.rasmussen@regionh.dk
Selina Kikkenborg Berg a,b, PhD, Selina.Kikkenborg.Berg.01@regionh.dk

a. Department of Cardiology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark
b. Faculty of Health and Medical Sciences, University of Copenhagen, Denmark
c. Department of Cardiothoracic Surgery, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/jocn.16023

This article is protected by copyright. All rights reserved
Authors contribution

SKB conceived the overall idea for the DenHeart study. All Authors contributed to the design of the present study. AVC and MB performed the statistical analyses. MB wrote the first draft of the manuscript. All authors revised the manuscript critically. All authors have given their final approval of the version to be published.

Information about previous presentations

Neither the manuscript, nor any part of it, have been published or are currently under consideration for publication by any other journal, and have not been previously published in similar form. All co-authors have read the manuscript and approved its submission to Journal of Clinical Nursing. The authors declare that they have no competing interests.

This article is protected by copyright. All rights reserved
Acknowledgement

We wish to sincerely thank the participants who volunteered and generously gave of their time to take part in the cognitive interview sessions. Your contribution has been vitally important. Also, we wish to thank Jan Christensen for overall guidance on the statistical analysis and Camilla Rotvig Jensen for helping to perform the statistical analysis.

Conflict of interest

The authors declare that they have no competing interests.

Sources of support

The author disclosed receipt of the following financial support for the research of this article: University hospital of Copenhagen, Rigshospitalet research grant [grant number E-22281-07].
Title

Prognostic value of a brief loneliness questionnaire for patients with coronary heart disease; proposal for a prediction model.

Abstract

**Background:** In patients with coronary heart disease (CHD), loneliness is associated with increased risk of morbidity and mortality. No predictive tool is available to detect patients who are influenced by loneliness to a degree that impacts mortality.

**Aim:** To: i) Propose a prediction model that detects patients influenced by loneliness to a degree that increases one-year all-cause mortality, ii) Evaluate model classification performance of the prediction model, iii) Investigate potential questionnaire response errors.

**Method:** A cohort of patients with CHD (n=7,169) responded to a national cross-sectional survey, including two questions on loneliness. Information on cohabitation and follow-up information on one-year all-cause mortality were obtained from national registers. Prediction model development was based on the prognostic values of item responses in the questionnaire on loneliness and of
cohabitation, evaluated with Cox-proportional Hazards Ratio (HR). Item responses which significantly predicted one-year mortality were included in the High-Risk Loneliness (HiRL) prediction model. Sensitivity, specificity and likelihood ratio were calculated to evaluate model classification performance. Sources of response errors were evaluated using verbal probing technique in an additional cohort (n=7). The TRIPOD checklist has been used to ensure transparent reporting.

**Results:** Two item responses significantly predicted one-year mortality HR=2.24 (95%CI=1.24-4.03) and HR=2.65 (95%CI=1.32-5.32) and were thus included in the model. Model classification performance showed a likelihood ratio of 1.89. Response error was evaluated as low.

**Conclusion:** Based on prognostic value in a loneliness questionnaire, a prediction model suitable to screen CHD patients for high-risk loneliness was suggested.

**Relevance to clinical practice:** The HiRL prediction model is a short and easy-to-use screening tool that offers clinical staff the opportunity to identify patients with established CHD who are influenced by loneliness to an extent that impacts mortality. However, further evaluation of model performance and questionnaire validation is recommended before integrating the model into clinical practice.

**Keywords**

Loneliness, social support, screening, coronary heart disease, prognostic research, prognostic tool

**Introduction**

In health care research the term “loneliness” is often used interchangeably with “lack of social support” and “social isolation”, and although the terms are interrelated the theoretical definitions are heterogeneous (Bucholz & Krumholz, 2012; Valtorta, Kanaan, Gilbody, & Hanratty, 2016). However, overall consensus exists that loneliness can be defined as: A distressing feeling that accompanies the perception that one’s social needs are not being met by the quantity or especially
the quality of one’s social relationships (Hawkley & Cacioppo, 2010). Depending on the measurement used, evidence show that 5-30% of the general adult population in high-income countries experience loneliness as a chronic state (A. I. Christensen et al., 2012; Hawkley & Cacioppo, 2010; Heinrich & Gullone, 2006; Victor & Yang, 2012).

Loneliness has received growing attention as an important etiological and prognostic factor, especially in relation to coronary heart disease (CHD) (Barth, Schneider, & von Kanel, 2010; Burg et al., 2005; A. V. Christensen et al., 2019; Kuper, Marmot, & Hemingway, 2002; Lett et al., 2005; Murphy et al., 2008; Reblin & Uchino, 2008). A recent systematic review found that loneliness was associated with a 29% increase in risk of incident CHD (Valtorta, Kanaan, Gilbody, Ronzi, & Hanratty, 2016), and in prognostic studies loneliness is shown to nearly double the risk of mortality (Barth et al., 2010; Kuper et al., 2002). This indicates that loneliness may be the cause of an increased risk of mortality comparable to other known risk factors such as severe obesity and hypercholesterolemia (Piepoli et al., 2016).

The link between loneliness and health outcomes is explained by a combination of two main hypotheses. The first main hypothesis “The buffering model” posits that especially functional social support protects persons from the potentially pathogenic influence of stress-induced cardiovascular reactivity caused by stressful events (Cohen, 2004; Cohen & Wills, 1985). The biological process in stress-buffering has been linked to immune function, cortisol response and levels of protective hormones (Cohen & Janicki-Deverts, 2009; Uchino, 2006). The other main hypothesis “The main-effect model” posits that social relationships promote healthy behavior, as social support increase the motivation to make healthier choices (Cohen & Janicki-Deverts, 2009; Cohen & Wills, 1985).

Based on the substantial amount of evidence linking loneliness to worsened health outcome, the European guidelines on cardiovascular disease prevention recommends inclusion of loneliness in the initial assessment of psychosocial risk factors in clinical practice (Albus, Jordan, & Herrmann-Lingen, 2004; Piepoli et al., 2016).

Measuring loneliness in clinical practice, however, is not straight forward, as loneliness arises as a consequence of lack of social support which is composed of different dimensions. Within health and social science, these dimensions are often conceptualized in two broad domains; functional and structural support (Bucholz & Krumholz, 2012; Cohen, 2000, 2004; Valtorta, Kanaan, Gilbody, &
Hanratty, 2016). Structural support is the existence of family and friends or other social network members within an individual’s environment. Important issues when measuring structural support are the number of contacts (network size), frequency of contact, and marital status (Cohen, 2004; Valtorta, Kanaan, Gilbody, & Hanratty, 2016). Functional support on the other hand, deals with the quality of the social support provided from social network members, for example, instrumental (help getting tasks done), informational (providing information) or emotional (feelings of being loved) (Cohen, 2004; Valtorta, Kanaan, Gilbody, & Hanratty, 2016). Functional support is considered to be especially essential after critical events, where it is believed to have a central effect as a buffer on stress-induced cardiovascular reactivity and also to be effective for an adaptive psychological coping response (Barth et al., 2010; Cohen & Wills, 1985).

Existing measurement tools to measure loneliness weight the structural and functional dimensions of social support differently. An often used tool is the validated scale “UCLA (University of California and Los Angeles) loneliness scale” (Velarde-Mayol, Fragua-Gil, & Garcia-de-Cecilia, 2016), which primarily measures functional support. Also, shorter instruments have been developed, for example, the Close Persons Questionnaire (Stansfeld & Marmot, 1992). The available tools are mainly developed to measure loneliness in general and healthy populations, but as the need for social support, and consequently the experience of loneliness, seemingly differs in a population affected by a critical event (AUTHOR, 2021; Pryor, Page, Patsamanis, & Jolly, 2014; Uchino, 2006; Vassilev, Rogers, Kennedy, & Koetsenruijter, 2014), a generic tool might not be adequate to measure loneliness in a CHD population.

Even though loneliness is a negative feeling that is worth addressing as a matter of importance in itself, identifying loneliness in clinical practice is also based in an interest in detecting patients at risk of poor health outcomes. Consequently, in clinical practice a prognostic tool is needed to identify and address loneliness in patients with CHD. A short and easy to use predictive tool, capable of detecting patients influenced by loneliness to a degree that impacts mortality, may facilitate targeted care pathways in clinical practice in accordance with the recommendations from the European Guidelines on cardiovascular disease prevention.
Objectives

The objectives of this study were to: i) Propose a prediction model that detects patients influenced by loneliness to a degree that increases one-year all-cause mortality, ii) Evaluate model classification performance of the prediction model, iii) Investigate potential questionnaire response errors.

Method

The scientific and theoretical framework in this study was based on the conceptualization of loneliness as: “A distressing feeling that accompanies the perception that one’s social needs are not being met by the quantity or especially the quality of one’s social relationships” (Hawkley & Cacioppo, 2010). Consequently, loneliness was assessed in a questionnaire based on both structural (quantity) and functional (quality) aspects of social support.

As the overall aim of the study was to perform a preliminary investigation of the performance of a short and easy-to-use prediction tool, the study was completed in three parts, in a complementary structure. In the following, the three parts will be described separately in more detail. The Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) checklist has been used to ensure transparent reporting of the study (Supplementary File 1).

Development of the prediction model

Eligibility criteria

During one year (April 15th 2013 to April 15th 2014) all patients aged ≥ 18 discharged or transferred from the five Danish heart centres were invited to participate in the DenHeart survey (Berg et al., 2014). Demographics of patient included in the study is presented in Table 1.

>Table 1<

This article is protected by copyright. All rights reserved
The DenHeart study was a national cross-sectional survey combined with one-year follow-up data from national registers. Patients who did not have a Danish civil registration number, did not understand Danish, or were unconscious at the time of transfer from the heart centre were not invited to participate. Further details are described elsewhere (Berg et al., 2014; Rasmussen et al., 2019). Patients from the survey with CHD as the primary diagnosis (n = 7,169) were included in the present study. A flowchart is shown in Figure 1.

Figure 1

Baseline characteristics
At baseline patients answered questions about health behaviour, including current and previous smoking behaviour, alcohol intake during a typical week and medication adherence and height, and weight for the calculation of Body Mass Index (BMI). Information on sex and age were obtained from The Danish Civil Registration System (Pedersen, 2011). Cardiac diagnosis at discharge and comorbidity were obtained from The Danish National Patient Register (Lynge, Sandegaard, & Rebolj, 2011). Information on comorbidity was obtained 10 years back, the index diagnosis excluded, and used to calculate the Tu comorbidity index score (Tu et al., 2001). The Tu score was calculated with information on primary and secondary diagnoses, including congestive heart failure, cardiogenic shock, arrhythmia, pulmonary oedema, malignancy, diabetes, cerebrovascular disease, acute/chronic renal failure and chronic obstructive pulmonary disease. All diagnoses are weighted equally. A Tu score of zero equals no co-morbidities, a score of one means one of the included co-morbidities etc., and the score was divided into four categories; 0, 1, 2, and 3+. Educational level was obtained from The Danish Education Registers (Jensen & Rasmussen, 2011).

Loneliness measurement at baseline
Cohabitation was chosen as a proxy for structural social support. Data on cohabitation was obtained from the Danish Civil Registration System concerning cohabitation status “yes” or “no”. Cohabitation “yes” was defined by the following categories: married couple, other couple, and
household consisting of several people from more than one family (e.g. nursing home or communal living). Cohabitation “no” was defined as not living in an identifiable cohabitation.

The functional aspects of loneliness were measured by patients responding to two questions in the DenHeart survey: 1) “Does it ever happen that you are alone even though you would prefer to be with other people?” with four possible response options: i) “yes, often” ii) “yes, sometimes” iii) “yes, but rarely” iv) “no” and 2) “Do you have somebody to talk to if you experience problems or need support?” with four possible response options: i) “yes often”, ii) “yes most of the time”, iii) “yes sometimes” and iv) “no never or almost never”. The questions originated from the Danish National Health Survey (A. I. Christensen et al., 2012) and were included in the DenHeart Survey (Berg et al., 2014). Patients were asked to complete and return the questionnaire before leaving the hospital or to complete it at home within three days of discharge.

Prognostic outcome
Information on all-cause mortality during the first year after the index admission was obtained from The Danish Civil Registration System (Pedersen, 2011). Follow-up was continued until death, emigration, or end of one-year follow-up. One-year follow-up period was chosen as it is a common follow-up period in health science and thus, results can be compared across studies within the field.

Statistical analysis; Investigating candidate prognostic variables
Categorical variables are presented as frequencies (n) and percentages, while continuous variables are presented as mean ± Standard Deviation (SD). In the development phase, Cox proportional hazards regression models, with age as the time scale, were used to explore the univariate and multivariable prognostic value of item responses in the questionnaire. Multivariable analyses were adjusted for variables known to be additional risk factors for mortality and therefore may serve as confounding factors, i.e. age, educational level, Tu comorbidity score, body mass index, smoking behaviour, alcohol intake and medication adherence. Univariate and multivariable prognostic values are presented as Hazard Ratios (HR) with 95% Confidence Intervals (CI). Additionally, we performed an exploratory inspection of a combination of item responses in univariate analysis.

A total of 462 respondents were excluded from the analysis due to incomplete survey response or lack of information on cohabitation status.
SAS version 9.4. was used to conduct all analysis.

Development of the HiRL prediction model

The Prognosis Research Strategy (PROGRESS) group defines a prognostic variable as any measure, e.g., symptoms, behavioural or psychosocial measures, that are associated with a subsequent clinical outcome among people with a given health condition (Hemingway et al., 2013; Riley et al., 2013).

In the present study, we investigated item responses in a loneliness questionnaire as candidate prognostic variables using prospective data in a multivariable statistical model, as recommended when conducting exploratory prognostic research (Kent, Cancelliere, Boyle, Cassidy, & Kongsted, 2020; Riley et al., 2013). Furthermore, we explored the prognostic value of possible combinations of co-existing item responses.

If the prognostic value for the item responses had a significant impact on one-year mortality in both the univariate and multivariable analysis as well as analysis of possible combination of co-existing item responses, the item responses were chosen to classify high-risk loneliness in the HiRL prediction model. This pragmatic approach on which responses should define high-risk, is a common first step in prediction model development (Riley et al., 2013; E.W. Steyerberg, 2019).

Evaluation of the HiRL prediction model

As recommended when performing the apparent validation of a prediction model, model classification performance was evaluated (E.W. Steyerberg, 2019). The classification performance of the derived prediction model was assessed by calculating sensitivity, specificity, positive and negative likelihood ratio in the development cohort. Given the recognition that loneliness is not a strong predictor of mortality in itself, no attempt was made to construct receiver operating characteristic curves, overall performance, or calibration.
Investigating sources of questionnaire response errors

Questionnaire response errors were evaluated using the cognitive interviewing technique ‘verbal probing’ (Beatty, 2007; Willis, 1999). The probing was performed retrospectively as it is the preferred way to test self-completion questionnaires (Willis, 1999). The cognitive interviews were conducted in an additional cohort of patient admitted at Rigshospitalet in the capital region of Denmark in the period July 1st to July 7th 2019 (n=7). Inclusion and exclusion criteria were similar to the DenHeart survey. The two questions related to loneliness concerning “being alone unwished-for” and “lack of someone to talk to” were answered on a four-item scale similar to the DenHeart survey, while the question on cohabitation was asked as “Do you live alone”, with the possible answers “Yes” and “No”. The cognitive interview technique ‘verbal probing’ was used to identify potential response errors by focusing on respondents’ interpretation of words used in the questionnaire (Beatty, 2007; Willis, 1999). In the present study this was completed by asking “What does this question mean to you in your own words?”. To reconfirm their conceptualization, additional questions were asked that required respondents to verbalize their thought processes as they responded to the questions. Statements were noted during the interview. All sessions were conducted by the first author.

Ethics

According to Danish legislation surveys are only required to be approved by the Danish Data Protection Agency (2007-58-0015/30-0937). The Danish National Board of Health permitted use of register data. The Danish Data Protection Agency approved the cognitive interview sessions (journal number: VD-2018-490). Informed consent was obtained from each patient. The study conforms to the Declaration of Helsinki (“THE WORLD MEDICAL ASSOCIATION I. DECLARATION OF HELSINKI


Results

Investigating candidate prognostic variables

This article is protected by copyright. All rights reserved
Of the 7,169 patients included in the development cohort, 72.5 % (n=5,196) were male. Mean age was 65.4 years (SD=10.6). In the one-year follow-up period 156 patients died.

Results from the univariate and multivariable Cox-proportional hazards regression analyses of the prognostic value of item responses on one-year mortality are presented in Table 2.

In the exploratory inspection of potential combinations of item responses, HRs for one-year mortality were calculated for a possible combination of co-existing item responses, resulting in multiple group classifications. A selection of the analysis is presented in Figure 2.

The item responses related to “cohabitation” did not independently influence mortality in the univariate (HR 1.15 95% CI 0.76-1.74) nor multivariable analysis (HR 1.07 95% CI 0.60-1.92) (Table 2). In the analysis of the possible combination of co-existing item responses, “cohabitation” was correlated with the two survey questions on loneliness concerning “being alone unwished-for” and “lack of someone to talk to” The analysis did not consistently increased HR for mortality when co-existing with other possible item responses (Figure 2).

Item responses to the survey question concerning ““being alone unwished-for” showed a proportionally increasing risk of mortality in line with the frequency of being alone when wanting to be with others, where the response “yes, often” significantly increased the risk of mortality, in univariate analysis (HR 2.09 95% CI 1.29-3.40) and multivariable analysis (HR 2.24 95% CI 1.24-4.03) (Table 2). When analysing the possible combinations of co-existing item responses, the response “often” similarly increased HR for mortality when co-existing with other responses. (Figure 2).
Responses to the question concerning “lack of someone to talk to” did not show a linear increase in the risk of mortality in conjunction with the response scale, as the answer “Yes, often” and “sometimes” resulted in opposing HR. However, the response “No, never or almost never” showed a significantly increased risk in both univariate (HR 2.71 95% CI 1.55-4.74) and multivariable analysis (HR 2.65 95% CI 1.32-5.32 ) (Table 2) and likewise in the analysis of the possible combination of co-existing item responses (Figure 2).

Development of the HiRL prediction model

The prognostic properties showed an overall trend in the survey questions on functional support, as the decrease of functional support resulted in an increased risk of one-year mortality. Two item responses on functional support (“Does it ever happen that you are alone even though you would prefer to be with other people? ‘often’” and “Do you have somebody to talk to if you experience problems or need support?” “No, never or almost never” ) were chosen to classify high-risk loneliness, as the responses had a significant impact on one-year mortality in both univariate and multivariable analysis as well as analysis of the possible combination of co-existing item responses. The risk-stratified points related to prognostic value for one-year mortality in the developed HiRL prediction model is presented in Table 3.

>Table 3<

Evaluation of classification performance

The development cohort (n=7169) was classified into subgroups of “high-risk lonely” and “not high-risk lonely” according to the HiRL prediction model. In the analysis 167 respondents were excluded due to incomplete survey responses in one or both item responses which classified high-risk loneliness . Demographics of the cohort and the derived subgroups are presented in Table 4.

>Table 4<
The classification performance of the derived HiRL prediction model was assessed by calculating sensitivity, specificity, negative likelihood ratio, and positive likelihood ratio.

The analysis of model classification performance revealed a sensitivity of 19.9% and specificity of 89.5%. The positive likelihood ratio was 1.89 indicating that the positive test result for high-risk loneliness was nearly twice as often in patients who died within one year. The negative likelihood ratio was 0.89, indicating that a negative test result was almost as frequent in those who died as in those who did not.

We also tested classification performance in a similar prediction model including “Cohabitation” “Yes”. In this analysis the sensitivity increased (32%) while the specificity decreased (69%), indicating that the inclusion of this item response in the model resulted in an increase of true positive test results, but also a decrease in true negative results.

Evaluation of questionnaire response errors

Potential questionnaire response errors were evaluated in cognitive interviews, using a verbal probing technique (Beatty, 2007; Willis, 1999). The interviews revealed that the informants’ perception of the question “Do you live alone” was similar, as they comprehended the question as sharing a household with another person. However, one informant shared a household with a teenage son and doubted which response to provide to the question.

When informants were encouraged to verbalize their thought process as they responded to the question “Does it ever happen that you are alone even though you would prefer to be with other people?”, some informants stated that they were often alone but that they were comfortable with it. These informants answered “No” or “Yes but rarely”. Other informants described that being alone resulted in an unwanted feeling of loneliness. These informants had answered “Yes sometimes” or “Yes often”. As the question intended, these statements of conceptualization revealed that patients responded to the question based on whether they were alone, but also on the subjective experience of whether they were alone unwished-for.

Concerning the question “Do you have somebody to talk to if you experience problems or need support?”, the informants’ conceptualization showed a distinction between the possibility of talking to someone and a subjective desire to talk to someone. However, two informants had both a desire and a possibility to talk to someone but did not feel that they could talk in a meaningful way with
the people in their existing network. These informants perceived the response options in the questionnaire as deficient and were unsure which response to give. This reveals that the possible responses to the question could uncover the informant’s opportunity to talk to someone, but were incomplete to uncover whether such conversation was perceived as rewarding and meaningful to the informant.

Discussion

Multiple studies have verified that loneliness has a prognostic value in patients with established CHD, and as such is relevant to identify in clinical practice (Barth et al., 2010; Burg et al., 2005; A. V. Christensen et al., 2019; Kuper et al., 2002; Lett et al., 2005; Murphy et al., 2008; Reblin & Uchino, 2008; Valkorta, Kanaan, Gilbody, Ronzi, et al., 2016). In the present study, we aimed to investigate the prognostic value of three survey components on loneliness and cohabitation from a national survey (Berg et al., 2014), to suggest a predictive tool capable of detecting CHD patients influenced by loneliness to a degree that affects one-year mortality. A short self-reported questionnaire was chosen to form the basis of the HiRL prediction model, since a short and easy to use predictive tool will be easiest to integrate into clinical practice.

The investigation of the prognostic value of each item response in a loneliness questionnaire revealed that “Cohabitation” had a marginal impact on one-year mortality while the item response “being alone unwished-for” “often” and the item response “lack of someone to talk to” “Never” resulted in a significantly increased risk of one-year mortality in both the univariate and the multivariable analysis, as well as the analysis of the possible combinations of co-existing item responses. Therefore, these two item responses were included in the model as a prognostic variable for “high-risk loneliness”.

In the present study, the two survey questions related to the functional dimensions of social support had the most severe influence on one-year mortality. The “buffering model” which posits that especially functional social support is associated with stress-induced cardiovascular reactivity (Cohen, 2004; Cohen & Wills, 1985), and the main effect model which posits that adequate social support may promote healthy behaviour, are plausible reasons why in the present study, a higher HR for mortality is seen in regard to patients’ functional support measured by the subjective feeling
of “being alone unwished-for” and “lack of someone to talk to”, relative to the structural support measured by cohabitation status.

However, the overall trend in the results, that decrease of functional support resulted in an increased risk of one-year mortality, was non-linear in the responses to the question “lack of somebody to talk to”. The contradictory prognostic properties in the response related to this question might be explained by the findings in the cognitive interview, as some informants stated that the response options to this question were deficient. The informants explained this deficiency in the following way; as an experience of having the opportunity to talk to someone in the social network, but at the same time not feeling they could talk in a meaningful way. Therefore, the distinction of the structural (someone to talk) and functional (talking in a meaningful way) dimensions of social support, must be considered inadequately addressed in the wording of this survey question. In future research, it is desirable to formulate such a survey question so that the respondent can answer unambiguously based on the functional support provided by talking with people in the social network in a meaningful way, and not only the opportunity to talk to someone.

Within prognostic research, exploratory studies are considered an essential first step towards undertaking a confirmatory study (Kent et al., 2020; Riley et al., 2013; E.W. Steyerberg, 2019). In the present study, we chose a pragmatic approach, recognizing that loneliness cannot function as a prognostic variable independently of other prognostic variables e.g. obesity or comorbidity. Therefore, we did not aim to conduct a model with a high sensitivity and specificity, but merely to investigate a prediction model with potential to identify patients in clinical practice with an increased risk of one-year of mortality due to loneliness. However, before such a prediction model might be adopted in clinical practice, it is recommended that further research show that it provides predictions that are valid outside the development sample by conducting external validation studies (E. W. Steyerberg et al., 2013).

Strengths and limitations

The questionnaire on loneliness used in the present study has been used repeatedly in large national health population surveys and in health care research (A. I. Christensen et al., 2012), which is why the prognostic value of the questionnaire was relevant to investigate. However, the questionnaire is...
not validated, which stresses caution in the interpretation of the present study. This limitation has been diminished by the evaluation of response errors via cognitive interviews.

The data used to identify candidate prognostic variables originated from the DenHeart survey in which 53% of the eligible patients completed and returned the questionnaire. The high number of non-responders introduced selection bias in the study population. A comparative analysis of sociodemographic, clinical, and self-reported health in non-responders and responders among CHD patients in the survey, revealed that significantly more respondents were younger, had a higher income and educational level and a lower comorbidity burden (Rasmussen et al., 2019). Consequently, we hypothesize that responders have an advantageous health outcome, and our results thus do not completely reflect a CHD population.

We chose to include all patients treated medically, invasively or surgically for CHD, despite knowing from previous research that physical and psychological consequences can differ among treatment groups. The decision was based on evidence demonstrating how social support is associated with health outcomes across CHD treatment groups (Barth et al., 2010; A. V. Christensen et al., 2019; Kuper et al., 2002; Valtorta, Kanaan, Gilbody, Ronzi, et al., 2016). Also, the qualitative literature in the field has revealed that CHD patients who experience loneliness in their everyday life, experience an even greater degree of loneliness in the early rehabilitation period, as this period is characterized by basic changes in ways of dealing with health and illness, regardless of what treatment the patient has undergone (AUTHOR, 2021; Pryor et al., 2014; Vassilev et al., 2014).

We investigated model classification performance in the total cohort from which the model is derived. This approach may lead to an optimistic estimation of performance. However as 100% of the available data is used, this approach leads to a more stable estimation of model classification performance (E.W. Steyerberg, 2019).

Conclusion

Two questionnaire item responses on loneliness were significantly associated with one-year mortality, and therefore chosen as prognostic markers in the HiRL prediction model. Model classification performance revealed suboptimal sensitivity, specificity and likelihood ratio.
However, as intended the model managed to identify patients with high-risk loneliness, i.e. patients classified as high-risk lonely had nearly two-fold risk of one-year mortality. Sources of response error were evaluated as low in cognitive interviews. Consequently, the HiRL prediction model is suitable to screen CHD patients for high-risk loneliness, but further evaluation of model performance is recommended to be carried out, as well as validation of the questionnaire, before integrating the tool in clinical practice.

Relevance to clinical practice

In clinical practice a short and easy-to-use screening tool is needed to identify and address loneliness in patients with CHD and thus, accommodate the recommendations from the European Guidelines on cardiovascular disease prevention. The HiRL prediction model offers clinical staff the opportunity to identify patients with established CHD who are influenced by loneliness to a degree that negatively influence health outcomes.

What does this paper contribute to the wider global clinical community?

- Based on the prognostic value of three loneliness survey questions, a prediction model suitable to screen CHD patients for high-risk loneliness was proposed.
- The HiRL prediction model mainly measures functional components of social support, which is substantiated by theory from health and social science literature.
- The HiRL prediction model has potential to identify patients influenced by loneliness to a degree that increases risk of mortality, in a uniform way.

References


contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J, 37(29), 2315-2381. doi:10.1093/eurheartj/ehw106


This article is protected by copyright. All rights reserved


Velarde-Mayol, C., Fragua-Gil, S., & Garcia-de-Cecilia, J. M. (2016). [Validation of the UCLA loneliness scale in an elderly population that live alone]. Semergen, 42(3), 177-183. doi:10.1016/j.semerg.2015.05.017


THE WORLD MEDICAL ASSOCIATION I. DECLARATION OF HELSINKI

Table 1: Demographics of patients with coronary heart disease included in the study

<table>
<thead>
<tr>
<th></th>
<th>Total CHD cohort (n=7169)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>5194 (72)</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>65.4 (10.6)</td>
</tr>
<tr>
<td>Comorbidity Tu Index, n (%)</td>
<td></td>
</tr>
<tr>
<td>Score 0</td>
<td>4158 (58)</td>
</tr>
<tr>
<td>Score 1</td>
<td>1936 (27)</td>
</tr>
<tr>
<td>Score 2</td>
<td>717 (10)</td>
</tr>
<tr>
<td>Score ≥ 3</td>
<td>430 (6)</td>
</tr>
<tr>
<td>Educational level, n (%)</td>
<td></td>
</tr>
<tr>
<td>Basic school</td>
<td>2292 (32)</td>
</tr>
<tr>
<td>Upper secondary or</td>
<td></td>
</tr>
<tr>
<td>vocational school</td>
<td>3194 (45)</td>
</tr>
<tr>
<td>Higher education</td>
<td>1511 (21)</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>1236 (18)</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>27.6 (4.9)</td>
</tr>
<tr>
<td>Mortality, n (%)</td>
<td>160 (2.2)</td>
</tr>
</tbody>
</table>
Table 2: Hazard Ratio for one-year mortality in patients with Coronary Heart Disease, calculated in univariate and multivariable analysis on each item response.

<table>
<thead>
<tr>
<th>Item</th>
<th>Item response</th>
<th>Responses n (%)</th>
<th>Univariate* HR (95% CI)</th>
<th>Multivariable** HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Cohabitation&quot; a</td>
<td>Yes</td>
<td>5221 (72.8)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>1879 (26.2)</td>
<td>1.15 (0.76-1.74)</td>
<td>1.07 (0.60-1.92)</td>
</tr>
<tr>
<td>&quot;Does it ever happen that you are alone even though you would prefer to be with other people?&quot; b</td>
<td>No</td>
<td>3417 (47.7)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Yes, but rarely</td>
<td>1705 (23.8)</td>
<td>0.87 (0.55-1.36)</td>
<td>0.89 (0.52-1.54)</td>
</tr>
<tr>
<td></td>
<td>Yes, sometimes</td>
<td>1318 (8.4)</td>
<td>1.49 (0.98-2.27)</td>
<td>1.13 (0.65-1.98)</td>
</tr>
<tr>
<td></td>
<td>Yes, often</td>
<td>538 (7.5)</td>
<td>2.09 (1.29-3.40)</td>
<td>2.24 (1.24-4.03)</td>
</tr>
<tr>
<td>&quot;Do you have somebody to talk to if you experience problems or need support?&quot; c</td>
<td>Yes, often</td>
<td>4303 (59.9)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Yes, most of the time</td>
<td>1801 (25.1)</td>
<td>1.30 (0.90-1.88)</td>
<td>1.20 (0.75-1.92)</td>
</tr>
<tr>
<td></td>
<td>Yes, sometimes</td>
<td>592 (8.3)</td>
<td>0.92 (0.47-1.78)</td>
<td>0.72 (0.30-1.69)</td>
</tr>
<tr>
<td></td>
<td>No, never or almost never</td>
<td>291 (4.1)</td>
<td>2.71 (1.55-4.74)</td>
<td>2.65 (1.32-5.32)</td>
</tr>
</tbody>
</table>

* Univariate Cox proportional hazards regression model with age as the time scale.
** Multivariable Cox proportional hazards regression model with age as the time scale adjusted for educational level, comorbidity (Tucomorbidity index), smoking, alcohol intake, medicine compliance, body mass index.

a Missing n=69, b Missing = 201, c Missing =192.
Table 3: HiRL prediction model to identify patients influenced by loneliness to a degree that impacts one-year mortality.

<table>
<thead>
<tr>
<th>Screening question</th>
<th>Answer</th>
<th>Point</th>
<th>Classification of high-risk loneliness</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Do you live alone?”</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>“Does it ever happened that you are alone even though you wish to be with others?”</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes, but rarely</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes sometimes</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes, often</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>“Do you have somebody to talk to if you experience problems or need support?”</td>
<td>Yes always</td>
<td></td>
<td>≥ 1 point in total</td>
</tr>
<tr>
<td></td>
<td>Yes often</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes sometimes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 4: Demographic of subgroups “high-risk lonely” and “not high-risk lonely” derived from the HiRL prediction model.

<table>
<thead>
<tr>
<th></th>
<th>High-risk lonely (n=749)</th>
<th>Not high-risk lonely (n=6253)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>485 (64.8)</td>
<td>4603 (73.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>66.8 (11.2)</td>
<td>65.2 (10.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Comorbidity Tu Index, n (%)</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Score 0</td>
<td>341 (45.5)</td>
<td>3721 (59.5)</td>
<td></td>
</tr>
<tr>
<td>Score 1</td>
<td>246 (32.8)</td>
<td>1617 (25.9)</td>
<td></td>
</tr>
<tr>
<td>Score 2</td>
<td>101 (13.5)</td>
<td>595 (9.5)</td>
<td></td>
</tr>
<tr>
<td>Score ≥ 3</td>
<td>61 (8.1)</td>
<td>318 (5.1)</td>
<td></td>
</tr>
<tr>
<td>Educational level, n (%)</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Basic school</td>
<td>318 (43.9)</td>
<td>1894 (30.9)</td>
<td></td>
</tr>
<tr>
<td>Upper secondary or vocational school</td>
<td>302 (41.8)</td>
<td>2845 (46.5)</td>
<td></td>
</tr>
<tr>
<td>Higher education</td>
<td>103 (14.3)</td>
<td>1383 (22.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>151 (20.4)</td>
<td>890 (14.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>27.7 (5,5)</td>
<td>27.6 (4.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mortality, n (%)</td>
<td>30 (4.0)</td>
<td>121 (1.9)</td>
<td>&lt;0.0002</td>
</tr>
</tbody>
</table>
Figure 1: Patient flowchart

Patients with ischemic heart disease discharged/transferred from a Heart centre April 15th, 2013 to April 15th, 2014 (n=14,115)

Excluded (n=639)
Not able to participate due to illness (n=290)
Not able to participate due to language barriers (n=308)
Non relevant diagnosis (n=41)

Eligible patients (n=13,476)

Non-respondents (n=6,309)
- Not returned questionnaire (n=4,398)
- Returned non-completed questionnaire:
  - Did not want to participate (n=788)
  - Questionnaire not handed out (n=756)
  - Questionnaire returned blank (n=155)
  - Other reason, not specified (n=212)

Patients with completed questionnaire (n=7,169)
Figure 2: Hazard Ratio for one-year mortality in patients with Coronary Heart Disease, calculated on the possible combination of co-existing item responses.

<table>
<thead>
<tr>
<th>Question</th>
<th>Response item</th>
<th>Group classification</th>
<th>HR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Live alone</td>
<td>No</td>
<td>Response group (grey): n=122</td>
<td>3.37 (1.78-6.40)</td>
</tr>
<tr>
<td>Dose it ever happened that you are alone even though you wish to be with others?</td>
<td>Yes, but rarely; Yes, sometimes; Yes, often</td>
<td>Reference group (white): n=7043</td>
<td></td>
</tr>
<tr>
<td>Do you have anybody to talk to if you experience problems or need support?</td>
<td>Yes, always; Yes, often</td>
<td>Reference group (white): n=6521</td>
<td>6.61 (3.32-13.16)</td>
</tr>
<tr>
<td>Live alone</td>
<td>Yes</td>
<td>Reference group (grey): n=270</td>
<td>1.65 (0.86-3.16)</td>
</tr>
<tr>
<td>Dose it ever happened that you are alone even though you wish to be with others?</td>
<td>Yes, but rarely; Yes, sometimes; Yes, often</td>
<td>Reference group (white): n=6792</td>
<td></td>
</tr>
</tbody>
</table>