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Abstract

Background: Given the importance of improving health for patients with heart failure (HF), the present study examined the temporal associations between eHealth literacy, insomnia, psychological distress, medication adherence, quality of life (QoL), and cardiac events among older patients with HF.

Methods: With a longitudinal design older patients with echocardiography verified HF (N=468; 50.4 % New York Heart Association (NYHA) class II, mean age=69.3±7.3; 238 males) in need of cardiac care at seven Iranian university outpatient clinics went through clinical examinations and completed the following questionnaires at baseline: eHealth literacy Scale (eHEALS; assessing eHealth literacy), 5-Item Medication Adherence Report Scale (MARS-5; assessing medication adherence), Minnesota Living with Heart Failure Questionnaire (MLHFQ; assessing QoL), Insomnia Severity Index (ISI; assessing insomnia), and Hospital Anxiety and Depression Scale (HADS; assessing psychological distress). All the patients completed ISI and HADS again 3 months later; MARS-5 6 months later. Also, their cardiac events were collected 18 months later. Three mediation models were then conducted.

Results: eHealth literacy had direct and indirect effects (through insomnia and psychological distress) on medication adherence and QoL. Moreover, eHealth literacy had protecting effects on cardiac events (Hazard Ratio [HR]=0.53; 95% CI=0.37, 0.65) through the mediators of insomnia (HR=0.19; 95% CI=0.15, 0.26), psychological distress (HR=0.08; 95% CI=0.05, 0.12), and medication adherence (HR=0.05; 95% CI=0.04, 0.08).

Conclusion: As eHealth literacy was a protector for patients with HF, healthcare providers may plan effective programs to improve eHealth literacy for the population. Additional benefits of

improving eHealth literacy in HF may be decreased insomnia and psychological distress, improved QoL, as well as decreased cardiovascular events.

Keywords: cardiac events; eHealth literacy; heart failure; mediation model; quality of life

Introduction

Heart failure (HF), a prevalent chronic condition with high lifetime risk (~20%), creates several negative health consequences and substantial care demands, both pharmacological and self-care related.[1] As a result, the whole life situation for the patient is affected. The condition can be defined into different levels of severity by the New York Heart Association (NYHA) classification and left ventricular ejection fraction (LVEF), and the 5-year mortality rate after diagnosis is estimated to be approximately 50% for patients with severe HF. With a high prevalence and rising incidence, about 3.5% of Iranian adults are estimated to suffer HF in the near future[2]. The poor prognosis, adherence to both medication and lifestyle modifications are of great importance. However, treatment is tough, and re-hospitalizations frequent, which causes high costs for both the individual and the society.[1] Indeed, the estimated overall cost (including direct and indirect costs) for treating a patient with HF in Iran was 343 million USD in 2012, which occupies 1.1% of the total health expenditure in Iran and 0.07% of Iran GDP.[3] With such tough situation, exploring potential factors that protect or prevent patients with HF from serious health outcomes is thus crucial.

According to the literature, potential factors that facilitate cardiac events (i.e., cardiac emergency department visits, cardiac hospitalizations, and cardiac mortality) for patients with HF include poor sleep such as insomnia,[4,5] psychological distress,[6,7] and non-adherence to medication.[8,9] Among these potential risk factors, unhealthy behaviors (e.g., medication non-adherence) are deemed to be the most important factor.[1] Also, unhealthy behaviors or healthy behaviors are proposed to be the mediators in the association between poor sleep/psychological distress and cardiac events.[10] Specifically, Knafl and Riegel[5] suggested that poor sleep

contributes to cardiac events through non-adherence to medication. That is, poor sleep and the following excessive daytime sleepiness may result in poor adherence that subsequently develops the cardiac events. Similarly, Hamer et al.[7] found that (un)healthy behaviors (smoking, drinking, and low levels of exercising) as compared with pathophysiological factors (e.g., C-reactive protein, fibrinogen, and lipoprotein cholesterol) had greater ability in mediating the association between psychological distress and cardiac events. Furthermore, psychological distress is found to be an important factor in medication non-adherence.[1,10] That is, medication non-adherence seems to be an important mediator in developing cardiac events; therefore, tackling insomnia and psychological distress for patients with HF may enhance their medication adherence and further decrease cardiac events.

Apart from the aforementioned factors, eHealth literacy is deemed to be another potential protector to prevent cardiac events for patients with HF. Specifically, any individuals can seek health information through the internet if they have appropriate devices available, such as WiFi-enabled smartphones, tablets, and laptops.[11] With the capability to interpret the health information retrieved from the internet, patients can develop their own self-care behaviors that prevent them from serious health consequence.[12] Also, patients with HF may use the health information from the internet to tackle problems which are hard (or too embarrassing) to discuss with healthcare providers.[13] In addition, it is possible that patients with HF can use the internet to take care of the three aforementioned problems (i.e., insomnia, psychological distress, and medication adherence) that are highly related to the cardiac events. As a result, patients who have a high level of eHealth literacy (i.e., they are capable of retrieving, interpreting, and using health-related knowledge from the internet) may decrease their problems in insomnia,

psychological distress, and improve their medication adherence. Consequently, the chances of developing a cardiac event may be reduced. Older patients, especially with different disabilities, may be at higher risk for low eHealth literacy and slower adoption of new technologies than younger patients, due to knowledge, traditions, ownership of computer and other barriers.[14,15] Meanwhile, older adults are those who are more likely to suffer from many of the above-mentioned conditions, including the impaired quality of life (QoL) among patients with HF.[16,17] However, to the best of our knowledge, no studies have examined our proposed routes to provide the beneficial evidence of eHealth literacy on older patients with HF.

We therefor hypothesized that insomnia and psychological distress are two important mediators in the relationship between eHealth literacy and QoL. Patients with high levels of eHealth literacy as compared to those with low levels of eHealth literacy tended to have better self-management in healthcare needs, engage in more healthy behaviors, and interact better with healthcare providers.[18] Hence, patients with good eHealth literacy are very likely to have fewer problems in insomnia and psychological distress because they know how to take care of these issues. Moreover, insomnia and psychological distress showed negative impacts on QoL.[19,20] As a result, insomnia and psychological distress are potential mediators in the relationship between eHealth literacy and QoL. However, empirical evidence is needed to confirm our postulation.

The main purpose of this study was to use a longitudinal design to examine the temporal associations between eHealth literacy, insomnia, psychological distress, medication adherence, and cardiac events among older patients with HF, where insomnia, psychological distress, and medication adherence are mediators in the relationship between eHealth literacy and cardiac events. A second purpose of this study was to examine the mediator roles of insomnia and

psychological distress in the relationship between eHealth literacy and QoL among older patients with HF.

Methods

Participants and procedure

This prospective study comprised 468 patients with HF from seven Iranian outpatient university hospitals located in the cities of Tehran, Qazvin, and Tabriz with data collected from July 2015 to December 2018. Originally, a total of 724 HF patients who had been referred to the cardiac unit of the hospitals for receiving routine cardiac care were assessed by three trained research assistants (i.e., cardiovascular nurses) for their eligibility. Patients were recruited consecutively, if they fulfilled the following criteria: equal to or older than 65 years, objectively confirmed diagnosis of HF by a cardiologist based on the European Society of Cardiology guidelines using echocardiographic evidence with NYHA class II-IV, ability to communicate in Persian, stable HF medication regimen for at least four weeks prior to the commencement of the study. Patients were excluded if they had intellectual disability or cognitive impartment (as assessed using the mini-mental status exam: MMSE<20), severe psychiatric problems, severe renal failure, untreated anemia, an unstable cardiac condition within the past 3 months (i.e., unstable angina pectoris, significant cardiac arrhythmias, symptomatic valvular heart disease, or myocardial infarction) and disagreed to participate. The study was approved by the Ethics Committee of Qazvin University of Medical Sciences. All participants provided written, informed consent prior to participating in the study. Additionally, all the participants had internet access during the study period.

Those patients who wanted to participate (468; response rate: 65%) signed a written informed consent. Afterward, sociodemographic and clinical data were collected from patients' medical records and a face-to-face interview by the research assistants. Other data collected using questionnaires were self-administered by patients at baseline. Three months later, patients were asked to complete insomnia and psychological distress measures again. Patients' medication adherence was collected six months later, and QoL and cardiac events were collected eighteen months later. Except for insomnia, psychological distress, medication adherence, QoL, and cardiac events, all other information (including eHealth literacy) was only collected at baseline.

Instruments

Clinical data

Clinical data comprised a patient history, NYHA functional class, body mass index (BMI), blood pressure, heart rate, LVEF, and medication use. BMI was calculated using available height and weight recordings closest to baseline. LVEF was collected as a continues variable from the transthoracic echocardiograms by an experienced cardiologist. Medication use was collected from medical records.

eHealth literacy Scale (eHEALS).

The eHEALS contains eight self-reported items for assessing eHealth literacy (for detailed item content, see Supplementary Table S1). Sample items include: "I know what health resources are available on the Internet" and "I know how to use the Internet to answer health questions"). The item score was between 1 and 5, with a total score ranges between 8 and 40 (higher score indicates better eHealth literacy). The psychometric properties of the eHEALS

have been verified in different populations, including those with HF.[11] More specifically, the internal consistency using Cronbach's α for the Persian eHEALS was 0.89, and the unidimensionality of the Persian eHEALS was supported by Rasch analysis.[11]

5-Item Medication Adherence Report Scale (MARS-5).

The MARS-5 contains five self-reported items on assessing medication adherence for people with a chronic illness. The item score was between 1 and 5, with a total score ranges between 5 and 25 (higher score indicates better adherence). The psychometric properties of the MARS-5 have been verified in different populations, including those with stroke.[21] More specifically, the internal consistency using ordinal α for the Persian MARS-5 was 0.85, and the unidimensionality of the Persian MARS-5 was supported by Rasch analysis.[21]

Minnesota Living with Heart Failure Questionnaire (MLHFQ).

The MLHFQ contains 21 self-reported items on assessing quality of life (QoL) for people living with HF. The item score was between 0 and 5, with a total score ranges between 0 and 105 (higher score indicates worse QoL). The psychometric properties of the MLHFQ have been verified in patients with HF.[22] More specifically, the internal consistency using Cronbach's α for the Persian MLHFQ was 0.95, and the construct validity of the Persian MLHFQ was supported by the moderate to high correlation with SF-36 (r=0.4 to 0.7).[23]

Insomnia Severity Index (ISI).

The well-established ISI contains seven self-reported items on assessing insomnia. The item score was between 0 and 4, with a total score ranges between 0 and 28 (higher score

indicates severer insomnia). The psychometric properties of the ISI have been verified in different languages, including Persian.[24] More specifically, the internal consistency using Cronbach's α for the Persian ISI was 0.87, and the construct validity of the Persian ISI was supported by the moderate correlation with Pittsburg Sleep Quality Index (r=0.58).[24]

Hospital Anxiety and Depression Scale (HADS).

The HADS contains 14 self-reported items on assessing anxiety (seven items) and depression (seven items). The item score was between 0 and 3, with each subscale score ranges between 0 and 21 (higher score indicates more anxiety or more depressed). The psychometric properties of the HADS have been verified in different languages, including Persian.[25] More specifically, the internal consistency using Cronbach's α of the Persian HADS was 0.78 (Anxiety subscale) and 0.86 (Depression subscale). Additionally, the unidimensionality of each subscale in the Persian HADS was supported by Rasch analysis.[25] Due to the high correlation between the HADS subscales (i.e. depression and anxiety, $r = 0.75$, $p < 0.001$), total score of the HADS (score-ranges from 0–42) was used as global measure of psychological distress.

Medication Regimen Complexity Index (MRCI).

The MRCI developed by George and his colleagues[26] is the frequently used instrument to evaluate the medication complexity for elderly patients. The MRCI contains 65 items embedded in three sections of dosage forms, dosage frequency, and additional user instructions. Detailed scoring method is described by George et al.,[26] and a higher MRCI score indicates more complexity. The psychometric properties of the MRCI have been verified in different languages; however, there is no psychometric evidence in Persian MRCI. Therefore, we ensured the

linguistic validity of the MRCI through standard translation process described in the international guidelines, including forward translation, back translation, reconciliation, and cognitive interview. In the cognitive interview, 18 patients with HF were recruited. All interviews were conducted face-to-face in Persian and all interviews verified the item clarity, redundancy, and appropriateness of the MRCI. More specifically, interviewees were asked to complete the MRCI and to remark on any doubts or comments concerning the MRCI items before conducting the interview. Afterwards, a psychometrician conducted the interviews and began with "Did this item make sense to you?" and "Can you elaborate?" to clarify the item appropriateness.

Cardiac events

The cardiac events were defined and recorded as times from baseline to the first cardiac event (cardiac emergency department visits, cardiac hospitalizations, and cardiac mortality). More specifically, the cardiac variable was the composite end point of time to the first occurrence of one of the following events: cardiac emergency department visit, cardiac hospitalization, and cardiac mortality. Three trained cardiovascular nurses contacted the patients or families by telephone monthly to inspect if any cardiac event had occurred. This correspondence, together with information in their medical records, death certifications and hospital notes were used by the nurses to confirm the accuracy of data. The nurses were blinded to the patient characteristics and clinical data.

Statistical analysis

Multivariate survival analysis was performed using the Cox proportional hazards model. The survival analysis was adjusted for potential confounding variables, including age, gender,

HF characteristics (duration of heart failure, NYHA classification, LVEF, medication use, blood pressure, and heart rate), and MRCI.

Mediation analysis was conducted using the PROCESS SPSS macro (Model 4). Similarly, potential confounding variables, including age, gender, HF characteristics and MRCI were controlled. More specifically, the MRCI was controlled because it was significantly correlated to eHealth literacy (r=-0.23, p<0.01) although it was not significantly correlated to cardiac events (r=0.09, p=0.38). Age, gender, and HF characteristics were controlled for because they were significantly correlated with ehealth literacy or cardiac event. The model used 10,000 bootstraps to generate confidence intervals. In terms of the indirect effect of eHEALS on cardiac event, an approach proposed by Lange et al.[27] was used. Specifically, the indirect effects of three continuous mediators (i.e., ISI, HADS, and MARS) were explored using an unbiased estimate (weighted Cox regression). Hazard ratio (HR) with its 95% confidence interval (CI) was used as the effect size estimate. Because education was an important covariate in this survey, we further made two subgroups to determine the effect of education: Low education indicated individuals with 6 or less years of education and high education indicated individuals educated higher than 6 years. Statistical analysis was performed using SPSS software version 25.0 (IBM SPSS Statistics, IBM Corporation, Chicago, IL) and R version 3.2.5

Results

Of the 724 patients approached for study, 211 (29.1%) were not eligible to participate in the study. In addition, 45 patients (8.8%) refused to take part in the study. Over the 18 months, 14 participants dropped out (attrition rate=3%) and the missing data were handled using the multiple imputation approach. The mean (SD) days for follow-up were 492.56 days (120.22) and

the median days were 540. Table 1 illustrates the participant characteristics. Among 468 patients, 50.8% were males and 17.9% were current smokers. The mean (SD) age was 69.3 years (7.3) with 6.8 (2.9) years of education, 28.5 (5.4) kg/m^2 of BMI, and 27.1 (2.2) points of MMSE score. In terms of their characteristics on HF, the mean HF duration was 5.5 (3.6) years with half of the participants were classified as NYHA classification II (50.4%). Most of the participants had taken beta blockers (88.0%) and angiotensin-converting-enzyme (ACE) inhibitors (81.0%) The top three comorbidities for the participants were hypertension (66.2%), hyperlipidemia (50.8%), and coronary artery disease (48.9%). Moreover, the mean LVEF was 7.6%. Additionally, all the studied variables (medication adherence, eHealth literacy, QoL, insomnia, depression, and anxiety) were mutually and significantly correlated (Table 2).

(Insert Tables 1 and 2 here)

After verifying the significant correlations between studied variables, the mediation models suggest that eHealth literacy had direct (coefficient=0.53; SE=0.14; $p<0.001$) and indirect (coefficient=0.11; bootstrapping SE=0.05; 95% CI=0.03, 0.21) effects on medication adherence. Moreover, the indirect effects were significantly via insomnia (coefficient=-0.05; bootstrapping SE=0.04; 95% CI=-0.15, -0.01) and psychological distress (coefficient=-0.06; bootstrapping SE=0.03; 95% CI=-0.13, -0.01). Similarly, eHealth literacy had direct (coefficient=-0.36; SE=0.09; $p<0.001$) and indirect (coefficient=0.13; bootstrapping SE=0.04; 95% CI=0.06, 0.22) effects on QoL. Moreover, the indirect effects were significantly via insomnia (coefficient=0.07; bootstrapping SE=0.03; 95% CI=0.03, 0.14) and psychological distress (coefficient=0.06; bootstrapping SE=0.03; 95% CI=0.01, 0.12) (Table 3; Figure 1).

Although a sample size calculation was not performed, an ad-hoc power analysis showed that the study's sample size had sufficient power: 0.81 and 1.00 for mediation model on MARS-5; 1.00 and 1.00 for mediation model on MLHFQ; and 0.99 to 1.00 for mediation model on cardiac events.

(Insert Table 3 and Figure 1 here)

The HR of eHealth literacy directly on cardiac events was 0.53 (95% CI=0.37, 0.65). Moreover, the HR of eHealth literacy indirectly on cardiac events was 0.22 (95% CI=0.16, 0.30), where HR was 0.19 (95% CI=0.15, 0.26) via insomnia, 0.08 (95% CI=0.05, 0.12) via psychological distress, and 0.05 (95% CI=0.04, 0.08) via medication adherence (Table 4; Figure 1).

As Figure 2 shows, a total of 42 of 468 patients died of cardiac reasons (42/468) or had at least one cardiac-related admission (31/468) or emergency department visit due to HF (9/468). Of the 42 patients who died during the study, 12 had a NYHF classification of IV. eHEALS scores were an independent predictor of cardiac events after controlling for covariates.

(Insert Figure 2here)

Discussion

This is, to the best of our knowledge, the first study that used a relatively large sample of patients with HF (n=468) to investigate the protecting effects of eHealth literacy on cardiac events through different mediators, including insomnia, psychological distress, and medication adherence. Our findings revealed that eHealth literacy totally reduced the chance of a cardiac event by 69% (i.e., HR=0.31), while the effects on reducing chance of a cardiac event were

mediated through improved insomnia, psychological distress, and medication adherence (Table 4). Furthermore, medication adherence and QoL among our sample were associated with eHealth literacy with significant mediating effect from insomnia and psychological distress (Table 3).

Our findings indicate the benefits of improving eHealth literacy among patients with HF agree prior research on the benefits of using internet among older adults with or without disability.[28,29] Tennant et al.[29] found that older adults, who did have HF with an average age of 67 years, used popular websites, such as Facebook or Twitter, to obtain and share health information. Additionally, as compared with those website non-users, the website users had greater health literacy. Moreover, with an appropriate approach used, elderly population has the potential to improve the eHealth literacy: LaMonica et al.[28] revealed that older adults with cognitive impairments can gain benefit from web-based intervention though those who are retired or have low levels of education obtain little benefit. Meanwhile, those with low knowledge, skills and eHealth literacy are at risk for exclusion,[14] and according to our results; at risk of severe events.

Although some may argue that patients with HF are usually older individuals and do not have sufficient ability to use internet, prior research[29] suggests that such notion is challengeable. More specifically, a recent review on patients with HF stated:[30] “The use of smartphones, software applications, and connected diagnostic sensors has the potential to further the improvements accomplished by conventional interventions for heart failure and provide additional support for patients by promoting medication adherence and overall disease management.” Given that older individuals may be able to use internet, the findings shed further

light in highlighting a possible mechanism to explain how eHealth literacy is associated to medication adherence among older patients with HF.

Our results revealed that the benefits of eHealth literacy could be mediated through insomnia, psychological distress, and medication adherence. The negative effects of insomnia and psychological distress include reduce the medication adherence[5] and impair the QoL.[19,20] Moreover, the lowered medication adherence may further develop cardiac events for patients with HF.[8,9] However, to the best our knowledge, no studies have applied robust statistical testing (i.e., a mediation model) to examine whether insomnia, psychological distress, and medication adherence are true mediators in the association between eHealth literacy and health outcomes (i.e., cardiac event and QoL) among patients with HF. Therefore, our findings that clearly demonstrate the mediator roles of insomnia, psychological distress, and medication adherence can guide healthcare providers to understand the importance of improving eHealth literacy for patients with HF. Nevertheless, future studies may want to extend the findings shown in Figure 1c. More specifically, Figure 1c only showed whether insomnia severity, psychological distress, and medication adherence can be concurrent mediators in the temporal association between ehealth literacy and cardiac events. Further study based on the results here should explore whether medication adherence mediates the association between insomnia severity/psychological distress and cardiac events.

The study has the following strengths. First, we recruited a relatively large sample with HF (N=468). With such a large sample, the internal validity of our findings was somewhat satisfactory. Second, we applied a robust statistical testing to examine the proposed mediation

models. Specifically, the use of bootstrapping approach is the state-of-art method to test the mediation. Third, we collected data through six months for medication adherence information and eighteen months for cardiac events. Thus, the findings from our longitudinal design somewhat indicate the temporal effects among the studied variables, including eHealth literacy, insomnia, psychological distress, medication adherence, QoL, and cardiac events.

There are some limitations in this study. First, the generalizability of our findings may be restricted because of our inclusion and exclusion criteria. For example, young patients with HF (i.e., aged below 65 years) were not our studied population, and we cannot guarantee whether young patients with HF perform similarly to our older sample. Those with cognitive impairment (i.e., screened by the MMSE with a score less than 20) were excluded. Thus, we are unsure whether our results can be generalized to patients with cognitive impairment. Second, although we used the longitudinal design to reveal part of the causality among these studied variables, our design did not provide strong evidence in the causality. Thus, future studies using a randomized controlled design to examine the effects of eHealth literacy on patients with HF are strongly recommended. Third, some of the studied variables (e.g., medication adherence, QoL, and psychological distress) are reported using self-administered questionnaires. Thus, our findings may suffer from the negative effects of recall bias and social desirability. Fourth, our research design could not answer an important question for clinical practitioners; that is, at which specific time/timeframe, eHealth literacy is most effective for heart failure management? For example, if a patient has NYHF IV, would improving the patient's eHealth literacy have any influence on the overall self-management of their HF? Future studies are therefore warranted to further explore this research question. Fifth, several factors (e.g., computer literacy, information literacy, and

lifestyle variables)[31] have been found to have significant associations with eHealth literacy. Unfortunately, the study did not collect and control these factors. Future studies that have controlled for these factors are needed to verify the findings of the present study. Finally, the present study only discussed the mediation effect; consequently, it is unclear whether there was any modifying or confounding effect in the studied variables. Therefore, future studies are needed to examine whether any modifying or confounding effect exists in the model tested in the present study.

In conclusion, eHealth literacy could be a protector for patients with HF to avoid serious health outcomes, including cardiac events and poor HQoL. Through improved eHealth literacy, patients with HF may reduce their sleep and psychological problems, which subsequently improve their health. Thus, healthcare providers may plan effective programs to improve the eHealth literacy for patients with HF.

Implications for Practice:

- Healthcare providers may want to improve the eHealth literacy for patients with heart failure (HF).
- Patients with HF may avoid cardiac events if they have good eHealth literacy.
- Patients with HF may have satisfactory quality of life if they have good eHealth literacy.

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Declaration of conflicting interests

The Authors declare that there is no conflict of interest.

REFERENCES

1. Riegel B, Lee CS, Dickson VV; Medscape. Self care in patients with chronic heart failure. *Nat Rev Cardiol* 2011; 8: 644-654.
2. Bahrami M, Etemadifar S, Shahriari M, Farsani AK. Caregiver burden among Iranian heart failure family caregivers: a descriptive, exploratory, qualitative study. *Iran J Nurs Midwifery Res* 2014; 19(1): 56-63.
3. Cook C, Cole G, Asaria P, Jabbour R, Francis DP. The annual global economic burden of heart failure. *Int J Cardiol* 2014; 171(3): 368-376.
4. Johansson P, Svensson E, Alehagen U, et al. The contribution of hypoxia to the association between sleep apnoea, insomnia, and cardiovascular mortality in community-dwelling elderly with and without cardiovascular disease. *Eur J Cardiovasc Nurs* 2015; 14: 222-231.
5. Knafl GJ and Riegel B. What puts heart failure patients at risk for poor medication adherence? *Patient Prefer Adherence* 2014; 8: 1007-1018.
6. González-Chica DA, Mnisi Z, Avery J, et al. Effect of Health Literacy on Quality of Life amongst Patients with Ischaemic Heart Disease in Australian General Practice. *PLoS One* 2016; 11: e0151079.
7. Hamer M, Molloy GJ, and Stamatakis E. Psychological distress as a risk factor for cardiovascular events: pathophysiological and behavioral mechanisms. *J Am Coll Cardiol* 2008; 52: 2156-2162.
8. Hood SR, Giazzon AJ, Seamon G, et al. Association between medication adherence and the outcomes of heart failure. *Pharmacotherapy* 2018; 38: 539-545.

9. Wu JR, Lennie TA, Chung ML, et al. Medication adherence mediates the relationship between marital status and cardiac event-free survival in patients with heart failure. *Heart Lung* 2012; 41: 107-114.
10. Johansson P, Broström A, Sanderman R, et al. The Course of Sleep Problems in Patients with Heart Failure and Associations to Rehospitalizations. *J Cardiovasc Nurs* 2015; 30: 403-410.
11. Lin C-Y, Broström A, Griffiths MD, et al. Psychometric evaluation of the Persian eHealth literacy Scale (eHEALS) among elder Iranians with heart failure. *Eval Health Prof* 2019; doi: 10.1177/0163278719827997. [Epub ahead of print]
12. Lin C-Y, Pakpour AH, Broström A, et al. Psychometric Properties of the 9-item European Heart Failure Self-care Behavior Scale Using Confirmatory Factor Analysis and Rasch Analysis Among Iranian Patients. *J Cardiovasc Nurs* 2018; 33: 281-288.
13. Lin, C.-Y., Broström, A., Årestedt, K., et al. Using extended Theory of Planned Behavior to determine factors associated with help-seeking behavior of sexual problems in women with heart failure: A longitudinal study. *J Psychosom Obstet Gynaecol* 2019; doi: 10.1080/0167482X.2019.1572743. [Epub ahead of print]
14. Olsson T, Samuelsson U, and Viscovi D. At risk of exclusion? Degrees of ICT access and literacy among senior citizens. Inf Commun Soc 2019; 22: 55-72.
15. Vaportzis E, Clausen MG, and Gow AJ. Older Adults perceptions of technology and barriers to interacting with tablet computers: A focus group study. *Front Psychol* 2017; 8: 1687.

16. Barnett K, Mercer SW, Norbury M, et al. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet* 2012; 380: 37-43.

17. Lesman-Leegte I, Jaarsma T, Coyne JC, et al. Quality of life and depressive symptoms in the elderly: A comparison between patients with heart failure and age- and gender-matched community controls. *J Card Fail* 2009; 15: 17-23.

18. Neter E and Brainin E. eHealth literacy: extending the digital divide to the realm of health information. *J Med Internet Res* 2012; 14: e19.

19. Atkins J, Naismith SL, Luscombe GM, et al. Psychological distress and quality of life in older persons: relative contributions of fixed and modifiable risk factors. *BMC Psychiatry* 2013; 13: 249.

20. Ishak WW, Bagot K, Thomas S, et al. Quality of life in patients suffering from insomnia. *Innov Clin Neurosci* 2012; 9: 13-26.

21. Lin CY, Ou HT, Nikoobakht M, et al. Validation of the 5-Item Medication Adherence Report Scale in Older Stroke Patients in Iran. *J Cardiovasc Nurs* 2018; 33: 536-543.

22. Bilbao A, Escobar A, García-Perez L, et al. The Minnesota living with heart failure questionnaire: comparison of different factor structures. *Health Qual Life Outcomes* 2016; 14: 23.

23. Eskandari S, Heravi-Karimooi M, Rejeh N, et al. Translation and validation study of the Iranian version of Minnesota Living with Heart Failure Questionnaire. *PAYESH* 2015; 14: 475-484.

24. Yazdi Z, Sadeghniiat-Haghighi K, Zohal MA, et al. Validity and reliability of the Iranian version of the Insomnia Severity Index. *Malays J Med Sci* 2012; 19: 31.

25. Lin C-Y and Pakpour AH. Using Hospital Anxiety and Depression Scale (HADS) on patients with epilepsy: confirmatory factor analysis and Rasch models. *Seizure* 2017; 45: 42-46.

26. George J, Phun YT, Bailey MJ, et al. Development and validation of the medication regimen complexity index. *Ann Pharmacother* 2004; 38: 1369-1376.

27. Lange T, Vansteelandt S, and Bekaert M. A simple unified approach for estimating natural direct and indirect effects. *Am J Epidemiol* 2012; 176: 190-195.

28. LaMonica HM, English A, Hickie IB, et al. Examining internet and eHealth practices and preferences: Survey study of Australian older adults with subjective memory complaints, mild cognitive impairment, or dementia. *J Med Internet Res* 2017; 19: e358.

29. Tennant B, Stellefson M, Dodd V, et al. eHealth literacy and Web 2.0 health information seeking behaviors among baby boomers and older adults. *J Med Internet Res* 2015; 17: e70.

30. Talmor G, Nguyen B, Keibel A, et al. Use of software applications to improve medication adherence and achieve more integrated disease management in heart failure. *Trends Cardiovasc Med* 2018; 28: 483-488.

31. Xesfingi S, Vozikis A. eHealth Literacy: In the Quest of the Contributing Factors. *Interact J Med Res* 2016;5(2):e16.

Figure legends

Fig. 1. Mediation models. ehealth literacy was assessed using the eHealth Literacy Scale, insomnia severity was assessed using the Insomnia Severity Index, psychological distress was assessed using the Hospital Anxiety and Depression Scale, medication adherence was assessed using 5-Item Medication Adherence Report Scale, and quality of life was assessed using Minnesota Living with Heart Failure Questionnaire. Age, gender, heart failure characteristics, and Medication Regimen Complexity Index score were controlled for.

Fig. 2. Survival of the participants across 18 months. Kaplan-Meier model is the curve that did not adjust for mediators; Cox model is the curve that adjusted for mediators. X axis is the survival time in days; Y axis is the survival rate.