Prediction of outcomes in patients with heart failure
Sokoreli, I.

Citation
Sokoreli, I. (2019, March 19). *Prediction of outcomes in patients with heart failure*. Retrieved from https://hdl.handle.net/1887/69813

Version:	Not Applicable (or Unknown)
License:	Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden
Downloaded from:	https://hdl.handle.net/1887/69813

Note: To cite this publication please use the final published version (if applicable).

Cover Page

Universiteit Leiden

Leiden University Repository

The following handle holds various files of this Leiden University dissertation:
http://hdl.handle.net/1887/69813

Author: Sokoreli, I.
Title: Prediction of outcomes in patients with heart failure
Issue Date: 2019-03-19

7 General discussion

Heart failure (HF) patients have high hospitalization rates followed by high readmission rates with about 25% of them being readmitted within 30 days [1] leading to worse quality of life for the patient [2] as well as high financial implications for the health care systems [3]. Although clinical treatment is constantly being optimized [4], further optimization is needed with respect to community care, social care or psychological support provided to the patient. Identifying risk factors affecting adverse events in HF patients is important for the patients and the care providers, since new risk factors may lead to new methods to manage patients and optimize services. Tailored treatment to the specific needs of the patient including non-medical services, well-coordinated amongst multiple professional care disciplines could lead to better outcomes.

The aim of this thesis was to expand our knowledge on risk factors affecting recurrent readmissions or mortality in HF patients, develop a predictive model for early adverse events by taking into account the added predictive value of non-clinical factors and test the transferability of the model by externally validating it in a different geography. The specific research questions are listed in Table 7.1 along with some of the main findings.

TABLE 7.1: Research questions and findings

Research question	**Findings**
What is the impact of depression and anxiety on mortality in HF patients?	**Depression** - Prevalence: 29% - Unadjusted effect: HR = 1.6; 95%CI 1.3 – 1.9 - Adjusted effect: HR = 1.4; 95%CI 1.2 – 1.6 - Heterogeneous effect due to population sizes and prevalence - OPERA-HF: HR: 3.0; 95% CI: 1.3 to 7.0 (adjusted effect) **Anxiety** - Prevalence: 29% - No significant effect

Continued on next page

Table 7.1 – *Continued from previous page*

Research question	**Findings**
Which other psychosocial factors affect adverse outcomes in HF? What is their association with first and recurrent events?	Composite endpoint: readmission or mortality OPERA-HF: 70% event rate at 1 year follow up **Depression** - First event: HR = 1.7; 95%CI 1.2 – 2.4 - Recurrent events: HR = 1.8; 95%CI 1.4 – 2.2 **Anxiety** - First event: HR = 1.7; 95%CI 1.2 – 2.3 - Recurrent events: HR = 1.4; 95%CI 1.1 – 1.7 **Cognitive impairment** - First event: HR = 1.4; 95%CI 0.9 – 2.3 - Recurrent events: HR = 1.4; 95%CI 1.1 – 1.9 **Living alone** - First event: HR = 1.0; 95%CI 0.9 – 1.3 - Recurrent events: HR = 1.2; 95%CI 1.1 – 1.4 **Frailty (trouble bathing or dressing)** - First event: HR = 1.3; 95%CI 1.1 – 1.7 - Recurrent events: HR = 1.2; 95%CI 1.0 – 1.4 **Frailty (timed get-up-and-go test)** - First event: HR = 1.02; 95%CI 1.01 – 1.03 - Recurrent events: HR = 1.01; 95%CI 1.01 – 1.02
Can we predict early readmission or mortality with a model that is transportable to a different geography?	Improved discrimination by adding physical frailty and social support to clinical variables Discrimination still modest - Internal validation on OPERA-HF (AUC 0.7 – corrected for optimism: 0.67) Good calibration from EU to US - External validation on SAPHIRE-HF (AUC 0.7)

MAIN FINDINGS

Research question 1: What is the impact of depression and anxiety on mortality in HF patients?

To address the first research question we followed a twofold approach. First, we conducted a systematic review and meta-analysis followed by the use of data from the OPERA-HF study to validate our findings from the systematic review on this cohort. In the systematic review, we identified 26 and 6 articles meeting inclusion criteria for depression and anxiety, respectively. The prevalence of both depression and anxiety in the identified studies was on average 29%. We found that depression is a significant and independent predictor of all-cause mortality among HF patients but with very heterogeneous effects reported across the different studies. For example, the adjusted effect of depression on mortality reported by Kato [5] was Hazard Ratio (HR) = 5.52, while the effect on the same outcome reported by Junger [6] was HR = 1.08. We performed a random-effect meta-regression to explore possible sources of this heterogeneity and we found that significant heterogeneity was associated with the total study population size and the prevalence of the depression in the study. The effect of depression was smaller in larger studies, which might reflect publication bias with small studies more often being published when reporting large effect estimates and less often published when reporting low effect estimates. Smaller effects were also observed in studies with higher prevalence of depression. That may relate to the use of different cut-offs on an underlying, latent, scale for depression. If a more liberal cut-off was used, those labeled as depressed actually were milder than with a more strict definition of depression.

The pooled unadjusted effect estimate from the literature for depression was 1.6 (HR = 1.6; 95%CI 1.3 – 1.9, $P < 0.001$) similar to the effect when adjusting for confounders (HR = 1.4; 95%CI 1.2 – 1.6; $p < 0.001$). On the other hand, there was no significant effect of anxiety on mortality identified.

In the OPERA study, we confirmed the strong association of depression with increased risk of mortality. Moderate-to-severe depression was independently associated to all-cause mortality in the year following discharge after an admission to hospital for HF when controlling for age, Charlson Comorbidity Index, NYHA class IV, NT-proBNP and treatment with mineralocorticoid receptor antagonist, beta-blocker and diuretics

(HR: 3.0; 95% CI: 1.3 to 7.0; $P < 0.05$).

Research question 2: Which other psychosocial factors affect adverse outcomes in HF? What is their association with first and recurrent events?

HF studies mostly focus on demographics or clinical risk factors, such as increasing age, male, the presence of co-morbidities, reduced left ventricular ejection fraction (LVEF), increasing New York Heart Association class of symptoms and worse serum markers and ignore psychosocial or other non-clinical factors [7]. However, as we showed in the first part of the thesis, depression may have a strong impact on the outcomes. Other previous research has also proved the association of (physical) frailty with increasing risk of first readmission or mortality in heart failure [8, 9]. In Chapter 4 we confirmed that depression and frailty were some of the non-clinical factors independently associated with increased risk of unplanned readmissions or mortality. Also moderate-to-severe anxiety was independently associated with the combined outcome of readmission or mortality, even though it was not associated with mortality outcome alone [10].

Most HF studies are focusing on the impact on the first event; readmission or mortality. Most research, in particular, focuses on 30-day readmission as an outcome of interest because of the payment reform incentives pushed by policy makers / payers aiming to improve outcomes. However, HF patients are often experiencing recurrent hospitalizations reflecting progression of the underlying disease or exacerbations due to comorbidities and suboptimal self-care and medication. Taking into account more events will lead to more power and efficiency in estimating potential risk factors. Therefore, we extended our analysis to study the recurrent events. In the OPERA-HF study, there was an event rate of 70% of patients being readmitted or dying at 1-year follow-up. The 779 patients discharged from the hospital till July 2016 had 559 first events and 1600 recurrent events. Hence, there would have been 1041 events ignored if looking only into the first events that the patients experienced.

In the recurrent event analysis, psychosocial or other non-clinical variables independently associated with increasing risk of recurrent events in the year following discharge after a HF admission to hospital were: presence of frailty, moderate-to-severe depression, and moderate-to-severe anxiety, living alone and the presence of cognitive impairment. Those remained significant predictors when adjusting for age, diabetes, history of myocardial infarction, chronic obstructive pulmonary disease, urea and creatinine at discharge. The effect of depression on the outcome was greater in the recurrent event analysis than in the first event analysis, while the effect of anxiety was smaller. Living alone and the presence of cognitive impairment were significant predictors of recurrent events but not of first event alone.

Research question 3: Can we predict early readmission or mortality with a model that is transportable to a different geography?

HF patients often experience adverse events early after being discharged from the hospital, with approximately 25% been readmitted within the first 30 days [1]. Readmissions within 30 days may be caused by worsening of clinical conditions of the patient but also due to other factors including lacking social support, being physically frail or having cognitive issues.

Available risk stratification algorithms for 30-day events (unplanned readmission or mortality) perform poorly [11] and include mostly risk factors reflecting the clinical profile of the patient. In Chapter 5, we used data from the OPERA-HF study to develop a 30-day composite outcome model, and we explored the added predictive value of non-clinical predictors to early outcomes: 30-day unplanned readmission or mortality within 30 days. The model containing clinical variables alone (not in sinus rhythm, worst symptoms, increasing urea and NT-proBNP at discharge, and higher daily pill count) and health care utilization (number of prior emergency hospitalizations in 6 month and length of stay) gave an area under the receiver operating characteristic curve (AUC) of 0.68 [95% CI 0.64 - 0.72]. By including in the model physical frailty and social support the AUC increased to 0.70 [95% CI 0.66 – 0.74] ($p<0.05$). In this model, we achieved an absolute increase in performance of 0.02 when taking into account non-clinical factors. The discrimination of the model remained modest reflecting the difficulty in early readmission or mortality prediction due to the diversity in the readmission root causes. However, we showed that by including less frequently evaluated patient characteristics (physical and social frailty), we can increase the discriminative value of the model. Another advantage is that our model is based on simple and easy to obtain variables, it can easily be used as part of the routine care practice and results can be easily interpreted by the clinicians.

External validation. Most available risk stratification algorithms are only internally validated [12]. Internal validation is important to prove the reproducibility of the model on the original population [13]. This step is important but not enough when aiming to prove the validity of a model beyond the original population. It should be followed by external validation that proves the transportability of a model to a different 'plausibly related' population [13, 14, 15].

In the last part of this thesis we evaluated the transportability of the OPERA model to a different geography. The performance of the model was evaluated by discrimination and calibration. We used data from the SAPHIRE study, conducted in US, to externally validate the model. In SAPHIRE study, we collected similar data to the OPERA-HF. The external validation of the OPERA model was performed on 513 HF patients enrolled in the SAPHIRE study. Our results showed a good calibration and discrimination similar to the original. This means that the model can overcome any difference between the populations of two locations. It can be used in the new population to discriminate patients at risk of an early event with a performance equal to the one from the original derivation setting without any adjustment to the original model.

Early event prediction remains challenging, however, our findings suggest that non-clinical factors may improve the predictions. Further evidence towards this direction has been provided by another recent study demonstrating that causes of potentially preventable readmissions are mostly human-related caused by coordination and communication failures [16]. Furthermore, the generalizability of our model to a different geography indicates that the model designed for one setting can be used for another setting, as well.

METHODOLOGICAL CONSIDERATIONS

Study design

It is widely reported in literature that early outcomes and especially readmissions are generally hard to predict, due to the heterogeneity of the population characteristics, the reasons that might be causing a readmission, the short prediction window and the rare frequency of these events [17, 18, 19]. In the OPERA-HF study, we set up an intentionally broad protocol to explore different potential predictors. Our analysis showed that by taking into account frailty or lack of social support we can improve the discrimination for 30-day emergency readmission or mortality, while more psychosocial factors affect longer term outcomes. However, the discrimination of early events remains modest recommending further research on other important non-clinical predictors not yet identified. For instance, a recent study by van Galen et al. [20] reported that the patient reporting not feeling ready for discharge at index admission was significantly associated with the early readmission outcome.

Patient data

One limitation of the OPERA-HF study was that 20% of the patients had missing data for one or more of the predictors included in the model. The broad protocol requiring intense data collection, patient burden, collecting data for which diagnostic ground exists may be some or the reasons explaining the high missing data rates for some of the parameters. On the other hand, the SAPHIRE-HF/COPD study protocol was limited to the most important factors identified from the OPERA-HF study or other clinically significant factors indicated by domain experts. The difference in the size of the protocol may be one of the reasons explaining the smaller number of missing data in the SAPHIRE-HF/COPD study. In both studies, to overcome the missing data issue we used the multiple imputation technique [21].

With respect to follow-up data, we anticipated only a limited amount of outcome data missing in both studies. In both cases, we recruited study participants living in the local areas. However, there is still a possibility of missed events due to seeking care outside of the local areas that may result in an underestimation of readmission rates.

Additional assessment

In both studies, patients were asked to complete additional physical exams or psychosocial assessments via questionnaires in order to obtain a more holistic assessment of their status. These additional assessments are not part of the routine care provided to the patients.

There are different methods available that can provide assessments of depression, anxiety, social support, frailty or other characteristics of the patients. A limitation of some of the assessment methods used in our studies, for instance the HADS questionnaire for depression and anxiety [22], is that they have been developed primarily for research and have not been extensively tested in routine practice for patients with heart failure.

Another potential limitation of these assessments is that they may be subjective depending on the patient's physical or mental condition at the time of administration. They may rely on participant's perception of their own health and their ability to recall past experiences and events. Next to that, most of these assessments were performed once during patient's hospitalization. Hence, we may have missed significant changes of patient's status during or after hospitalization.

IMPLICATIONS AND FUTURE RESEARCH

The OPERA model takes into account frailty and social support next to healthcare utilization and clinical predictors to calculate a risk score of early adverse events for the patients. This risk score can be used by the discharge teams as part of the routine practice to identify patients at different risk levels. The model does not aim to replace but to assist clinicians or discharge teams to identify optimal care pathways for their patients. Some examples of interventions linked to different risk levels are given in Table 7.2. Further research is recommended to identify the optimal thresholds for the risk levels.

Patients with the highest risk scores are typically very complex, end stage heart failure patients who would benefit mainly from interventions such as palliative care. High risk patients usually require intense care and support by specialist, primary care and informal caregivers. One possible solution to support high risk patients effectively in their own home is telehealth [23]. HF patients in the medium risk levels, on the other hand could benefit by less intense interventions such as structured m-health support or lower intensity telehealth solutions [24]. HF patients with the lowest risk scores are usually well self-managed and they might only need clinical and social support with respect to health coaching and lifestyle management in order to maintain their risks low.

Often a multidisciplinary management approach is needed in order to identify the patients' needs and the interventions that would benefit them the most. The knowledge on the impact of specific factors on the outcomes can improve discharge management and explore interventions tailored to patient needs that may improve the outcomes. Our study recommends that non-clinical or non-disease specific factors should not be neglected when assessing a patient's status and needs. A holistic assessment of the patients' status with them also engaged in the process of deciding what is best for them (shared decision making) may help to optimize the care provided to the patients and identify avoidable hospitalizations. Depression or frailty are some of the factors that appear to be strongly related to the outcomes and it could be beneficial to include their assessment as part of the routine care provided to HF patients. The presence of certain non-disease specific factors should be taken into account while defining interdisciplinary treatment programs tailored to individual patient needs. The multidisciplinary management team may consist of HF specialist, physiotherapist, geriatrician, rehabilitation physician, nurse and dietician depending on each patient's needs.

Cognitive Behavioral Therapy (CBT) or physical exercise are some of the interventions with positive effect on outcomes for patients with depression or frailty [24, 25, 26, 27, 28]. On the contrary, there is no evidence that antidepressants could positively affect the outcomes in patients with HF [29]. Multidisciplinary collaborative management to identify individual patients' needs, physical exercise or support groups are some of the interventions with positive impact on outcomes when the patient is lacking social support [28, 30]. Randomized controlled trials are recommended to evaluate the impact of these interventions on HF patients also in combination with other interventions such as telehealth.

In this thesis, we have reported a strong impact of psychosocial factors and frailty on several adverse outcomes of HF patients. There is evidence that many of these factors are affecting other groups of patients, as well. For example, frailty is increasingly recognized as an important factor in managing patients with long term conditions [31]. Major depression [32, 33] and cognitive impairment [34] have also been associated with high risk of death in older populations. Next to them, lack of social support is often associated with adverse follow-up outcomes in hospitalized patients [35]. Further research and evaluation of our findings on other patient groups is recommended.

TABLE 7.2: HF patient characteristics and managements in different risk levels

Risk level	**Patient profile**	**Possible interventions at discharge**
Very high risk	Terminal ill or very severe/ complex patients (e.g. transplantation or having other dominant (chronic) disease)	Nursing home, palliative care
High risk - complex needs	At risk of (recurrent) hospital emergency admissions or attendances to hospital. Unstable condition. Have difficulty following medication or treatment regimes.	Intense care (e.g. high intensity telemonitoring), community specialist nurse support, multidisciplinary management, social care
Medium risk - less complex needs	Lower chance to have unplanned readmissions within the next year, chance of deterioration.	Lower intensity telemonitoring, multidiciplinary management, Community specialist nurse support, social care, proactive care planning
Low risks	Well self-managed or early stage/ low severity HF patients. Able to maintain a good health management.	GP/practice nurse follow up in CDM clinics, primary care management, health coaching and lifestyle management, community activities

CONCLUSIONS

The research in this thesis aims to highlight new risk factors for HF adverse events and contribute in the improvement of predictive models for HF patients. We showed the strong effect of several psychosocial or non-disease specific factor with adverse outcomes in HF patients. Depression is strongly associated with increasing risk of recurrent hospitalizations or mortality in the year following discharge after an admission to hospital for HF. Other factors also related to increasing risk of recurrent events are the presence of frailty, moderate-to-severe anxiety, living alone and the presence of cognitive impairment. When looking into short-term outcomes, frailty and lack of social support both improved the discriminative power of a model predicting 30-day readmission or mortality.

These findings may enable researchers and health care providers to identify patients at risk of adverse events that are potentially avoidable and to adjust their decisions about patients' discharge to optimize the care provided them. Currently, the patient's status and post-discharge services are assessed by the professionals at the cardiology ward (cardiologists, nurses and/or the care managers) in an ad-hoc way, which may vary between professionals and institutions based on experience and knowledge. Our tool enables them to assess the patient's condition in a more systematic way from a holistic perspective, to stratify the patients in different risk levels and to recommend a multidisciplinary management or other interventions where needed.

RECOMMENDATIONS

The findings of our research allow for the following recommendations to health care professionals and researchers.

Recommendations for clinical practice

- Holistic assessment of the patient as part of routine care by a multidisciplinary team might be beneficial. The team may consist of HF specialist, physiotherapist, geriatrician, rehabilitation physician, nurse and dietician depending on each patient's needs.
- Do not neglect psychosocial aspects or frailty when assessing patients' condition.
- Use the OPERA model as part of routine care to identify patients at high risk of early events.

Recommendations for research

- Explore further non-clinical factors that may improve the prediction of outcomes for HF patients.
- Investigate the added value of frailty, social support and depression in predictive models for long-term outcomes.
- Validate our findings beyond HF patients on COPD or other chronic disease patients.
- Use the knowledge on impact of non-clinical factors to improve discharge management by involving a multidisciplinary team and next to the HF related interventions take into account interventions such as CBT, multidisciplinary management, physical exercise, counseling and education tailored to individual patient's needs.

REFERENCES

[1] M. R. Cowie, S. D. Anker, J. G. F. Cleland, G. M. Felker, G. Filippatos, T. Jaarsma, P. Jourdain, E. Knight, B. Massie, P. Ponikowski, and J. López-Sendón, "Improving care for patients with acute heart failure: before, during and after hospitalization," *ESC Heart Failure*, vol. 1, pp. 110–145, dec 2014.

[2] M. Emdin, A. Aimo, G. Vergaro, and C. Passino, "Predicting readmissions after hospitalization for heart failure: medical reasoning vs calculators," *International journal of cardiology*, vol. 236, pp. 348–349, jun 2017.

[3] D. Mozaffarian, E. J. Benjamin, A. S. Go, D. K. Arnett, M. J. Blaha, M. Cushman, S. de Ferranti, J.-P. Després, H. J. Fullerton, V. J. Howard, M. D. Huffman, S. E. Judd, B. M. Kissela, D. T. Lackland, J. H. Lichtman, L. D. Lisabeth, S. Liu, R. H. Mackey, D. B. Matchar, D. K. McGuire, E. R. Mohler, C. S. Moy, P. Muntner, M. E. Mussolino, K. Nasir, R. W. Neumar, G. Nichol, L. Palaniappan, D. K. Pandey, M. J. Reeves, C. J. Rodriguez, P. D. Sorlie, J. Stein, A. Towfighi, T. N. Turan, S. S. Virani, J. Z. Willey, D. Woo, R. W. Yeh, M. B. Turner, and American Heart Association Statistics Committee and Stroke Statistics Subcommittee, "Heart disease and stroke statistics—2015 update," *Circulation*, vol. 131, pp. e29–e322, jan 2015.

[4] T. A. McDonagh, R. S. Gardner, A. L. Clark, and H. Dargie, *Oxford textbook of heart failure*, vol. 1. Oxford University Press, jul 2011.

[5] N. Kato, K. Kinugawa, A. Yao, M. Hatano, T. Shiga, and K. Kazuma, "Relationship of depressive symptoms with hospitalization and death in Japanese patients with heart failure," *Journal of Cardiac Failure*, vol. 15, pp. 912–919, dec 2009.

[6] J. Jünger, D. Schellberg, T. Müller-Tasch, G. Raupp, C. Zugck, A. Haunstetter, S. Zipfel, W. Herzog, and M. Haass, "Depression increasingly predicts mortality in the course of congestive heart failure," *European Journal of Heart Failure*, vol. 7, pp. 261–267, mar 2005.

[7] J. S. Ross, "Statistical models and patient predictors of readmission for heart failure: a systematic review," *Archives of Internal Medicine*, vol. 168, no. 13, p. 1371, 2008.

[8] J. Lupón, B. González, S. Santaeugenia, S. Altimir, A. Urrutia, D. Más, C. Díez, T. Pascual, L. Cano, and V. Valle, "Prognostic implication of frailty and depressive symptoms in an outpatient population with heart failure," *Revista Española de Cardiología (English Edition)*, vol. 61, pp. 835–842, aug 2008.

[9] Y. Shao, A. F. Mohanty, A. Ahmed, C. R. Weir, B. E. Bray, R. U. Shah, D. Redd, and Q. Zeng-Treitler, "Identification and use of frailty indicators from text to examine associations with clinical outcomes among patients with heart failure," vol. 2016, p. 1110, 2016.

[10] I. Sokoreli, J. J. G. de Vries, S. C. Pauws, and E. W. Steyerberg, "Depression and anxiety as predictors of mortality among heart failure patients: systematic review and meta-analysis," *Heart Failure Reviews*, vol. 21, no. 1, pp. 49–63, 2016.

[11] K. Rahimi, D. Bennett, N. Conrad, T. M. Williams, J. Basu, J. Dwight, M. Woodward, A. Patel, J. McMurray, and S. MacMahon, "Risk prediction in patients with heart failure: a systematic review and analysis," *JACC: Heart Failure*, vol. 2, no. 5, pp. 440–446, 2014.

[12] D. Kansagara, H. Englander, A. Salanitro, D. Kagen, C. Theobald, M. Freeman, and S. Kripalani, "Risk prediction models for hospital readmission: a systematic review," *JAMA*, vol. 306, pp. 1688–98, oct 2011.

[13] A. C. Justice, K. E. Covinsky, and J. A. Berlin, "Assessing the generalizability of prognostic information," *Annals of internal medicine*, vol. 130, pp. 515–24, mar 1999.

[14] E. W. Steyerberg and Y. Vergouwe, "Towards better clinical prediction models: seven steps for development and an ABCD for validation," *European Heart Journal*, vol. 35, no. 29, pp. 1925–1931, 2014.

[15] E. W. Steyerberg, *Clinical prediction models: a practical approach to development, validation, and updating*. Springer, 2009.

[16] K. Fluitman, L. van Galen, H. Merten, S. Rombach, M. Brabrand, T. Cooksley, C. Nickel, C. Subbe, M. Kramer, P. Nanayakkara, and S. consortium, "Exploring the preventable causes of unplanned readmissions using root cause analysis: coordination of care is the weakest link," *European Journal of Internal Medicine*, vol. 30, pp. 18–24, may 2016.

[17] J. Billings, T. Georghiou, I. Blunt, and M. Bardsley, "Choosing a model to predict hospital admission: an observational study of new variants of predictive models for case finding," *BMJ open*, vol. 3, p. e003352, aug 2013.

[18] S. R. Deeny and A. Steventon, "Making sense of the shadows: priorities for creating a learning healthcare system based on routinely collected data," *BMJ quality & safety*, vol. 24, pp. 505–15, aug 2015.

[19] H. Zhou, P. R. Della, P. Roberts, L. Goh, and S. S. Dhaliwal, "Utility of models to predict 28-day or 30-day unplanned hospital readmissions: an updated systematic review," *BMJ Open*, vol. 6, no. 6, 2016.

[20] L. S. van Galen, M. Brabrand, T. Cooksley, P. M. van de Ven, H. Merten, R. K. So, L. van Hooff, H. R. Haak, R. M. Kidney, C. H. Nickel, J. T. Soong, I. Weichert, M. H. Kramer, C. P. Subbe, and P. W. Nanayakkara, "Patients' and providers' perceptions of the preventability of hospital readmission: a prospective, observational study in four European countries," *BMJ Quality & Safety*, pp. bmjqs–2017–006645, 2017.

[21] D. B. Rubin, *Multiple imputation for nonresponse in surveys*, vol. 81. John Wiley & Sons, 2004.

[22] A. S. Zigmond and R. P. Snaith, "The hospital anxiety and depression scale," *Acta Psychiatrica Scandinavica*, vol. 67, no. 6, pp. 361–370, 1983.

[23] S. Inglis, "Structured telephone support or telemonitoring programmes for patients with chronic heart failure," *Journal of Evidence-Based Medicine*, vol. 3, no. 4, pp. 228–228, 2010.

[24] T. M. Gill, D. I. Baker, M. Gottschalk, P. N. Peduzzi, H. Allore, and A. Byers, "A program to prevent functional decline in physically frail, elderly persons who live at home," *New England Journal of Medicine*, vol. 347, pp. 1068–1074, oct 2002.

[25] V. Konstam, D. K. Moser, and M. J. De Jong, "Depression and anxiety in heart failure," *Journal of Cardiac Failure*, vol. 11, pp. 455–463, aug 2005.

[26] J. A. Blumenthal, M. A. Babyak, C. O'Connor, S. Keteyian, J. Landzberg, J. Howlett, W. Kraus, S. Gottlieb, G. Blackburn, A. Swank, and D. J. Whellan, "Effects of exercise training on depressive symptoms in patients with chronic heart failure," *JAMA*, vol. 308, pp. 465–74, aug 2012.

[27] L. Seligman and L. W. Reichenberg, *Selecting effective treatments: a comprehensive, systematic guide to treating mental disorders*. John Wiley & Sons, 2007.

[28] J. Wallenborn and C. E. Angermann, "Comorbid depression in heart failure," *Herz*, vol. 38, pp. 587–596, sep 2013.

[29] C. M. O'Connor, W. Jiang, M. Kuchibhatla, S. G. Silva, M. S. Cuffe, D. D. Callwood, B. Zakhary, W. G. Stough, R. M. Arias, S. K. Rivelli, and R. Krishnan, "Safety and efficacy of sertraline for depression in patients with heart failure: Results of the SADHART-CHF (Sertraline against depression and heart disease in chronic heart failure) trial," *Journal of the American College of Cardiology*, vol. 56, pp. 692–699, aug 2010.

[30] S. Bunt, N. Steverink, J. Olthof, C. P. van der Schans, and J. S. M. Hobbelen, "Social frailty in older adults: a scoping review," *European Journal of Ageing*, vol. 14, pp. 323–334, sep 2017.

[31] J. Walston, E. C. Hadley, L. Ferrucci, J. M. Guralnik, A. B. Newman, S. A. Studenski, W. B. Ershler, T. Harris, and L. P. Fried, "Research agenda for frailty in older adults: toward a better understanding of physiology and etiology: summary from the american geriatrics society/national institute on aging research conference on frailty in older adults," *Journal of the American Geriatrics Society*, vol. 54, no. 6, pp. 991–1001, 2006.

[32] B. W. J. H. Penninx, S. W. Geerlings, D. J. H. Deeg, J. T. M. van Eijk, W. van Tilburg, and A. T. F. Beekman, “Minor and major depression and the risk of death in older persons,” *Archives of General Psychiatry*, vol. 56, pp. 889–895, oct 1999.

[33] R. Schulz, R. A. Drayer, and B. L. Rollman, “Depression as a risk factor for non-suicide mortality in the elderly,” *Biological Psychiatry*, vol. 52, pp. 205–225, aug 2002.

[34] S. S. Bassuk, D. Wypij, and L. F. Berkman, “Cognitive impairment and mortality in the community-dwelling elderly,” *American journal of epidemiology*, vol. 151, pp. 676–88, apr 2000.

[35] K. E. Joynt and A. K. Jha, “Thirty-day readmissions — truth and consequences,” *New England Journal of Medicine*, vol. 366, pp. 1366–1369, apr 2012.