Prediction of outcomes in patients with heart failure

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3 Depression as an independent prognostic factor for all-cause mortality after a hospital admission for worsening HF

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ABSTRACT

Background: Depression is associated with increased mortality among patients with chronic heart failure (HF). Whether depression is an independent predictor of outcome in patients admitted for worsening of HF is unclear.

Methods and results: OPERA-HF is an observational study enrolling patients hospitalized with worsening HF. Depression was assessed by the Hospital Anxiety and Depression Scale (HADS-D) questionnaire. Comorbidity was assessed by the Charlson Comorbidity Index (CCI). Kaplan-Meier and Cox regression analyses were used to estimate the association between depression and all-cause mortality.

Of 242 patients who completed the HADS-D questionnaire, 153, 54 and 35 patients had no (score $0-7$), mild (score $8-10$) or moderate-to-severe (score $11-21$) depression, respectively. During follow-up, 35 patients died, with a median time follow-up of 360 days amongst survivors (interquartile range, IQR $217 - 574$ days). In univariable analysis, moderate-to-severe depression was associated with an increased risk of death (HR: 4.9; 95% CI: 2.3 to 10.2; $P < 0.001$) compared to no depression. Moderate-to-severe depression also predicted all-cause mortality after controlling for age, CCI score, 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; $P < 0.05$).

Conclusions: Depression is strongly associated with an adverse outcome in the year following discharge after an admission to hospital for worsening HF. The association is only partly explained by the severity of HF or comorbidity. Further research is required to demonstrate whether recognition and treatment of depression improves patient outcomes.

INTRODUCTION

Psychosocial illness, including depression, is common in people with cardiovascular disease. Depression is particularly common in patients with heart failure (HF) [1]. Probably most patients with HF are depressed by their illness at some time but a meta-analysis suggests that depression affects about a 20% of patients at any time [2].

For patients with HF, depression is associated with an increased rate of adverse outcomes [2, 3], such as hospitalization and death. The aggregated risk-estimate derived from 26 studies was an approximately 1.5−fold risk of death in patients with HF if they had depression [3]. However, it can be difficult to disentangle whether depression causes a worse outcome, or merely reflects worse HF or more severe co-morbidity. We aimed to assess the prevalence and consequences of depression in patients admitted to hospital for worsening HF. We analyzed a prospective patient cohort and controlled for common covariates reflecting the severity of both the HF and any comorbidities.

METHODS

Study design

OPERA-HF is an ongoing prospective observational study, enrolling patients hospitalized with worsening heart failure (HF) to the Hull & East Yorkshire Hospitals NHS Trust, UK. The aim of the study is to gather a holistic view of the patients, their general condition and co-morbidities, and to identify predictors of mortality and re-admission to hospital. Clinical and psycho-social data were collected during hospital admission and just prior to discharge. The Charlson comorbidity index (CCI) was used to assess comorbidity (Appendix A).

Patients had to fulfill all of the following criteria to be included in the study: age $>$ 18 years; hospitalization for worsening HF; treatment with loop diuretics; and at least one of the following: left ventricular ejection fraction $\leq$ 40%, left atrial dimension $>$ 4.0 cm or NT-ProBNP $>$ 400 pg/ml (if in sinus rhythm) or $>$ 1200 pg/ml (if in atrial fibrillation). Patients unable to understand and comply with the protocol or unable or unwilling to give informed consent were excluded from the study. The study has full ethical approval from the South Yorkshire Research Ethics Committee (REC ref: 12/YH/0344) and is conducted in accordance with ICH-GCP, Declaration of Helsinki, the Data Protection Act 1998 and the NHS Act 2006.

Depression assessment

Depression was assessed by the Hospital Anxiety and Depression Scale (HADS-D) questionnaire [4] (Appendix B). The HADS-D focuses on questions about depression. The response to each of the 7 questions is graded from 0 to 3, giving a total score that ranges between 0 and 21. A score of 7 or less implies that there is no depression; a score of 8-10 suggests mild depression; and a score of 11 or higher reflects moderate-to-severe depression [4]. Among 12 studies assessing the HADS-D questionnaire (total N = 2109 patients), a cut point of 8 for the diagnosis of depression had a mean specificity of 0.79 and a mean sensitivity of 0.83 when compared with a 'gold standard' diagnosis using DSM-III/IV or similar codes [5].

Mortality

All patients enrolled in the study are followed subsequent to discharge. Readmissions and all-cause mortality are automatically recorded in the hospital's IT system. For the present report, the primary outcome of interest was all-cause mortality.

Statistical analysis

We report the baseline characteristics of the patients who participated in the study between 14/10/2012 and 16/06/2015 and who completed the HADS-D questionnaire. Follow up was censored at 13/07/2015. The consort diagram is given in Appendix C.

Univariable and multivariable Cox proportional hazard regression models were used to estimate the association between depression and all-cause mortality. Univariable analysis was performed to assess the relation between variables and outcome, including demographics, clinical assessment, echocardiography and medication. In the multivariable model, we adjusted for all the variables found to predict outcome ($P \leq 0.1$) in the univariable analysis. Multiple imputation [6] was used to impute missing data when needed. The Kaplan-Meier method was used to estimate survival time and produce a survival curve [7]. All analyses were conducted using R 3.1.3 statistical software (The R Foundation for Statistical Computing, Vienna, Austria). In particular, the R package mice [8] was used for the multiple imputation and the R package survival [9] for the Kaplan-Meier method and the survival analysis.

RESULTS

Baseline characteristics of the study population

The baseline characteristics of the 242 participants who completed the HADS-D questionnaire are reported in Table 3.1. The median follow-up was 315 days (interquartile range, IQR 167 - 519) for all patients and 360 days (IQR = 217 - 574) amongst survivors. The mortality rate estimated from the Kaplan Meier curve was 15% [95% CI 10% - 20%] at one year.

TABLE 3.1: Baseline characteristics stratified by HADS-D group and total population. Characteristics are summarized by their count and fraction (N (%)) for categorical or their median and interquartile range (Median [25th − 75th]) for continuous variables, respectively; (∗) all variables are evaluated at admission apart from NT−proBNP and LVEF which are evaluated at discharge and (∗∗) NYHA class which was evaluated as the worst class during the last 7-days before admission (∗ ∗ ∗) Diuretics: loop diuretics or thiazide

Depression Score	**All (N=242)**		**0 − 7 (N=153)**		**8-10 (N=54)**		**11-21 (N=35)**	
Characteristics (*)	**Valid N**	**Summary**	**Valid N**	**Summary**	**Valid N**	**Summary**	**Valid N**	**Summary**
Women, %	242	76 (31%)	153	48 (31%)	54	18 (33%)	35	10 (29%)
Age, years	242	74 [64−80]	153	73 [64−81]	54	74 [67−78]	35	73 [63−80]
CCI, score	221	3 [2 − 5]	143	3 [2 − 4]	46	3 [2 − 6]	32	3 [2 − 5]
NYHA**: Class I/II, %	209	32 (15%)	132	23 (18%)	48	7 (15%)	29	2 (6%)
NYHA: Class III, %	209	135(65%)	132	87 (66%)	48	32 (67%)	29	16 (55%)
NYHA: Class IV, %	209	42 (20%)	132	22 (17%)	48	9 (19%)	29	11 (38%)
Hypertension, %	235	130 (55%)	150	82 (55%)	53	27 (51%)	32	21 (66%)
NT-proBNP, pg/mL	204	4792[1694 − 9784]	130	5022[1782 − 9668]	45	3188[1323 − 9445]	29	5368[2830 − 12290]
Heart Rhythm: Sinus, %	242	92 (38%)	153	50 (33%)	54	25 (46%)	35	17 (49%)
LVEF at discharge: $\leq$ 40%	216	128(59%)	142	89 (63%)	48	23 (48%)	26	16 (62%)
Main presentation:								
- Severe peripheral oedema, %	236	24 (10%)	149	19 (13%)	52	3 (6%)	35	2 (6%)
- Severe breathlessness at rest, %	236	76 (32%)	149	56 (38%)	52	12 (23%)	35	8 (23%)
- Increasing exertional breathlessness, %	236	106(45%)	149	53 (36%)	52	31 (60%)	35	22 (63%)
- Chest pain - cardiac, %	236	21 (9%)	149	14 (9%)	52	6 (11%)	35	1 (3%)
- Other symptom, %	236	9 (4%)	149	7 (5%)	52	0 (0%)	35	2 (6%)
HF Medication (on admission)								
ACE inhibitor, %	242	98 (40%)	153	54 (35%)	54	24 (44%)	35	20 (57%)
ARB , %	242	48 (20%)	153	30 (20%)	54	12 (22%)	35	6 (17%)
Beta-blocker, %	242	126(52%)	153	70 (46%)	54	32 (59%)	35	24 (69%)
Aldosterone Antagonist,%	242	51 (21%)	153	29 (19%)	54	11 (20%)	35	11 (31%)
Digitalis, %	242	35 (14%)	153	19 (12%)	54	9 (17%)	35	7 (20%)
Diuretics ***, %	242	128(53%)	153	71 (46%)	54	30 (56%)	35	27 (77%)

NYHA, New York Heart Association; CCI, Charlson comorbidity index; LVEF, Left ventricular ejection fraction; SOB, Acute shortness of breath;ACE, Angiotensin-converting enzyme; ARB: Angiotensin Receptor Blockers.

Depression assessment

The median HADS-D score amongst the 242 HF patients was 6 (IQR = 3 - 9); 153 patients had no (score 0-7), 54 had mild (score 8-10) and 35 had moderate-to-severe (score 11-21) depression, respectively. Patients with moderate-to-severe depression were, on average, in a worse NYHA class, had more likely sinus heart rhythm and were taking more HF medications than those with no depression (Table 3.1).

Patients were more likely to give high (i.e. worse) scores to the questions "I can laugh and see the funny side of things" and "I feel as if I am slowed down" (Table 3.2).

TABLE 3.2: Patients scoring of HADS-D questions; the score for each question ranges from 0 (as the most positive response) to 3 (most negative response). The aggregated scores are calculated based on the 242 HF patients answering the HADS-D questionnaire.

Question	**Score per answer**	**Number of patients**	**Aggregated score for 242 patients**
I still enjoy the things	Definitely as much - 0	58	294
I used to enjoy	Not quite so much - 1	109	
	Only a little - 2	40	
	Hardly at all - 3	35	
I can laugh and see	As much as I always could - 0	1	623
the funny side of	Not quite so much now - 1	18	
things	Definitely not so much now - 2	64	
	Not at all - 3	159	
I feel cheerful	Most of the time − 0	145	119
	Sometimes - 1	79	
	Not often - 2	14	
	Not at all - 3	4	
I feel as if I am slowed	Not at all − 0	12	472
down	Sometimes - 1	78	
	Very often - 2	62	
	Nearly all the time - 3	90	
I have lost interest	I take just as much − 0	117	194
in my appearance	care as ever		
	I may not take quite	65	
	as much care - 1		
	I don't take so much	51	
	care as I should - 2		
	Definitely - 3	9	
I look forward with	As much as ever I did - 0	94	224
enjoyment to things	Rather less than I used to - 1	85	
	Definitely less than I used to - 2	50	

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Table 3.2 – *Continued from previous page*

Question	Score per answer	Number of patients	Aggregated score for 242 patients
I can enjoy a good book or radio or TV program	Hardly at all - 3	13	126
	Often − 0	155	
	Sometimes - 1	59	
	Not often - 2	17	
	Very seldom - 3	11	

Effect of depression on mortality

The unadjusted rate for all-cause mortality was almost five times higher amongst patients with moderate-to-severe depression compared to patients without depression (HR: 4.9; 95% CI: 2.3 to 10.2; $P < 0.001$, Table 3.3a and Figures 3.1a). Increasing age (as a continuous variable), increasing NT-proBNP (continuous), NYHA class IV within 7 days before admission (compared with patients with Class I/II), increasing CCI score, and use of a mineralocorticoid receptor antagonist, beta-blocker and diuretic were all associated with increasing mortality. We therefore corrected for these characteristics in the multivariable analysis (Table 3.3b, Figure 3.1b). Moderate-to-severe depression remained a significant predictor of all-cause mortality (HR: 3.0; 95% CI: 1.3 to 7.0; $P < 0.05$) along with NT-proBNP (HR: 1.7; 95% CI: 1.1 to 2.8; $P < 0.05$) and NYHA class IV (HR: 1.2; 95% CI: 1.0 to 4.6; $P < 0.1$). Further details on the association between the covariates and the outcome are provided in Table 3.4.

TABLE 3.3: (a) Univariable analysis, (b) Multivariable analysis; (*) HR based on Cox proportional hazard models; (**) adjusted for age (continuous), CCI score (continuous), NYHA class IV (worst NYHA class during 7 days before admission - binary), log(NT-proBNP) (continuous), Aldosterone Antagonist (binary), Beta-blocker (binary) and diuretics (binary)

(a) Univariable analysis (N = 242 / events = 35) - Likelihood ratio test = 15.25 for 2 df, p<0.001			
Depression status at admission	**HR for all-cause mortality***	**95% CI**	**p-value**
None (reference)	1	–	–
Mild	1.54	0.63 – 3.80	0.34
Moderate-to-severe	4.86	2.30 – 10.25	<0.001
(b) Multivariable analysis (N = 242 / events = 35) - Likelihood ratio test = 41.5 for 9 df, p<0.001**			
Depression status at admission	**HR for all-cause mortality**	**95% CI**	**p-value**
None (reference)	1	–	–
Mild	1.44	0.58 – 3.63	0.44
Moderate-to-severe	2.97	1.26 – 6.99	<0.05

HR, Hazard Ratio; CI, Confidence Interval.

FIGURE 3.1: (a) Unadjusted cumulative incidence plot [analysis based on the imputed dataset], (b) Cumulative incidence plot adjusted for age (continuous), CCI score (continuous), NYHA class IV (worst NYHA class during 7 days before admission - binary), log(NT-proBNP) (continuous), Aldosterone Antagonist (binary), Beta-blocker (binary) and diuretics (binary) [analysis based on the imputed dataset]

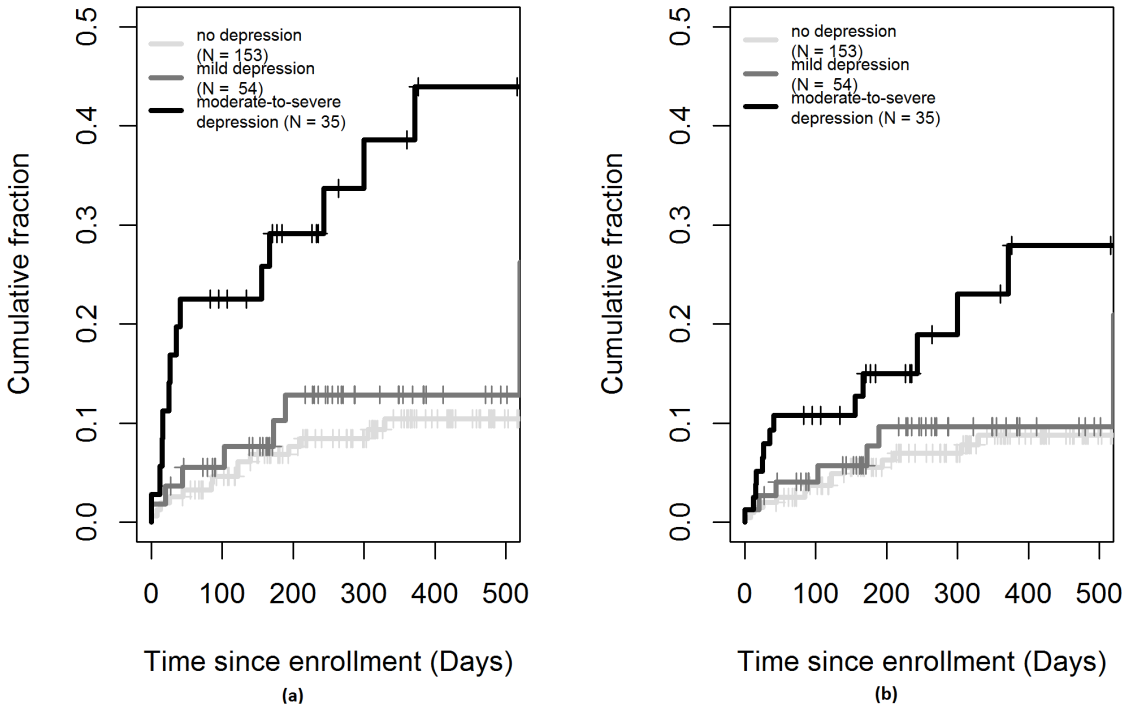

TABLE 3.4: Univariable/Multivariable analysis

	Univariable analysis (N = 242 / events = 35)			**Multivariable analysis (N = 242 / events = 35)**		
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Women, yes	0.78	0.37 – 1.67	0.52	-	-	-
Age at admission (10 year increase)	1.68	1.17 – 2.30	<0.01*	1.62	0.84 – 3.21	0.16
CCI at admission, score	1.13	1.00 – 1.29	<0.1*	1.08	0.93 – 1.26	0.39
NYHA**: Class I or II (reference)	1	–	–			
NYHA: Class III	0.72	0.26 – 2.02	0.52	-	-	-
NYHA: Class IV	2.62	0.95 – 7.27	<0.1*	2.15	1.00 - 4.59	<0.1*
Hypertension at admission, yes	0.85	0.43 – 1.65	0.63	-	-	-
$Log10$(NT-proBNP) at discharge, pg/mL	2.75	1.32 – 5.75	<0.05*	1.69	1.07 – 2.76	<0.05*
Sinus rhythm at admission, yes	1.17	0.60 – 2.28	0.65	-	-	-
LVEF $\leq$40 at discharge %	1.48	0.72 – 3.04	0.3	-	-	-
Main presentation:				-	-	-
- Severe peripheral oedema, yes	1	–	–			
- Severe breathlessness at rest, yes	0.42	0.15 – 1.14	0.11			
- Increasing exertional breathlessness, yes	0.48	0.18 – 1.25	0.13			
- Chest pain - cardiac, yes	0.26	0.05 – 1.31	0.11			
- Other symptom, yes	0.35	0.04 – 2.93	0.33			
HF Medication at admission						
- ACE inhibitor, yes	1.67	0.86 – 3.25	0.13	-	-	-
-ARB, yes	1.27	0.58 – 2.79	0.56	-	-	-
-Beta-blocker, yes	2.54	1.22 – 5.29	<0.1*	1.86	0.87 –3.99	0.15
-Aldosterone Antagonist, yes	2.27	1.13 – 4.58	<0.1*	1.69	0.79 – 3.62	0.18
-Digitalis, yes	1.36	0.56 – 3.27	0.5	-	-	-
-Diuretics, yes	2.44	1.17 – 5.09	<0.05*	1.1	0.48 – 2.53	0. 82

HR, Hazard Ratio; CI, Confidence Interval; NYHA, New York Heart Association;
CCI, Charlson comorbidity index; LVEF, Left ventricular ejection fraction;
ACE, Angiotensin-converting enzyme; ARB: Angiotensin Receptor Blockers.
*significance level of 0.1

DISCUSSION

Amongst patients admitted to hospital with worsening heart failure, the presence of moderate to severe depression is a strong predictor of mortality subsequent to discharge, even after correcting for potential confounders. This is consistent with evidence suggesting that depression predicts mortality amongst patients with chronic HF [2, 3] but the relationship may be even stronger for those admitted to hospital with worsening heart failure.

Whether the association between depression and mortality is causal and, if so, whether targeting this link could improve prognosis remains uncertain. Pessimism and depression may have biological effects that adversely affect prognosis [10]. Alternatively, depression may reduce adherence to lifestyle advice and heart failure medications leading to a worse prognosis [11, 12]. Health care professionals might be unconsciously less attentive to depressed patients. Finally, it is possible that we did not identify and measure some key prognostic variables; some patients may be depressed because they not only feel sicker but are indeed sicker. The clinical reality is that all of the above are probably relevant to different patients at different times. Teasing out which is the most important for an individual patient may be difficult.

It is unclear whether the recognition and management of depression might improve patient outcomes. Randomized trials of drug intervention with selective serotonin reuptake inhibitors have been disappointing [13, 14]. Interestingly, many patients admitted to hospital with worsening heart failure report good quality of life after discharge [15]. Maybe improving the patients' perception of their future and their enjoyment of their lives would have a positive feedback that improves outcome. Perhaps the focus should also be on serial assessment with intervention only when depression persists despite simple measures such as good treatment of the medical condition, social support and attention to health fears and loneliness. Trials of new interventions, such as cognitive behavioral therapy, use of self-management plans delivered by community health care teams or by tele-monitoring might be effective alternatives to drug therapy [16]. Tackling the problems that depression causes rather than depression itself could also be important; a diagnosis of depression should heighten awareness of the need for support, advice and encouragement of adherence.

Mild depression was not strongly associated with mortality in either the univariable

or multivariable models. This may reflect the attributes of the HADS score; several questions could reflect the severity of functional impairment due to HF itself rather than depression. For instance, one question asks the patient to rate this statement "I feel as if I am slowed down"; most patients gave themselves poor scores on this question, which could be interpreted as the inability to exercise due to heart failure: however, it leads to patients being given a HADS score suggesting mild depression.

Most patients gave themselves a worst-rank score for the statement "I can laugh and see the funny side of things". For other questions, there was a wider distribution of scores. It is not clear that the relatively complex questionnaires currently used to assess mood and quality of life are superior to single, simple, direct, intuitive questions in detecting important depression ("Are you depressed? If so, how badly does this affect you?") or assessing well-being ("On a scale of $1-10$ how well are you today?"); single questions are easy to administer and may be more efficient, although they may need to be interpreted in the context of the patients situation (for example, recent near-death experience, worsening heart failure or stable CHF) [17]. Indeed, responses to just two-questions (PHQ-2) appears to identify patients with depression fairly accurately compared to more complex instruments [18].

Other Limitations. The study is relatively small, with a modest number of events, but it is one of the first in patients hospitalized with worsening HF. The diagnosis of depression was made with a tool that does not give the same diagnostic certainty as DSM-III/IV or similar codes. The tool was only administered once, and we may have missed changes in mood during or after hospitalization. The HADS uses some colloquial language which may not be understood by patients from different backgrounds.

Conclusion. Moderate to severe depression is strongly associated with mortality in the year following discharge after a HF admission to hospital. The association is independent of HF severity and other comorbidity. New strategies are required to improve the recognition of depression and to target those with persistent problems who might benefit from intervention.

APPENDIX A: CHARLSON COMORBIDITY INDEX (CCI)

Comorbidity is assessed by Charlson Comorbidity Index (CCI) [19]. CCI is calculated during hospitalization by assigning to certain comorbidities a weighted value.

- 1 point: Myocardial infarction, congestive heart failure, peripheral vascular disease, dementia, cerebrovascular disease, chronic pulmonary disease, connective tissue disease, ulcer disease, mild liver disease, diabetes.
- 2 points: Hemiplegia, moderate or severe renal disease, diabetes with end organ damage, any tumor, leukemia, lymphoma.
- 3 points: Moderate or severe liver disease.
- 6 points: Metastatic solid tumor, AIDS.

APPENDIX B: HADS-D QUESTIONNAIRE ITEMS

In this analysis the depression related part of the HADS questionnaire is used. This part consists of the following seven questions and four possible answers per question.

1. I still enjoy the things I used to enjoy
   (a) Definitely as much
   (b) Not quite so much
   (c) Only a little
   (d) Hardly at all
2. I can laugh and see the funny side of things
   (a) As much as I always could
   (b) Not quite so much now
   (c) Definitely not so much now
   (d) Not at all
3. I feel cheerful
   (a) Not at all
   (b) Not often
   (c) Sometimes
   (d) Most of the time
4. I feel as if I am slowed down
   (a) Nearly all the time
   (b) Very often
   (c) Sometimes
   (d) Not at all
5. I have lost interest in my appearance
   (a) Definitely

(b) I don't take so much care as I should

(c) I may not take quite as much care

(d) I take just as much care as ever

6. I look forward with enjoyment to things

(a) As much as ever I did

(b) Rather less than I used to

(c) Definitely less than I used t o

(d) Hardly at all

7. I can enjoy a good book or radio or TV program

(a) Often

(b) Sometimes

(c) Not often

(d) Very seldom

APPENDIX C: CONSORT DIAGRAM

The consort diagram of the study is shown in Figure 3.2).

FIGURE 3.2: Consort diagram

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