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ORIGINAL RESEARCH ARTICLE

Use of novel non-invasive techniques and biomarkers to guide outpatient management of fluid overload and reduce hospital readmission: systematic review and meta-analysis

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Abstract

Aims Fluid congestion is a leading cause of hospital admission, readmission, and mortality in heart failure (HF). We performed a systematic review and meta-analysis to determine the effectiveness of an advanced fluid management programme (AFMP). The AFMP was defined as an intervention providing tailored diuretic therapy guided by intravascular volume assessment, in hospitalized patients or after discharge. The AFMP group was compared with patients who received standard care treatment. The aim of this systematic review and meta-analysis was to determine the effectiveness of an AFMP in improving patient outcomes.

Methods and results A systematic review of randomized controlled trials, case–control studies, and crossover studies using the terms 'heart failure', 'fluid management', and 'readmission' was conducted in PubMed, CINAHL, and Scopus up until November 2020. Studies reporting the association of an AFMP on readmission and/or mortality were included in our meta-analyses. Risk of bias was assessed in non-randomized studies using the Newcastle–Ottawa Scale. From 232 retrieved studies, 12 were included in the data synthesis. The 6040 patients in the included studies had a mean age of 72 ± 4 years and mean left ventricular ejection fraction of 39 ± 8%, there were slightly more men (n = 3022) than women, and the follow-up period was a mean of 4.8 ± 3.1 months. Readmission data were available in 5362 patients; of these, 1629 were readmitted. Mortality data were available in 5787 patients; of these, 584 died. HF patients who had an AFMP in hospital and/or after discharge had lower odds of all-cause readmission (odds ratio—OR 0.64 [95% confidence interval—CI 0.44, 0.92], P = 0.02) with moderate heterogeneity (I^2 = 46.5) and lower odds of all-cause mortality (OR 0.82 [95% CI 0.69, 0.98], P = 0.03) with low heterogeneity (I^2 = 0). The use of an AFMP was equally effective in reducing readmission and mortality regardless of age and follow-up duration. Effective pre-discharge diuresis was associated with significantly lower readmission odds (OR 0.43 [95% CI 0.26, 0.71], P = 0.001) compared with a fluid management plan as part of post-discharge follow-up.

Conclusions An effective AFMP is associated with improving readmission and mortality in HF. Our results encourage attainment of optimal volume status at discharge and prescription of optimal diuretic dose. Ongoing support to maintain euvolaemia and effective collaboration between healthcare teams, along with effective patient education and engagement, may help to reduce adverse outcomes in HF patients.

Keywords Fluid management; ADHF; Decongestion; Diuresis; Adherence; Guided treatment

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Introduction

Despite major treatment advances, short-term risks of mortality and readmission in heart failure (HF) remain high.[1] About 25% of patients admitted for HF are readmitted to hospital within 30 days,[2–4] and fluid congestion is a leading cause for short-term readmission.[1,5] The fundamental step to reduce readmission due to congestion is optimization of intravascular volume during the index hospitalization. While this is usually guided by signs and symptoms,[1] these are not reliable in advanced HF[6] and novel approaches are necessary. Although clinical congestion is rapidly improved following effective diuresis, readmission and mortality rates remain high if laboratory (e.g. natriuretic peptides) or imaging markers (e.g. estimated left ventricular filling pressure, inferior vena cava congestion, and pulmonary congestion) remain abnormal, indicating the need for further in-hospital diuresis or a post-discharge diuretic follow-up plan.[7] What is less clear is whether an advanced fluid management programme (AFMP), which is centred on guiding diuretic therapy by assessment of intravascular volume status, is effective in controlling readmission. Accordingly, we performed a systematic review and meta-analysis to determine whether management guidance according to fluid status was associated with improved outcomes.

Methods

Study design

In this study of fluid management programmes, the primary outcome was all-cause hospital readmission. The secondary outcome was all-cause mortality. Our systematic review was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[8] The systematic review was registered in February 2020 with the PROSPERO prospective register of systematic reviews (CRD42020138089).

Search strategy

We conducted a search of the literature in PubMed (from 1994), CINAHL (from 2004), and Scopus (from 2011) up until November 2020 for randomized controlled trials (RCTs), case–control studies, and crossover studies that included pre-discharge advanced diuretic plans or post-discharge fluid management follow-up plans in HF patients.

We used common search terms ('heart failure' and 'fluid management' or 'fluid retention' or 'fluid overload' and Re-admission or re-admitted or Readmission or readmitted or Rehospitali* or re-hospitali*). Searches were restricted to human research and English language. We did not include terms that would retrieve established guidance such as BNP-guided or surveillance that cannot be practically applied in all HF patients such us invasive monitoring.[9] The full search strategy is outlined in the Supporting Information.

Study selection

Two assessors (G. Z. and A. H.) independently reviewed the abstracts for inclusion/exclusion criteria. Studies were included based on the following criteria: index admission for acute decompensated HF (ADHF), age >18 years, fluid management, and/or intervention. Studies were excluded if (i) they did not report either readmission or mortality rates, (ii) HF was not confirmed by admission signs and symptoms, or (iii) study protocols and studies of which their methodology could not be critically appraised, such as conference abstracts. Systematic reviews were excluded, but their references were screened for any additional studies that could have been omitted from our search strategy. We used review software (Covidence®, Melbourne, Australia), to track articles retrieved from our search. Conflicts were resolved by a third reviewer (T. H. M.)

Data extraction

Extracted data included descriptive characteristics of the included studies, medical history, treatment history, and presenting symptoms (*Table 1*). Reported hazard ratios (HRs) with 95% confidence intervals (CIs) on readmission and/or mortality were also extracted.

Quality and risk of bias assessment

We used the Newcastle–Ottawa Scale (NOS) for assessing the quality and risk of bias of non-randomized studies.[10] NOS assessed quality based on three criteria: (i) patient selection, (ii) comparability, and (iii) outcomes. Studies were ranked as good, fair, or low quality.

Statistical analysis and data synthesis

Categorical variables were expressed as numbers (*n*) and proportions (%) and continuous variables as means and standard deviations. The treatment group consisted of patients that had an advanced diuretic plan or were subject to a post-discharge follow-up with an intervention plan to intervene, monitor, and control fluid status. In one study with multiple groups, data from the intervention and the equivalent control arm were extracted and included in our meta-analysis.[11] In another study of 74 enrolled patients, nine who did not complete the study were excluded from analysis.[12] HF type was

Table 1 Extracted data from included studies

Descriptive characteristics: year of publication, recruitment period, study design, sample size, number of groups, follow-up period in months, inclusion–exclusion criteria, mean age, gender, mean left ventricular ejection fraction (LVEF), HF of ischaemic cause, New York Heart Association (NYHA) class, and summary of outcomes
Medical history: cardiac co-morbidities [coronary artery disease (CAD), ischaemic heart disease (IHD), myocardial infarction (MI), peripheral vascular disease (PVD) or peripheral arterial disease (PAD), hypertension (HTN), cerebrovascular accident (CVA) or cerebrovascular disease (CVD) or stroke or transient ischaemic attack (TIA), valvular heart disease (VHD), atrial fibrillation (AF), or atrial flutter (A-Flutter)] and non-cardiac co-morbidities [chronic obstructive pulmonary disease (COPD), asthma, diabetes, hypercholesterinaemia, arthritis, gout, renal disease, and depression]
Treatment history: cardiac interventions [cardiac surgery (coronary artery bypass surgery—CABG) or valvular surgery], cardiac device [internal cardioverter defibrillator (ICD), permanent pacemaker (PPM), cardiac resynchronization therapy (CRT), and biventricular (BIV) device], and medical treatment [beta-blockers, diuretics, thiazides, angiotensin-converting enzyme inhibitors (ACEis), angiotensin II receptor blockers (ARBs), spironolactone, statins, digoxin, mineralocorticoid receptor antagonist (MRA), warfarin, and aspirin]
Presenting symptoms: mean weight, dyspnoea, peripheral oedema, jugular vein distention (JVD), third tone (S3), ventricular tachycardia (VT), and infiltrates and outcome rates (readmission and mortality)

HF, heart failure.

not reported by all studies, so included patients were categorized based on reported mean left ventricular ejection fraction (LVEF) and according to the guidelines[1] as reduced LVEF (<40%) or preserved and/or mid-range LVEF (≥40%).

Pooled data were used to calculate overall odds ratio (OR) with 95% CI. Forest plots were used to illustrate the effect size. Weighted averages were used to calculate pooled data and adjust differences in size groups. Reported co-morbid conditions are presented as cardiovascular and non-cardiac. Heterogeneity between studies was tested with χ^2 test and I^2 statistic, with a *P*-value <0.05 and $I^2 > 20\%$ being considered statistically significant. The statistical analysis was performed with STATA SE 16 and IBM SPSS Statistics Version 26.

Results

Study selection

The initial search process (*Figure 1*) identified 202 potential studies from PubMed, CINAHL, Scopus, and full-text review of included studies. The supplementary search identified another 30 studies. After removal of duplicates, 185 abstracts were screened for eligibility. After full-text review, 13 studies remained (six RCTs, four prospective case–controlled studies, and three crossover design studies). Of the seven non-RCT studies, which were assessed with NOS (Supporting Information, *Table S1*), one was of low quality and therefore was excluded from the meta-analysis.

Among the remaining 12 studies included in this meta-analysis (n = 6040), readmission events were reported in nine studies, which included a total of 5362 patients (2603 in the treatment group and 2759 in the control group).[11–19] Whereas mortality outcomes were reported in eight studies, which included a total of 5787 patients (2833 in treatment group and 2954 in the control groups).[13–16,18,20–22] The follow-up period was at least 1 month.

The characteristics of each study design are presented in *Table 2*. Patients that were allocated to the treatment arm followed in-hospital-guided fluid treatment protocols or were discharged with an advanced fluid management follow-up programme, whereas patients who were discharged with standard diuretic therapy or plan comprised the control group. The intervention follow-up plans (*Table 3*) focused on decongestion and optimized fluid treatment as well as education and fluid restriction adherence.

Patient characteristics

The patient characteristics (*Table 3*) were consistent with usual HF demographics. The mean age was 72 ± 4 years, and the mean LVEF was 39 ± 8%. The mean follow-up period was 4.8 ± 3.1 months. The most commonly reported cardiovascular co-morbidities in six studies[12,14–16,21,22] were hypertension (72%) and coronary artery disease in five studies[13,15,19,21,22] (52%) (Supporting Information, *Table S2*), and the most common non-cardiac co-morbidities were type 2 diabetes (35%) in eight studies[12–16,19,21,22] and chronic obstructive pulmonary disease (25%) in five studies[14,16,19,21,22] (Supporting Information, *Table S3*).

With regard to studies that reported HF therapies, 63% (3334/5301) were treated with beta-blocker and an angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker (3337/5301),[12–17,19,21] while 19% (173/907) had an internal cardioverter defibrillator[16,20–22] and 3% (35/380) had a permanent pacemaker.[21] At admission, in studies that reported symptoms, nocturnal (54%, 2487/4626)[14,22] or exertional (58%, 2540/4380)[14] dyspnoea and pulmonary rales (58%, 2629/4505)[14,16] were the most commonly reported symptoms. The mean creatinine level was 1.42 mg/dL.[11–16,18–21] However, therapies, symptoms, and laboratory reports were not consistently reported by each study (Supporting Information, *Tables S4–S7*).

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart. This figure illustrates literature review and study selection process. NOS, Newcastle–Ottawa Scale.

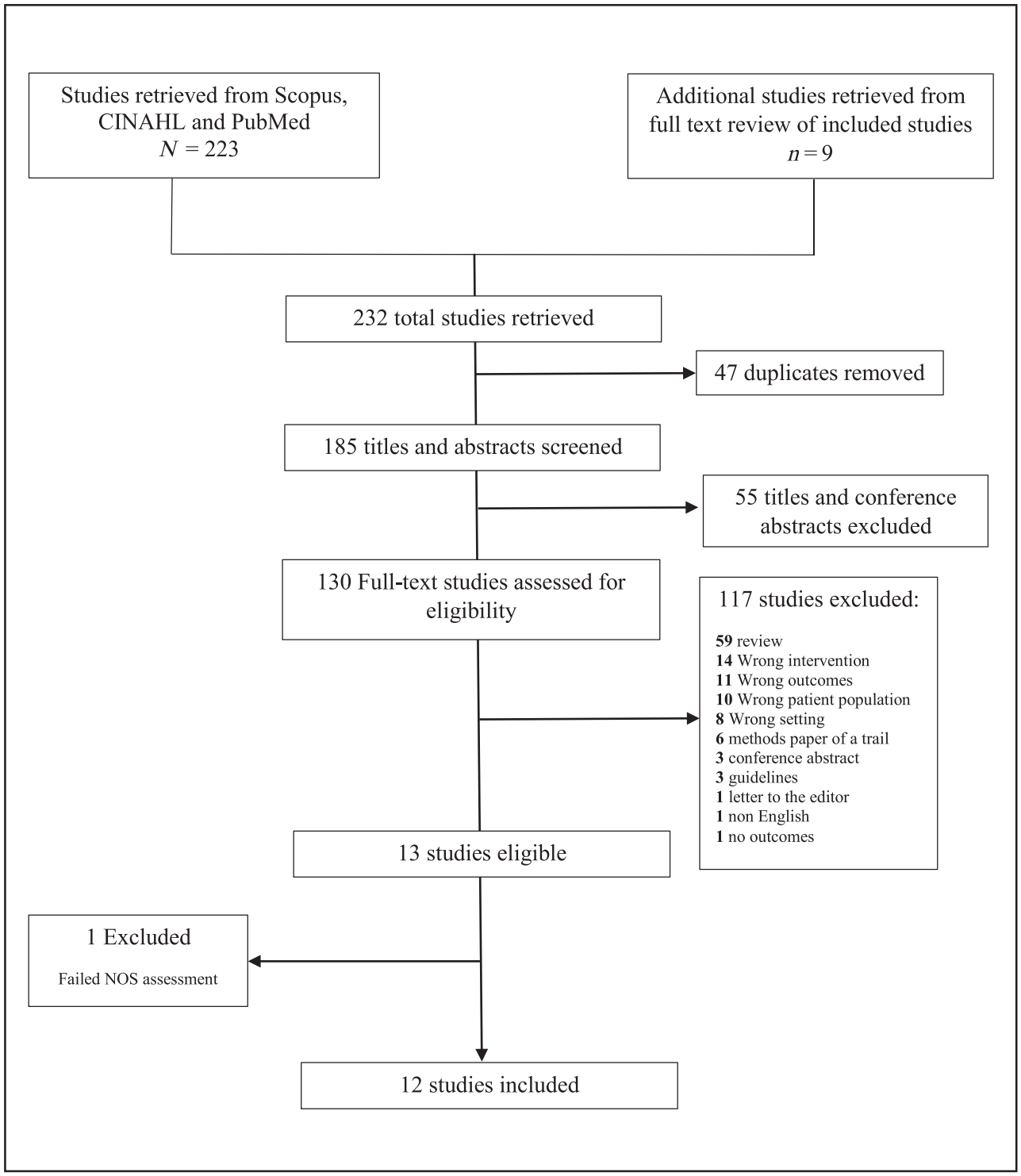


Table 2 Design and characteristics of studies included in data synthesis meta-analysis

Study	Year	Recruitment period	Design	Sample size[a]	Groups	Follow-up (months)	Inclusion criteria	Intervention
Amir *et al.*[13]	2017	October 2012 to February 2015	Crossover	50 (crossover)	2	6	AHDF and Stage C HF	ReDS to monitor changes in lung fluid accumulation and guided HF treatment
Bensimhon *et al.*[11]	2020	Not given	RCT	35[b]	2	3	Age ≥21 years or older, AHF hospitalization, BNP level ≥200 pg/mL, and ability to accept intervention programme (ReDS)	Congestion assessment with ReDS. Readings ≥39% triggered guided fluid treatment
Dendale *et al.*[20]	2012	April 2008 up to June 2010	RCT	160	2	6	Hospitalization for HF with fluid overload	Telemonitoring (BP, weight, and HR) through dedicated devices vs. usual care
Faselis *et al.*[14]	2020	1 March 2003 to 31 December 2004	Retrospective case–control	4382	2	2	*Inclusions*: patients enrolled at OPTIMIZED-HF registry *Exclusions*: patients taking diuretics prior to hospitalization for HF decompensation; patients with a history of dialysis, who received dialysis during hospitalization; and patients received thiazide diuretics or discharged on thiazide diuretics	Loop diuretics at discharge vs. no loop diuretics at discharge
Holst *et al.*[12]	2008	September 2002 to January 2005	Crossover	65 (crossover)	2	8	CHF with LVEF 45% or less, stable, and without clinical signs of significant fluid overload	Restricted (maximum 1.5 L daily) vs. liberal (30 mL/kg body weight per day to a max of 35 mL/kg) fluid intake
Hu *et al.*[15]	2020	April 2018 to September 2019	RCT	100	2	2	HF admission with fluid overload and age ≥18	Ultrafiltration before tolvaptan and torasemide vs. tolvaptan and torasemide without ultrafiltration
Nunez *et al.*[21]	2016	7 December 2011 to 17 July 2014	RCT	380	2	12	AHF up to 180 days prior to enrolment, NYHA III or IV at the enrolment, CA-125 > 35 U/mL, and either echo confirming HF or elevated peptides	Guided HF treatment based on CA-125 antigen
Rivas-Lasarte *et al.*[16]	2019	10 November 2016 to 19 June 2018	RCT	123	2	3	Age ≥18 and admission for HF	Post-discharge LUS-guided treatment vs. usual care
Rouse *et al.*[22]	2016	15 months	Prospective case–control	244	2	6	Age >18 and treated for CHF at a quaternary care clinic	Patient HF education, focus on control of symptoms and weight gain, and self-management
Sethares and Elliott[17]	2004	October 1999 and December 2000	RCT	70	2	3	Hospital admission for primary condition HF, at least 3 months ago confirmed by signs and symptoms	Tailored message on benefits and barriers to self-care
Valle *et al.*[18]	2011	24 months	Prospective case–control	300	3	6	AHF, Class III or IV, and echo confirming HF elevated peptides	Treatment group (early responders and late responders) vs. control groups (non-responders)
Woodruff *et al.*[19]	2016	January to December 2012	Retrospective case–control	131	2	1	HFrEF and fluid overload	Adjusting diuretic dose to optimal level
Cumulative	—	—	—	6040	—	Mean 4.8	—	—

ADHF, acute decompensated heart failure; AHF, acute heart failure; BNP, brain natriuretic peptide; BP, blood pressure; CA, carbohydrate antigen; CHF, chronic heart failure; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HR, heart rate; LUS, lung ultrasound; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; ReDS, remote dielectric sensing.

[a]Of the studies included in meta-analysis.

[b]ReDS ≥ 39% group.

Table 3 Patient characteristics

Study	Mean age (years)	Gender male, *n* (%)	Mean EF[a] % (SD)	Ischaemic cause, *n* (%)	NYHA I or II at discharge, *n* (%)	NYHA III or IV at discharge, *n* (%)	Outcomes
Amir *et al*.[13]	74	31 (62)	—	30 (60)	15 (10)	45 (90)	Heart failure readmission and all-cause death
Bensimhon *et al*.[11]	67.5[b]	25 (71)[b]	36.3 (13.2)[b]	—	—	—	*Primary outcomes*: proportion of patient who had guided fluid treatment based on ReDS readings at ≥39%, at the time of proposed hospital discharge *Secondary and exploratory outcomes*: (i) readmission at 30 and 90 days, stratified by treatment group; (ii) readmission rates at 30 and 90 days stratified by ReDS reading at the time of actual discharge; and (iii) change in weight, ReDS measurement, and serum creatinine from the day of proposed discharge to actual discharge
Dendale *et al*.[20]	76	104 (65)	35 (15)	—	—	—	*Primary all-cause mortality others*: days lost to death, hospitalization, or dialysis and number of hospitalizations
Faselis *et al*.[14]	78	2002 (46)	43 (15)	—	—	—	(i) 30 and 90 days of readmission, all-cause, or WHF; (ii) all-cause mortality; and (iii) combined readmission or mortality
Holst *et al*.[12]	70	54 (83)	—	48 (78)	60 (92)	6 (9)	QoL, physical capacity, thirst, and hospital admissions in CHF patients who had improved from NYHA Class III to IV
Hu *et al*.[15]	72.35	55 (55)	—	71 (71)[c]	—	—	*Primary outcomes*: weight loss and daily urine volume in the treatment group on the 4th and 8th days of treatment *Secondary outcomes*: readmission and mortality at 30 and 60 days. HF signs improvements
Nunez *et al*.[21]	73.50	212 (56)	45 (17)	122 (32)[c]	—	—	Composite all-cause mortality or readmission for AHF
Rivas-Lasarte *et al*.[16]	69	89 (72)	39 (15)	42 (34)	82 (67)	39 (32)	*Primary endpoints*: composite of urgent visits, hospitalization for WHF, and death *Secondary endpoints*: individualized primary endpoints
Rouse *et al*.[22]	65.8	167 (68)	30 (14)	126 (52)	—	—	Hospital consumption defined as HF rehospitalization ED and unplanned office visits and mortality
Sethares and Elliott[17]	76.3	33 (47)	40 (19)	—	—	—	Readmission, QoL, and improved self-care
Valle *et al*.[18]	77	165 (55)	46 (17)	117 (39)	—	—	Death and/or hospital readmission for AHF
Woodruff *et al*.[19]	66.30	84 (64)	25 (8)	63 (48)	—	—	All-cause 30 day readmission rates
Cumulative	72 (4)	3021 (50)	39 (8)	411 (7)	142 (2.3)	45 (1)	—

AHF, acute heart failure; CHF, chronic heart failure; ED, emergency department; EF, ejection fraction; HF, heart failure; NYHA, New York Heart Association; QoL, quality of life; ReDS, remote dielectric sensing; SD, standard deviation; WHF, worsening of heart failure.
[a]Of studies reported ejection fraction.
[b]ReDS ≥ 39% group.
[c]Of patients with a history of coronary artery disease.

Readmission

There were fewer readmissions in the treatment compared with the control group (29.0% vs. 31.7%) (*Table 4*). The readmission event per month is presented in *Table 5*. The pooled odds of readmission from nine studies (*Figure 2*)[11–19] in 5362 patients was 0.64 (95% CI 0.44, 0.92, $P = 0.02$) with moderate heterogeneity ($I^2 = 46.5$).

Three studies[13,14,16] reported the HR, one study reported the incidence rate ratio[21] for readmission, and all studies were adjusted for intervention (Supporting Information, *Table S8*). Two studies[14,16] reported the HR, one study[21] reported the incidence rate ratio for mortality, and all studies were adjusted for intervention (Supporting Information, *Table S9*). Amir *et al.*[13] reported a 14-fold greater risk for hospital readmission at 3 months prior to the intervention compared with during the intervention. The HR was reduced after discharge and after intervention, and the reported HR was nine-fold greater compared with 3 months prior to the intervention (Supporting Information, *Table S8*). This intervention guided in-hospital diuresis based on remote dielectric sensing (ReDS), and the patient group was assessed before, during, and after intervention.

The effects of intervention were slightly greater in older patients and in those with longer follow-up periods, but the differences observed between the groups were not statistically significant ($P = 0.75$ and 0.42, respectively; *Figure 3*). The effect of intervention was greater ($P = 0.001$) in patients who received AFMP before discharge[15,20,21] (OR = 0.43) compared with that in those who received AFMP during post-discharge follow-up[11–14,16–19,22] (OR = 0.78; *Figure 3*). The intervention seemed to provide benefit in both types of HF patients (reduced and preserved LVEF), but it was statistically significant only in patients with preserved LVEF $\geq$ 40% (OR = 0.65, $P = 0.02$, $I^2 = 70\%$; *Figure 4*).

Subgroup analysis

Advanced fluid management programme had a univariable association with reduced readmission in patients with co-morbid diabetes ($\beta = -0.03$ [95% CI -0.057, -0.005], $P = 0.018$). AFMP did not reduce the odds of readmission in subgroups classified by HF treatment, age, ejection fraction, creatinine level, and co-morbid chronic obstructive pulmonary disease (*Table 6*).

Mortality

Mortality events were reported by eight studies[13–16,18,20–22] (*Table 4*). The pooled odds ratio for mortality after AFMP[13–16,18,20–22] in 5787 patients was 0.82 (95% CI 0.69, 0.98, $P = 0.03$) with low heterogeneity ($I^2 = 0$) (*Figure 5*). The mortality event per month rate is presented in *Table 5*.

In the subgroup analysis (*Figure 6*), the differences in effect size of the intervention among the subgroups were trivial and there were no statistically significant associations between the LVEF groups (Supporting Information, *Figure S1*). Provision of a post-discharge AFMP seemed to be more effective than its restriction to within the hospital stay (*Figure 3*).

In the meta-regression analysis, AFMP was not significantly associated with any of the specified moderators as shown in Supporting Information, *Table S10*.

Discussion

Heart failure patients admitted with fluid overload have an increased risk for readmission and/or mortality; hence, decongestion and maintaining euvolaemia are important. Based on this meta-analysis, assessment of intravascular volume

Table 4 Readmission and mortality rates in heart failure patients treated with advanced fluid management plans compared with control subjects

Study	Readmission treatment group, events/group size (%)	Readmission control, events/group size (%)	Mortality treatment group, events/group size (%)	Mortality control, events/group size (%)
Amir *et al.*[13]	2/50 (4)	4/48 (8)	2/50 (4)	2/48 (4.2)
Bensimhon *et al.*[11]	1/11 (9)	4/17 (23.5)	—	—
Dendale *et al.*[20]	—	—	4/80 (5)	14/80 (17.5)
Faselis *et al.*[14]	693/2191 (31.7)	712/2191 (32.5)	201/2191 (9.2)	232/2191 (10.6)
Holst *et al.*[12]	5/65 (8)	5/65 (8)	—	—
Hu *et al.*[15]	8/40 (20)	34/60 (57)	0/40 (0)	1/60 (2)
Nunez *et al.*[21]	—	—	31/187 (16.5)	35/193 (18)
Rivas-Lasarte *et al.*[16]	14/61 (23)	13/62 (21)	3/61 (5)	2/62 (3)
Rouse *et al.*[22]	—	—	18/122 (15)	21/122 (17)
Sethares and Elliott[17]	6/33 (18)	12/37 (32)	—	—
Valle *et al.*[18]	16/102 (16)	59/198 (30)	4/102 (4)	14/198 (7)
Woodruff *et al.*[19]	10/50 (20)	31/81 (38)	—	—
Cumulative	755/2603 (29)	874/2759 (31.7)	263/2833 (9.3)	321/2954 (10.9)

status (especially in the post-hospital phase) can optimize diuresis, and this is associated with reduced odds for readmission and mortality. To the best of our knowledge, this is the first systematic review of ADHF patients, followed with a diuretic treatment plan based upon volume status, delivered in conjunction with standard medical treatment.[1] There was moderate heterogeneity among the selected studies for the readmission odds and no heterogeneity for the mortality odds. Guideline-directed treatments did not affect the intervention arm in readmission and mortality, but only about half of the total sample (in 9/12 included studies) received treatments with beta-blockers and/or angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers. Failure to treat with beta-blockers has been reported as a strong predictor of mortality but not for readmission.[23]

Table 5 Readmission and mortality event rates per month in heart failure patients treated with advanced fluid management plans vs. control subjects

	Readmission		Mortality	
Study	Treatment group	Control group	Treatment group	Control group
Amir *et al.*[13]	0.67	1.33	0.67	0.69
Bensimhon *et al.*[11]	3.00	7.83	—	—
Dendale *et al.*[20]	—	—	0.83	2.92
Faselis *et al.*[14]	15.80	16.25	4.60	5.30
Holst *et al.*[12]	1.00	1.00	—	—
Hu *et al.*[15]	10.00	28.00	0.00	0.83
Nunez *et al.*[21]	—	—	1.38	1.50
Rivas-Lasarte *et al.*[16]	7.65	7.00	1.60	1.08
Rouse *et al.*[22]	—	—	2.50	2.90
Sethares and Elliott[17]	6.00	10.67	—	—
Valle *et al.*[18]	2.60	5	0.65	1.20
Woodruff *et al.*[19]	20.00	38.30	—	—

Calculated as event monthly proportion rate study duration in months.

Effective in-hospital diuresis in index admission for acute decompensated heart failure

Chronic HF is frequently complicated by ADHF events, associated with increased risk of recurrent congestive HF and increased risk of readmission and mortality.[5,24] Adequate determination and quantification of congestion using established clinical and/or laboratory makers or techniques are important in order to guide treatment accordingly and avoid overtreatment or misguided dose escalation–reduction in diuretic treatment.[25] Effective decongestion and the ability to maintain euvolaemia are fundamental to prevent adverse

Figure 2 All-cause readmission. This forest plot summarizes the meta-analysis of total readmission. CI, confidence interval; REML, restricted maximum likelihood.

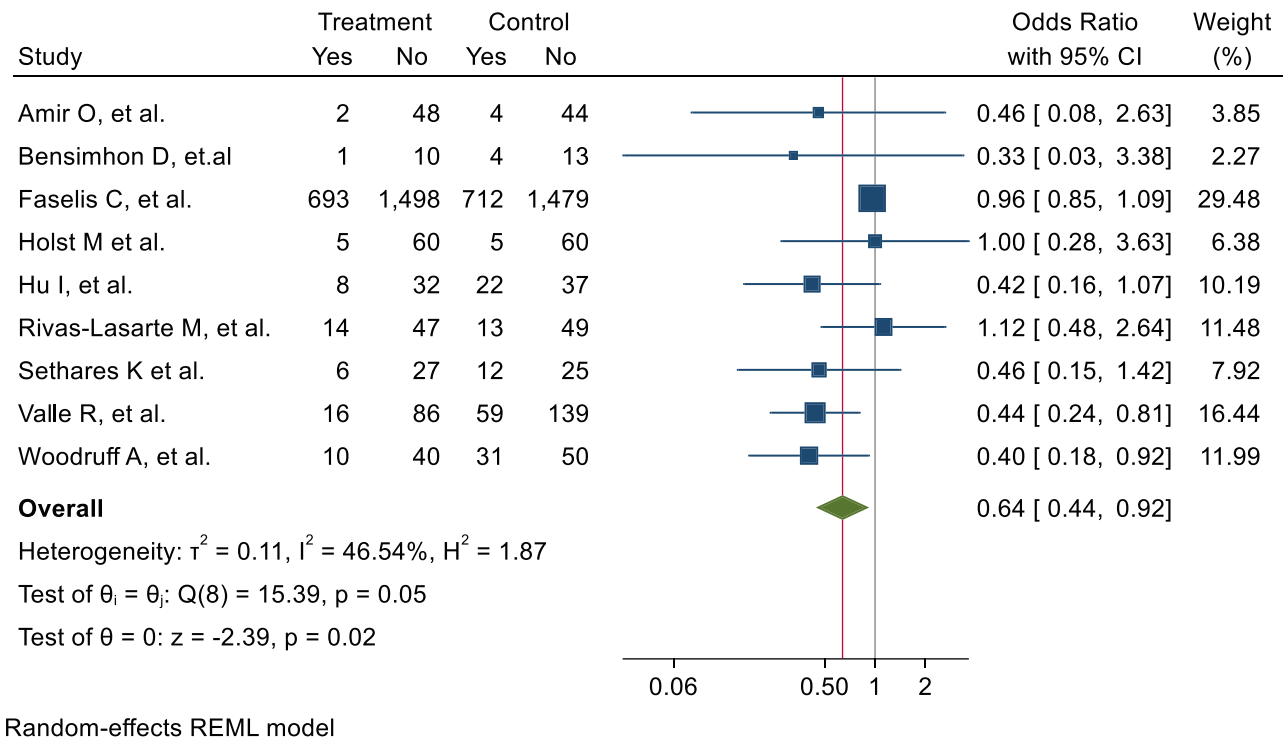
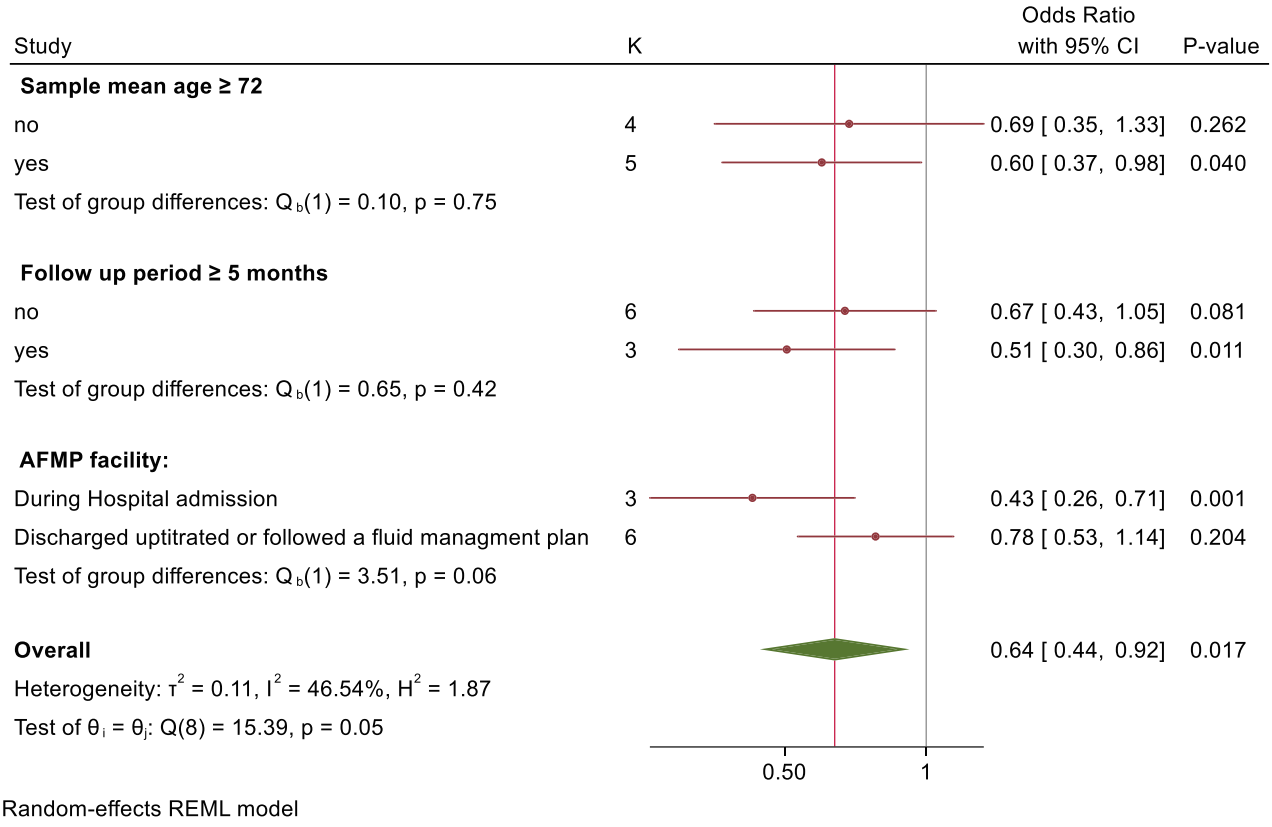


Figure 3 Subgroup analysis for readmission. Subgroups were defined by mean age, mean follow-up period, and pre-discharge vs. post-discharge advanced fluid management programme (AFMP). CI, confidence interval; REML, restricted maximum likelihood.



outcomes in chronic HF patients who are admitted for ADHF. Despite an index admission for decompensation, patients usually respond rapidly to diuretic treatment, but inadequate decongestion leads to readmission and mortality rates remain high.[7] Advanced treatment strategies to ensure decongestion prior to discharge are currently implemented, showing that outcomes can be improved along with optimized discharged diuretic treatment. Indeed, based on this systematic review, patients seem to have more benefits from effective in-hospital diuresis aiming to achieve minimal or no symptoms at rest. A recent review[26] has emphasized the importance of differentiating volume overload (treated with diuretics) from volume misdistribution (treated with vasodilators) in order to appropriately guide management. In both cases, achieving decongestion is important, and once achieved, patients may benefit from post-discharge HF care programmes and advanced therapies to prevent recurrence of ADHF.[26] The goals of decongestion in ADHF aim to ensure minimal or no residual congestion, appropriate perfusion, and encourage maintenance of medical therapy. Loop diuretics are encouraged in order to maintain euvolaemic status along with reference to specialized disease management programmes.[25]

Interventions

This systematic review summarized novel non-invasive techniques and biomarkers. We did not include guidance based on natriuretic peptides—although these assays have a clear role in the diagnosis of HF, their role during follow-up is controversial.[27] The included studies used BNP or N-terminal pro-brain natriuretic peptide to confirm HF diagnosis rather to guide HF treatment. Although CardioMEMS[9] was recently approved for guided treatment in HF patients and has been shown to be effective in reducing readmissions in HF patients[9] as well as a cost-effective monitoring method,[9,28,29] we did not include this in our review as CardioMEMS is an invasive technique, not broadly applicable to the majority of frail, elderly patients. Radhoe *et al.*[30] conducted a review of invasive remote haemodynamic sensors that monitor haemodynamic changes in HF patients and showed that CardioMEMS was the most effective device.

The various methods of guiding effective diuresis before and after discharge can be divided into those used in the pre-discharge and post-discharge phases. In the *pre-discharge phase*, non-invasive techniques to guide decongestion while the patient is an inpatient are currently being

Figure 4 Subgroup analysis for readmission defined by mean left ventricular ejection fraction (LVEF). CI, confidence interval; REML, restricted maximum likelihood.

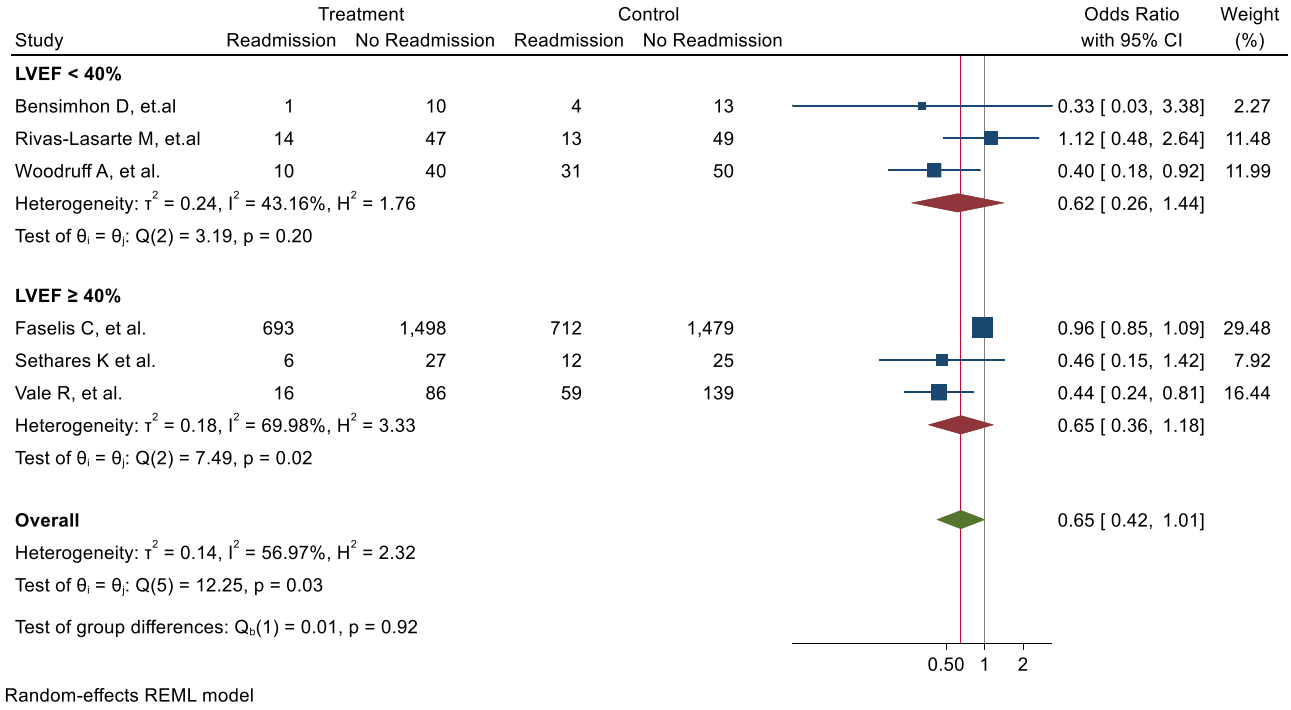


Table 6 Associations of primary outcome

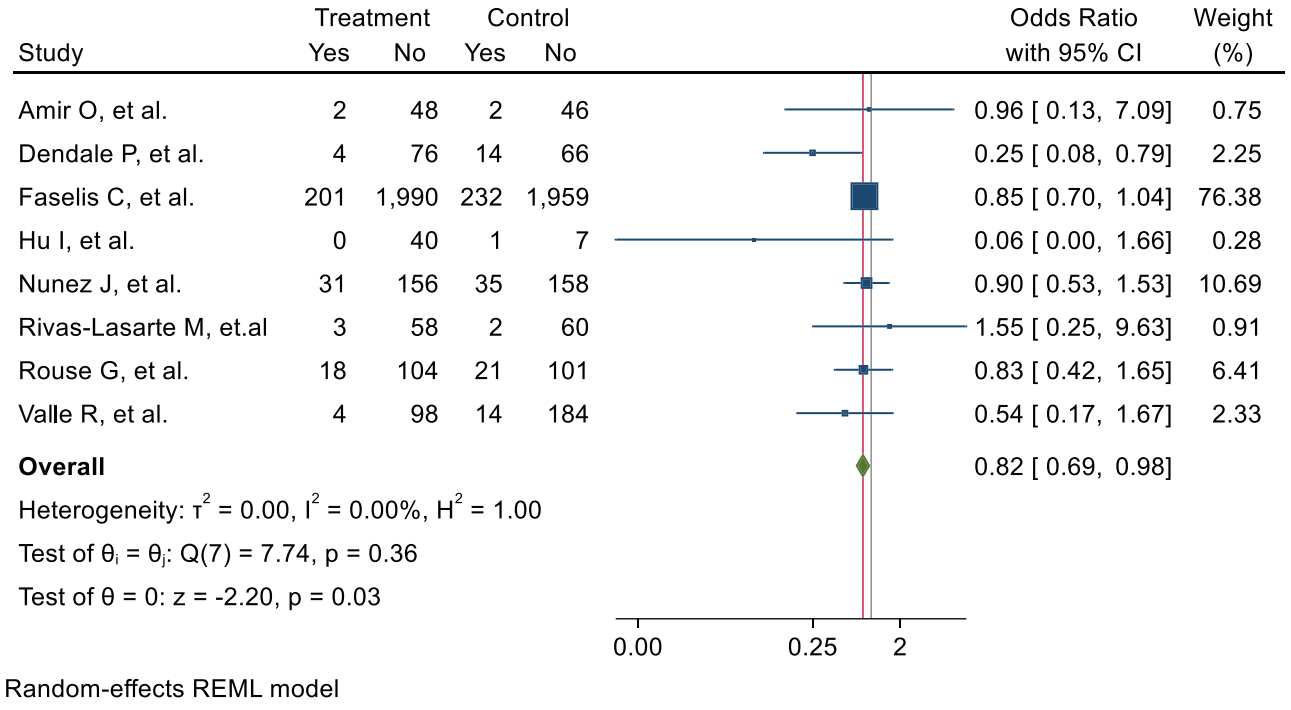
Factors	β-coefficient [95% CI]	*P*-value	References
Mean age	0.02 [−0.07, 0.10]	0.66	11–19
Gender male	0.00 [−0.03, 0.04]	0.85	11–19
Mean EF	0.03 [0.02, 0.09]	0.26	11, 14, 16–19
Diabetes	−0.03 [−0.05, −0.005]	**0.018**	12–16, 19
COPD	0.17 [−0.003, 0.35]	0.054	14, 16, 19
Diuretics	−0.03 [−0.08, 0.00]	0.11	12, 13, 15–17, 19
Beta-blocker	−0.01 [−0.03, 0.00]	0.314	12–17, 19
ACEi/ARB	−0.005 [−0.03, 0.025]	0.74	12–17, 19
Creatinine (mean)	−1.61 [3.8, 0.60]	0.15	11–15, 18, 19

ACEi, angiotensin-converting enzyme inhibitor; AFMP, advanced fluid management programme; ARB, angiotensin II receptor blocker; CI, confidence interval; COPD, chronic obstructive pulmonary disease; EF, ejection fraction.
Meta-regression of the association between AFMP, demographics, treatments, kidney function test, and co-morbid conditions with readmission. Bold emphasis indicates statistical significance at $P < 0.05$.

implemented. Bioelectrical impedance vector analysis and natriuretic peptides were used by Valle *et al*.[18] to guide fluid management during the hospital course and optimize hydration status and subsequent outcomes. Early response was associated with better achievement of euvolaemia and better outcomes.[18] ReDS, another promising and approved, non-invasive device that tracks changes in lung fluid volume, has been evaluated in crossover[13] and RCT[11] studies. ReDS readings were used during hospital admission[11] to guide fluid treatment, delay discharge if needed, encourage further diuresis, and refer patients to a post-discharge HF programme. In both studies, ReDS impressively improved outcomes. Furthermore, based on this meta-analysis, ReDS among other interventions had the greatest effect size in readmission events (OR = 0.33; *Figure 2*). There are similarities between the ReDS device and the CardioMEMS, but the non-invasive character of ReDS makes it potentially of use in everyday clinical practice by all healthcare professionals.

In addition to non-invasive techniques and devices, novel biomarkers to detect and track ongoing congestion are currently being studied. CA-125, an antigen that monitors ovarian cancer, has recently been studied in an RCT as a potential surrogate of fluid congestion, to guide fluid and medical treatment in patients hospitalized for ADHF. The intervention strategy included monitoring the CA-125 levels after discharge and showed that maintaining CA-125 levels

Figure 5 All-cause mortality. This forest plot summarizes the meta-analysis of mortality. CI, confidence interval; REML, restricted maximum likelihood.



≤35 U/mL after discharge could be beneficial and reduce mortality and HF recurrence.[21] The CA-125 is a fairly new congestion marker, and further research is required to determine its use in prevention of readmission and mortality.

Ultrafiltration was evaluated and was found to be superior to diuretics for rapidly reducing volume overload. Patients who started ultrafiltration before recommended treatment achieved greater weight loss quicker and had better outcomes.[15]

During *post-discharge follow-up*, patient education is fundamental and effective patient self-care is an important tool to guiding fluid management. In a case–control study, Rouse *et al*.[22] demonstrated that the three main aspects of patient management (daily weight to monitor hypervolemia, fluid management by limiting sodium intake, and contact a health professional following increase in weight) can reduce emergency visits due to HF as well as all-cause office visits.[22] Sethares and Elliott[17] demonstrated that a tailored message of benefits and assessment of barriers to self-care pre-discharge and post-discharge could improve outcomes, addressing the need of effective patient education before discharge.[17]

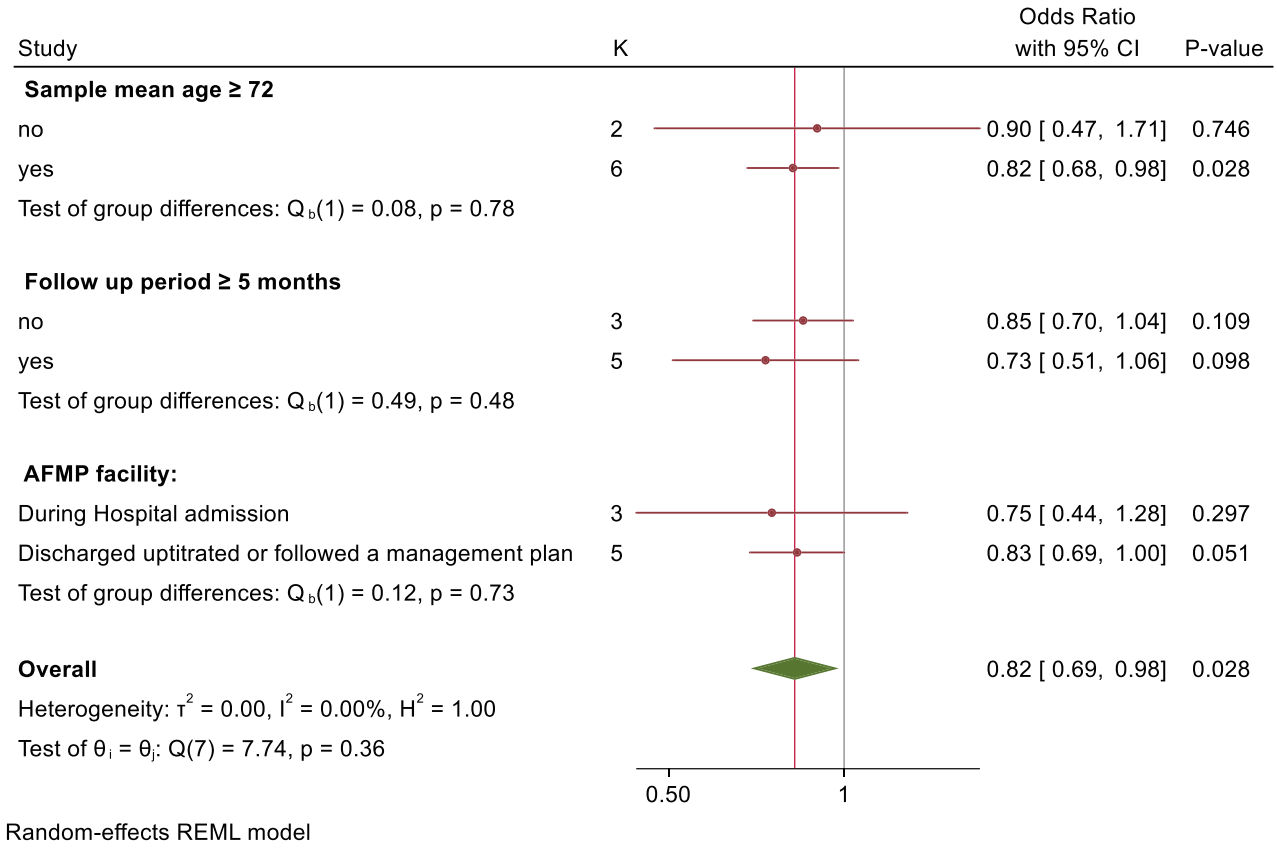
Intensity of diuretic treatment at discharge has a key role in short-term outcomes.[14,19] Woodruff *et al*.[19] followed up discharged patients who were admitted for ADHF and discharged either with an increased diuretic dose or without a diuretic dose increment, in a case–control study. The study concluded that patients with an increased diuretic dose had better outcomes at 30 day follow-up and lower odds for readmission.[19] Prescription of loop diuretics at discharge in older patients, not receiving diuretics before hospital admission for ADHF, is associated with reduced short-term HF readmission and all-cause mortality rates.[14]

Non-invasive techniques to assess volume status are not only being used before hospital discharge, but are emerging as tools for post-discharge follow-up, in order to detect early congestion. Lung ultrasound (LUS) is a reliable non-invasive technique for quantifying lung congestion, evidenced by the presence of B-lines. The findings correlate with natriuretic peptides, and the number of B-lines reflects the degree of congestion.[31,32] The recent LUS-HF study[16] showed that even though the readmission rate was slightly higher in the LUS-guided group, LUS-guided treatment successfully reduced the primary endpoint (a composite of urgent visits to emergency for ADHF, HF hospitalization, and all-cause death) and events.

Effective collaboration among health professionals provides better patient care and improved outcomes. In an RCT[20] where the intervention arm was followed by telemonitoring of weight scales, diuretic treatment was guided by general practitioners. Reduced mortality was observed through patient telemonitoring and effective collaboration.

In a different approach, stabilized HF patients followed a non-restrictive fluid intake algorithm, and thirst control was

Figure 6 Subgroup analysis for mortality. Subgroups were defined by sample mean age, mean follow-up period, and before discharge vs. after discharge. AFMP, advanced fluid management programme; CI, confidence interval; REML, restricted maximum likelihood.



used to monitor symptoms and ensure patient adherence.[12] While results were not different between the groups, the study suggested that it may be beneficial to restrict stabilized HF patients at a higher fluid intake in order to control thirst and maintain euvolaemia.

Safety of the application of an advanced fluid management programme

The application of a guided AFMP was safe and improved mortality rates in the vast majority of the included studies. Ultrafiltration that was added on top of treatment with tolvaptan and torsemide was safe, without any mortality events (OR = 0.06; *Figure 5*).

Patient engagement, adherence, and telehealth programmes

Patient engagement[1,33] with post-discharge programmes and adherence to treatment protocols is important in order to improve outcomes. Application of a simple telemonitoring programme, capable to detect early congestion signs and symptoms, can prevent mortality.[20] Nonetheless, results are heterogeneous. Another telemonitoring programme that delivered patient education and symptom monitoring did not improve outcomes,[34] possibly because the intervention required significant patient contribution (i.e. use of a phone device by patient), and patient engagement dropped by nearly 50% by the end of the study. In contrast, a simplified intensified and automated telemonitoring programme significantly reduced mortality odds (OR = 0.25; *Figure 5*),[20] in parallel with 83% patient engagement and only 2% dropout.[20] In the future, automatic telemonitoring programmes that are connected to local networks may become more broadly available and contribute greatly to improving outcomes.

The benefit of telemonitoring programmes in the chronic rather than post-acute phase is more questionable. One such study compared a combined assessment of patient mood with symptom management in a chronic cardiac care facility.[35] Although the primary outcome of improving patient-reported HF specific status was not achieved, mortality was significantly less in the intervention arm. Interestingly,

patient engagement was high, and there were minimal drop-outs.[35] Another RCT combining both telemonitoring of HF symptoms and psychological support at a chronic healthcare facility did not improve readmission and mortality outcomes. Nonetheless, depression and fatigue were both improved, both important in HF management.[36]

While disease management programmes (DMPs) delivered at chronic HF patients and may have different results from patients who were recently admitted for ADHF, important lessons can be taken into consideration. Simplicity and intensity of a telehealth/remote disease management programme, aiming to achieve patient engagement, may be fundamental in improving outcomes. Another factor to consider when assigning patients to disease management programmes is risk assessment, as not all patients have the same risk of readmission and/or mortality. Risk algorithms[23,37] could be used to target DMP to high-risk patients and guide volume management accordingly.

Limitations

Not all studies report HF readmissions; therefore, we reported outcomes as all-cause readmission. Thus, we could not determine whether effective diuresis reduced HF-related readmission. HF type was not reported, and effectiveness of the intervention in the HF type was based on mean LVEF. Only a small proportion of patients had an implantable device; therefore, the intervention effect could not be determined in patients with a cardiac device. Similarly, only a small portion of patients had a history of renal disease; therefore, we could accurately not determine the role of renal function in responding to intervention.

Conclusions

To the best of our knowledge, this is the first review of novel non-invasive congestion assessments and biomarkers that were used to guide fluid treatment. Our results support attainment of euvolaemia at discharge and patient encouragement and motivation to maintain it. Higher-risk patients seem to benefit most from AFMP. These non-invasive techniques and devices are broadly available and easy to use to guide fluid treatment. We support the use of REDs or similar non-invasive devices to track congestion and treatment response during the hospital course. A combination of effective diuresis post-hospital admission, optimal discharge diuretic dose, and patient education, along with a device for fluid monitoring, could potentially safely reduce adverse outcomes in HF. The simplicity of a post-discharge DMP may be a key contributor to patient engagement. Future studies are needed to determine the efficacy of initiating a rapid access clinic for patients who need up-titration after discharge.

Conflict of interest

None declared.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Quality assessment using the Newcastle-Ottawa quality assessment scale. * indicates the study has met the criteria.
Table S2. Studies reporting cardiovascular comorbidities.
Table S3. Studies reporting non-cardiac comorbidities.
Table S4. Studies that reported medical treatments.
Table S5. Studies that reported device therapy.
Table S6. Studies that reported presenting symptoms.
Table S7. Studies that reported pathology reports and vital signs.
Table S8. Hazard ratio reported by each study for heart failure re-admission.
Table S9. Hazard ratio reported by each study for all-cause mortality.
Table S10. Meta-regression of mortality on demographics, kidney function test, the most commonly reported treatments and comorbid conditions.
Figure S1. Sub-group analysis of mean LVEF in heart failure patients treated with AFMP; Mortality.

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