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Telemonitoring and hemodynamic monitoring to reduce hospitalization rates in heart failure: a systematic review and meta-analysis of randomized controlled trials and real-world studies

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Abstract

Background Heart failure is a significant problem leading to repeated hospitalizations. Telemonitoring and hemodynamic monitoring have demonstrated success in reducing hospitalization rates, but not all studies reported significant effects. The aim of this systematic review and meta-analysis is to examine the effectiveness of telemonitoring and wireless hemodynamic monitoring devices in reducing hospitalizations in heart failure. **Methods & Results** PubMed and Cochrane Library were searched up to 1st May 2017 for articles that investigated the effects of telemonitoring or hemodynamic monitoring on hospitalization rates in heart failure. In 31,501 patients (mean age: 68 ± 12 years; 61% male; follow-up 11 ± 8 months), telemonitoring reduced hospitalization rates with a HR of 0.73 (95% CI: 0.65–0.83; $P < 0.0001$) with significant heterogeneity ($I^2 = 94\%$). These effects were observed in the short-term (≤ 6 months: HR = 0.77, 95% CI: 0.65–0.89; $P < 0.01$) and long-term (≥ 12 months: HR = 0.73, 95% CI: 0.62–0.87; $P < 0.0001$). In 4831 patients (mean age 66 ± 18 years; 66% male; follow-up 13 ± 4 months), wireless hemodynamic monitoring also reduced hospitalization rates with a HR of 0.60 (95% CI: 0.53–0.69; $P < 0.001$) with significant heterogeneity ($I^2 = 64\%$).This reduction was observed both in the short-term (HR = 0.55, 95% CI: 0.45–0.68; $P < 0.001$; $I^2 = 72\%$) and long-term (HR = 0.64, 95% CI: 0.57–0.72; $P < 0.001$; $I^2 = 55\%$). **Conclusions** Telemonitoring and hemodynamic monitoring reduce hospitalization in both short- and long-term in heart failure patients.

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Keywords: Heart failure; Hemodynamic monitoring; Hospitalization; Telemedicine; Telemonitoring

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1 Introduction

Heart failure is characterized by structural abnormalities of left ventricular dysfunction and dilatation, a compensatory rise in systemic vascular resistance secondary to activation of neurohumoral pathways,[1] inflammation,[2] and metabolic adaptations to energy substrate utilization.[3] It is a major public health problem globally, causing significant mortality and morbidity and placing a significant burden on healthcare systems. Hospitalization rate, a measure of healthcare resource utilization, is estimated to be 20% at one month and 50% at 6 months.[4] A history of hospitalization is itself an independent predictor of long-term mortality. Therefore, measures to reduce hospitalization are likely beneficial in this patient population.[5]

Telemonitoring can be used to track patients' symptoms, adherence to medications and objective parameters such as blood pressure, heart rate, body weight and urine output.[6] However, the effectiveness of body weight monitoring has been disputed, as the largest randomized controlled trials to date failed to demonstrate a reduction in heart failure-related hospitalizations. The reasons behind this are complex, but can be partly explained by the fact that body weight and symptoms may not provide sufficient warning of impending decompensation of cardiac function.[7,8] Patient data from implantable hemodynamic monitoring studies have shown that weight is not a good measure of filling pressures that may be important determinants of decompensation.[9] Moreover, hospitalization in heart failure may be related to not only abnormal physiological factors, but also social factors.[10]

In addition to tele-monitoring, recent interests have focused on the roles of implantable hemodynamic monitors. Three devices, CardioMEMS, Chronicle and HeartPOD are commercially available to monitor pulmonary arterial pressure, right ventricular pressure and left atrial pressure, respectively. Several meta-analyses have been performed on remote monitoring for heart failure. For example, in 2009, the impact of remote monitoring on mortality and hospitalization rates was examined.[11] Recently, two meta-analyses of randomized controlled trials were performed.[12,13] This study complements these previous studies by providing an updated meta-analysis of both randomized controlled trials and observational studies on hospitalization rates.

2 Methods

2.1 Search strategy, inclusion and exclusion criteria

This systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[14] It has been registered with PROSPERO (CRD42017073934). PubMed and Cochrane Library were searched up to 1st May 2017, with no language restriction, for studies that investigated the hospitalization rates in heart failure. The following search terms were used for PubMed and Cochrane Library: "telemonitoring heart failure hospitalization" and "hemodynamic monitoring heart failure hospitalization).

The following inclusion criteria were applied: (1) the design was a case-control, prospective or retrospective observational study or randomized controlled trial in humans, (2) patients with heart failure (both preserved and reduced ejection fraction included) were analyzed, (3) hospitalization rates, whether heart failure-specific, cardiovascular-related or all-cause, were reported or could be calculated from the published data; (3) and (4) hazard ratios (HRs) or relative risks (RRs) and their corresponding 95% CIs or data necessary to calculate these were available.

Quality assessment of case-control and cohort studies included in our meta-analysis was performed using the Newcastle–Ottawa Quality Assessment Scale (NOS) (Tables 1S and 2S for telemonitoring, Tables 3S and 4S for hemodynamic monitoring),[15] and of randomized controlled trials using the Jadad scale (Oxford quality scoring system) (Table 5S and 6S for telemonitoring and hemodynamic monitoring, respectively). The NOS evaluated the categories of study participant selection, comparability of the results, and quality of the outcomes. The following characteristics were assessed: (1) representativeness of the exposed cohort; (2) selection of the non-exposed cohort; (3) ascertainment of exposure; (4) demonstration that outcome of interest was not present at the start of study; (5) comparability of cohorts on the basis of the design or analysis; (6) assessment of outcomes; (7) follow-up period sufficiently long for outcomes to occur; and (8) adequacy of follow-up of cohorts. This scale varied from zero to nine stars, which indicated that studies were graded as poor quality if they met < 5 criteria, fair if they met 5 to 7 criteria, and good if they met > 8 criteria. The Jadad score assessed the quality by the following criteria of (1) randomization, (2) allocation concealment, (3) double blinding and (4) withdrawal and dropouts. The total score is 7, scores 1 to 3 indicate low quality and 4 to 7 high quality.

2.2 Data extraction and statistics

Data from the different studies were entered in pre-specified spreadsheet in Microsoft Excel. All potentially relevant reports were retrieved as complete manuscripts and assessed for compliance with the inclusion criteria. In this meta-analysis, the extracted data elements consisted of: (1) publi-

cation details: last name of first author, publication year and locations; (2) study design (cohort study or randomized controlled trial); (3) follow-up duration; (4) endpoints; (5) the quality score; and (6) the characteristics of the population including sample size, gender, age and number of subjects. Meta-analyses of observational studies are challenging due to differences in study designs and inherent biases. Two reviewers independently reviewed each included study and disagreements were resolved by adjudication with input from a third reviewer.

The endpoints for this meta-analysis were hospitalization rates. Where different types of hospitalization rates were reported, heart failure-specific rates were used preferentially, followed by cardiovascular-related hospitalization rates, and finally all-cause hospitalization rates. Multivariate adjusted hazard ratios (HRs) or relative risks (RRs) with 95% CI were extracted for each study. When values from multivariate analysis were not available, those from univariate analysis were used.

When HRs were not provided, they were calculated using raw data. The pooled adjusted risk estimates from each study as the HR values with 95% CI were presented. Different types of hospitalization rates were pooled together.

Heterogeneity between studies was determined using Cochran's Q, which is the weighted sum of squared differences between individual study effects and the pooled effect across studies, and the I^2 statistic from the standard chi-square test, which is the percentage of the variability in effect estimates resulting from heterogeneity. $I^2 > 50\%$ was considered to reflect significant statistical heterogeneity. A fixed effects model was used if $I^2 < 50\%$, otherwise the random-effects model using the inverse variance heterogeneity method was selected. To find the origin of the heterogeneity, sensitivity analysis excluding one study at a time was performed. Subgroup analyses based on time-points or type of telemonitoring or hemodynamic monitoring were performed. Short-term was defined as those occurring within 6 months, whereas long-term was defined as 12 months or longer. Where a study reported effective estimates at successive time points, the longer time point was used. Funnel plots, Begg and Mazumdar rank correlation test and Egger's test[16] were used to assess for possible publication bias.

3 Results

Figure 1 shows a flow diagram detailing the search strategy and study selection process. For telemonitoring, a total of 120 and 111 entries were retrieved from PubMed and Cochrane Library, with 60 articles included in our final meta-analysis.[6,17–75] For hemodynamic monitoring, a total of 220 and 53 entries were retrieved from the same databases, with 12 articles included in our final meta-analysis.[4,76–86]

3.1 Telemonitoring

For telemonitoring, a total of 31,501 patients (mean age: 68 ± 12 years old; 61% male) were included. The baseline characteristics of these studies are listed in Table 1. Six were cohort studies and 55 were randomized controlled trials. The mean follow-up duration was 11 ± 8 months. Telemonitoring reduced hospitalization rates with a HR of 0.73 (95% CI: 0.65–0.83; $P < 0.0001$, Figure 2). The Cochran's Q value was greater than the degrees of freedom (994 *vs*. 59), suggesting the true effect size was different among the various studies. Moreover, I^2 took a value of 94%, indicating the presence of significant heterogeneity. Sensitivity analysis by leaving out one study at a time did not significantly alter the pooled HR (Figure 1S). Funnel plot plotting standard errors or precision against the logarithms of the odds ratio are shown in Figures 2S and 3S, respectively.

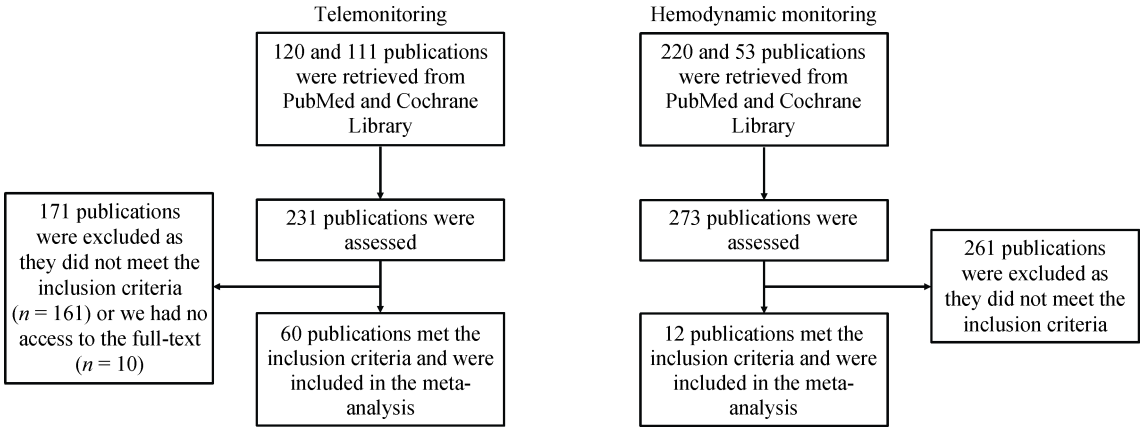

Figure 1. A flow diagram detailing the search strategy and study selection process for this systematic review and meta-analysis on the effects of telemonitoring and hemodynamic monitoring on hospitalization rates in heart failure.

Table 1. Characteristics of the 60 studies on telemonitoring included in this meta-analysis.

First author / Year	Study design	Sample size (*n*)	Age	SD	% Male	Ejection fraction, %	Endpoints	Follow-up (months)	Variables in multivariate model
Gallagher 2017	RCT	40	64	20	75	25	All-cause, HF	1	(Univariate)
Sardu 2016	RCT	183	72	7	76	< 35	HF	12	Age, chronic kidney disease, hypercholesterolaemia, LVEF, NYHA class
Hale 2016	RCT	25	72	11	64	-	All-cause, HF	3	(Univariate)
Ong 2016	RCT	1437	73	-	54	43	All-cause	3, 6	Age, sex, race/ethnicity, insurance, comorbidities based on the Health Care Utilization Project methods, 6 year and quarter of enrollment, social isolation as measured by the Lubben Social Network Scale score, 31 and income level
Kraai 2016	RCT	177	69	16	37	27	HF	9	(Univariate)
Smolis-Bąk 2015	Cohort	52	62	9	90	25	All-cause	18	(Univariate)
Kao 2016	Cohort	1246	78	12	54	-	All-cause	36	(Univariate)
Idris 2015	RCT	28	63	-	39	23	Cardiac	3, 6	(Univariate)
Pedone 2015	RCT	90	80	7	39	46	All-cause, HF	6	(Univariate)
Bekelman 2015	RCT	384	68	14	97	-	All-cause	12	(Univariate)
Vuorinen 2014	RCT	94	58	17	83	28	HF	6	(Univariate)
Blum 2014	RCT	203	73	13	71	29	All-cause	48	Age, gender, practice region (RRMA), and baseline NYHA class
Giacomelli 2014	RCT	285	80	-	60	-	All-cause	9	(Univariate)
Martín-Lesende 2013	RCT	58	81	8	59	-	All-cause, cause-specific	6, 12	(Univariate)
Krum 2013	RCT	405	73	15	63	36	All-cause, HF	12	Age, gender, practice region (RRMA), and baseline NYHA class
Sabatier 2013	RCT	90	-	-	-	-	HF	3	(Univariate)
Boyne 2012	RCT	382	71	11	59	36	All-cause, HF	12	Ischaemia, blood urea, haemoglobin level, heart rate, NYHA class, and systolic blood pressure
Lyngå 2012	RCT	319	73	10	75	-	All-cause, cardiac	12	(Univariate)
Seto 2012	RCT	84	54	19	59	38	All-cause	6	(Univariate)
Dendale 2012	RCT	160	76	10	65	35	All-cause, HF	6	(Univariate)
Koehler 2012	RCT	670	67	15	86	267	All-cause, cardiac, HF	26	(Univariate)
Kurtz 2011	Cohort	138	68	17	78	32	HF	12	Age, state of residence, presence of various comorbid conditions, and prior cardiac events including coronary artery bypass surgery
Wade 2011	RCT	316	77	10	53	-	All-cause, cardiac	6	(Univariate)
Domingo 2011	RCT	92	66	12	71	36	Cardiac excluding HF, HF	12	(Univariate)
Howlett 2011	RCT	122	67	-	65	46	All-cause	12	(Univariate)
Juan 2011	Cohort	120	76	-	-	-	All-cause	30	(Univariate)
Chaudhry 2010	RCT	1653	61	16	58	-	All-cause, HF	9	(Univariate)
Antonicelli 2010	RCT	57	78	7	58	-	HF	12	(Univariate)
Delaney 2010	RCT	24	79	12	42	-	All-cause, HF	3	(Univariate)
Peters-Klimm 2010	RCT	199	70	14	72	-	All-cause, HF	12	(Univariate)
Bowles 2009	RCT	303	75		37	-	HF	2	(Univariate)
Scherr 2009	RCT	108	66	11	79	25	All-cause	6	(Univariate)
Mortara 2009	RCT	461	60	17	86	29	All-cause, HF	12	New York Heart Association class, β-blocker use at baseline, sex, and Na levels
Dar 2009	RCT	182	71	16	66	-	All-cause, HF	6	(Univariate)
Goode 2009	RCT	201	70	11	70	24	All-cause	16	(Univariate)
Brown 2008	RCT	14663	-	-	-	-	All-cause	12	(Univariate)
Soran 2008	RCT	315	76	10	31	24	All-cause, HF	6	New York Heart Association class, β-blocker use at baseline, sex, and Na levels
Antonicelli 2008	RCT	57	78	10	58	36	HF	12	(Univariate)
Morguet 2008	Case-control	128	60	14	88	44	All-cause, cardiac	10	(Univariate)

Table 1. Cont.

First author / Year	Study design	Sample size (*n*)	Age	SD	% Male	Ejection fraction, %	Endpoints	Follow-up (months)	Variables in multivariate model
Kashem 2008	RCT	48	54	15	73	26	All-cause, HF	12	(Univariate)
Woodend 2008	RCT	121	67	17	72	-	All-cause, HF	3, 12	(Univariate)
Sisk 2006	RCT	406	59	19	54		All-cause	12	(Univariate)
Riegel 2006	RCT	134	72	11	46	43	All-cause	6	(Univariate)
Hudson 2005	Cohort	91	74	11	53	-	All-cause	6	(Univariate)
GESICA Investigators 2005	RCT	1518	65	13	71	-	All-cause, cardiac, HF	16	NYHA class, age, baseline treatment, comorbidity, and systolic dysfunction
Dunagan 2005	RCT	151	-	-	47		All-cause, HF	12	Severely impaired LV function, NYHA class, use of target or high doses of ACE inhibitor
Cleland et al. (2005)	RCT	253	67	16	53	25	All-cause, cardiac, HF	8	Age, NT proBNP, body mass index, systolic and diastolic blood pressure, hemoglobin, sodium, urea, creatinine, NYHA functional classification, loop and potassium-sparing diuretics, ACE inhibitors, beta blockers
Schofield 2005	Cohort	73	67	11	99	23	All-cause	6	(Univariate)
Capomolla 2004	RCT	133	57	10	47	29	All-cause, cardiac, HF	12	(Univariate)
Galbreath 2004	RCT	1069	71	10	71	54	All-cause, HF	6, 18	(Univariate)
DeBusk 2004	RCT	462	72	11	51	-	All-cause, cardiac, HF	12	(Univariate)
Roth 2004	Cohort	118	74	9	69	24	All-cause	12	(Univariate)
Goldberg 2003	RCT	208	59	15	68	< 35	All-cause, cardiac	6	(Univariate)
Laramee 2003	RCT	287	71	12	54	-	All-cause, HF	1.5	(Univariate)
McDonald 2002	RCT	98	71	10	66	37	HF	3	(Univariate)
Riegel 2002	RCT	358	72	12	49	43	All-cause, HF	3, 6	(Univariate)
Kasper 2002	RCT	200	62	20	33	27	HF	6	(Univariate)
Krumholz 2002	RCT	88	76	13	57	38	All-cause, cardiac, HF	12	(Univariate)
Jerant 2001	RCT	25	70	16	48	-	All-cause, HF	2	(Univariate)
Blue 2001	RCT	165	75	12	58	-	All-cause, HF	12	(Univariate)

ACE: angiotensin converting enzyme; HF: heart failure; LV: left ventricular; NT proBNP: N-terminal pro brain natriuretic peptide; RCT: randomized controlled trial.

Begg and Mazumdar rank correlation suggested a significant publication bias (Kendal's Tau value = –0.2, $P < 0.05$); Egger's test demonstrated significant asymmetry (intercept: –1.4, *t*-value: 2.6; $P < 0.05$).

Because of the substantial heterogeneity present, we explored its possible origins. As we initially combined mortality assessed at different durations, univariate and multivariate HRs, and study design, the following subgroup analyses were performed. Firstly, we found that telemonitoring reduced hospitalization rates in the short-term ($n = 27$; ≤ 6 months; HR = 0.77, 95% CI: 0.65–0.89; $P < 0.01$; $I^2 = 67\%$; Figure 4S) and long-term ($n = 32$; ≥ 12 months: HR = 0.73, 95% CI: 0.62–0.87; $P < 0.0001$; $I^2 = 97\%$; Figure 5S). Secondly, subgroup analysis was performed for the type of HR. Meta-analysis of univariate HRs produced a pooled effect estimate of 0.94 (95% CI: 0.93–0.95; $P < 0.0001$) without significantly affecting heterogeneity ($I^2 = 95\%$, *vs*. 94% previously). By contrast, meta-analysis of multivariate HRs produced a similar pooled effect estimate of 0.91 (95% CI: 0.84–0.99; $P < 0.05$) whilst reducing I^2 to 71%. Thirdly, subgroup analysis was performed for study design. Meta-analysis of randomized controlled trials (RCTs) yielded a pooled effect estimate of 0.96 (95% CI: 0.95–0.97; $P < 0.0001$) whilst reducing I^2 to 72%. By contrast, meta-analysis of cohort studies yielded a significantly lower HR of 0.38 (95% CI: 0.36–0.41; $P < 0.0001$) whilst preserving I^2 at 94%. Together, these findings suggest the duration over which mortality was assessed, type of HRs and study design to be possible sources of heterogeneity.

3.2 Hemodynamic monitoring

For wireless hemodynamic monitoring, a total of 4831 patients were included. The baseline characteristics of these studies are listed in Table 2. Four publications were cohort studies and eight publications were based on data from three randomized controlled trials (CHAMPION, COMPASS-HF

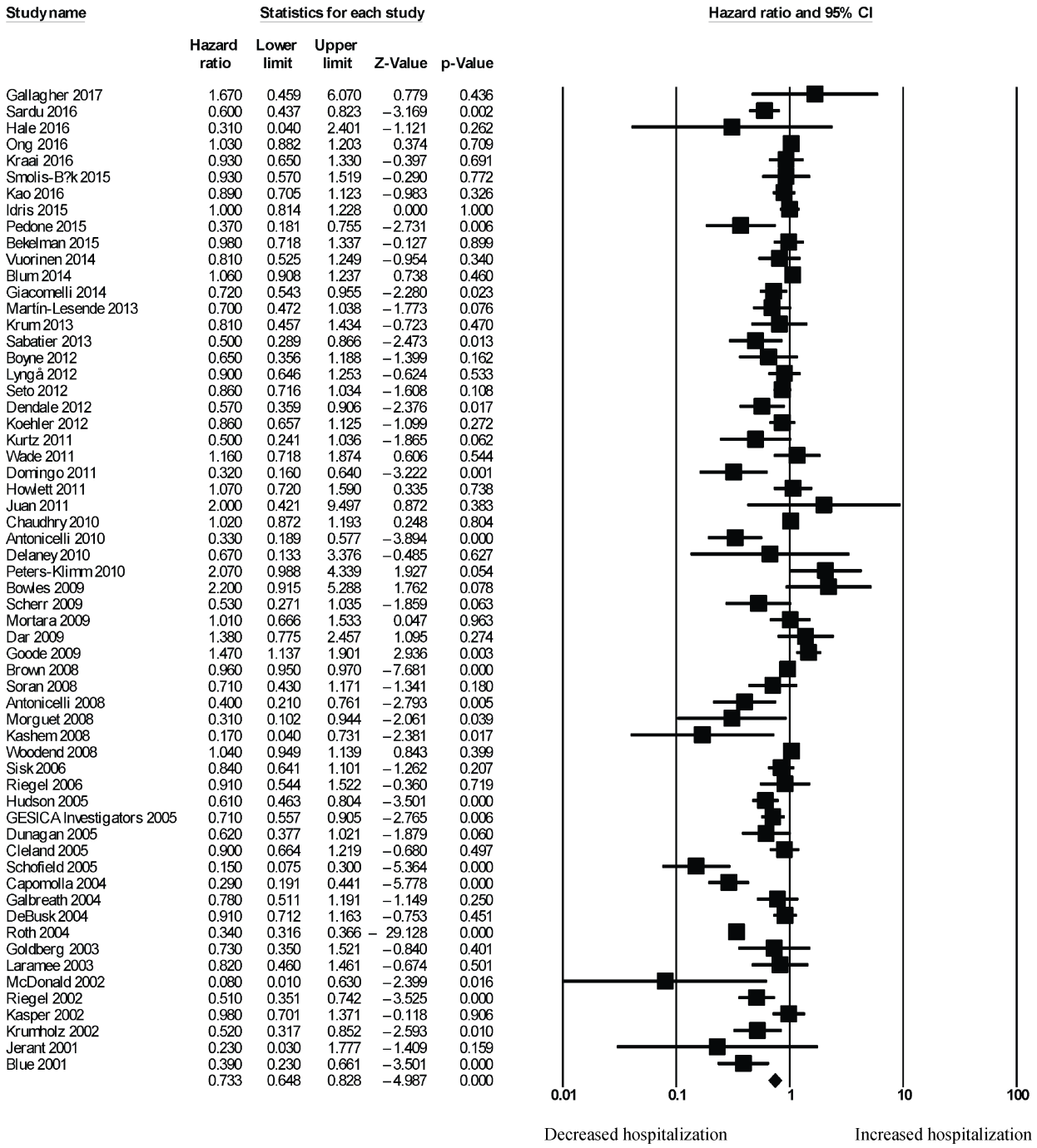

Figure 2. Pooled hazard ratios for studies examining the effects of telemonitoring on hospitalization rates in heart failure.

and REDUCEhf). The mean follow-up duration was 13 ± 4 months. The mean age was 66 ± 18 years) of whom 66% were male. Wireless hemodynamic monitoring significantly reduced hospitalization rates with a HR of 0.60 (95% CI: 0.53–0.69; $P < 0.001$). The Cochran's Q value was greater than the degrees of freedom (36 *vs.* 13), suggesting the true effect size was different among the various studies. I^2 took a value of 64%, indicating the presence of significant heterogeneity. Sensitivity analysis by leaving out one study at a time did not significantly alter the pooled HR (Figure 6S). Funnel plot plotting standard errors or precision against the logarithms of the odds ratio are shown in Figures 7S and 8S, respectively. Begg and Mazumdar rank correlation suggested a significant publication bias (Kendal's Tau value = –0.5, $P < 0.05$). Egger's test demonstrated significant asymmetry (intercept: –2.2, t-value = 3.2; $P < 0.01$).

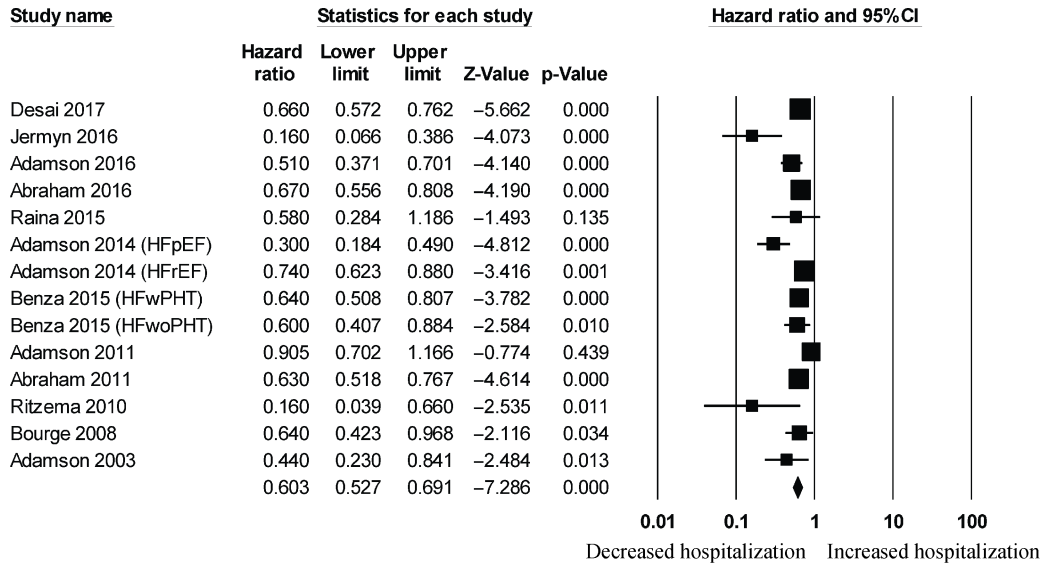

Figure 3. Pooled hazard ratios for studies examining the effects of hemodynamic monitoring on hospitalization rates in heart failure.

Table 2. Characteristics of the 12 studies on hemodynamic monitoring included in this meta-analysis.

First author/ Year	Study design	Population	Type of hemodynamic monitoring	Sample size (n)	Age, yrs	SD	% Male	Ejection fraction, %	Endpoints	Follow-up (months)	Variables in multivariate model
Desai 2017	Cohort	HF	Pulmonary arterial pressure	1114	71	11	64	-	All-cause, HF	6	(Univariate)
Jermyn 2016	Cohort	HF	Pulmonary arterial pressure	77	-	-	-	-	HF	12	(Univariate)
Adamson 2016	RCT	HF	Pulmonary arterial pressure	245	73	8	-	-	HF	17	(Univariate)
Abraham 2016	RCT	HF	Pulmonary arterial pressure	347	62	18	-	-	All-cause, HF	17	(Univariate)
Raina 2015	RCT	HF	Pulmonary arterial pressure	537	62	18	-	-	HF	18	(Univariate)
Adamson 2014	RCT	HF with preserved ejection fraction	Pulmonary arterial pressure	119	66	12	60	51	HF	18	(Univariate)
		HF with reduced ejection fraction		66	60	13	76	23		18	(Univariate)
Benza 2015	RCT	HF with pulmonary hypertension	Pulmonary arterial pressure	314	62	13	72	-	HF	15	(Univariate)
		HF without pulmonary hypertension		236	61	13	74	-	HF	15	(Univariate)
Adamson 2011	RCT	HF	Right ventricular pressure	400	55	21	34	23	All-cause, HF	12	(Univariate)
Abraham 2011	RCT	HF	Pulmonary arterial pressure	550	62	18	73	60	HF	6	(Univariate)
Ritzema 2010	Cohort	HF	Left atrial pressure	40	66	10	78	32	Combined HF hospitalization and all-cause mortality	3	(Univariate)
Bourge 2008	RCT	HF	Right ventricular pressure	274	58	19	65	33	HF	6	(Univariate)
Adamson 2003	Cohort	HF	Right ventricular pressure	32	59	10	38	29	HF	17	(Univariate)

HF: heart failure; RCT: randomized controlled trial.

Significant reductions in hospitalization rates were observed in both short-term (HR: 0.55, 95% CI: 0.45–0.68; $P < 0.001$; $I^2 = 72\%$; Figure 9S) and long-term (HR: 0.64, 95% CI: 0.57–0.72; $P < 0.001$; $I^2 = 55\%$; Figure 10S). For the different types of hemodynamic devices, hospitalization rates were significantly reduced using pulmonary pressure monitoring (HR: 0.58, 95% CI: 0.50–0.66; $P < 0.001$; $I^2 = 67\%$; Figure 11S) or left atrial pressure monitoring (HR: 0.16, 95% CI: 0.04–0.68; $P < 0.05$). It was not possible to perform a meta-analysis for left atrial pressure monitoring because this was only assessed by one study. Right ventricular pressure monitoring tended to reduce hospitalization

rates (HR: 0.69, 95% CI: 0.47–1.01; I^2 = 61%; Supplementary Figure 12S) but this did not reach statistical significance (P = 0.058).

4 Discussion

This is a systematic review and meta-analysis of randomized controlled trials and real-world studies on the effects of remote patient monitoring on hospitalization rates in heart failure, complementing previous meta-analyses.[11–13] The main findings are the following: (1) hospitalization rates can be reduced by remote patient monitoring using either telemonitoring or hemodynamic monitoring by 26% (95% CI: 17%–35%) and 40% (95% CI: 31%–47%), respectively; (2) telemonitoring reduced hospitalization rates by 24% in the short-term (≤ 6 months) and 27% in the long-term (≥ 12 months); and (3) hemodynamic monitoring reduced hospitalization rates by 45% in the short-term and 37% in the long-term.

Telemonitoring is a broad term referring to the making telephone contact with patients to enquire about symptoms, adherence to pharmacotherapy, and obtain information on clinically important parameters such as heart rate, blood pressure, body weight and urine output. This in turn enables appropriate advice to be offered to patients.[17] The benefits of home monitoring systems on hospitalization are possibly due to its good potential for detecting early signs of decompensation and reinforcement of patient's self-care education, and are especially useful for those who needs extra support, such as older and more frail patients.[87,88] Telemonitoring appears to have limited potential in early detection of worsening heart failure, but most effective when patient education toward medical adherence and patient self-care efficacy are reinforced. These different effects of telemonitoring could be attributable to the wide distribution or the disparate outcome of the effects on hospitalization, and to the heterogeneity observed. There are different vital signs that could be used to provide a warning for heart failure decompensation. These are heart rate, heart rate variability,[89] blood pressure, body weight and urine output.[6,89–91] For example, increases in body weight can predict acute decompensation requiring hospitalization.[91] However, a study found that diastolic blood pressure, systolic blood pressure x heart rate and diastolic blood pressure x heart rate, but not heart rate or systolic blood pressure by itself, predicted 3-month major adverse cardiac events.[90]

Hemodynamic monitoring refers to the continuous measurement of cardiac chamber or vascular pressures. Three devices are available: CardioMEMS (pulmonary arterial pressure),[92] Chronicle (right ventricular pressure)[93] and HeartPOD (left atrial pressure).[94] The rationale behind hemodynamic monitoring is that increases in intracardiac and pulmonary arterial pressures were detectable several weeks prior to worsening of clinical symptoms and signs.[4,9] Subgroup analyses were performed for the different hemodynamic parameter measured. The evidence for pulmonary artery pressure monitoring is the strongest, with a 42% reduction in hospitalization rates. Right ventricular pressure monitoring tended to reduce hospitalization rates by around 31% but this was not statistically significant. It was not possible to perform a meta-analysis for left atrial monitoring, as only one study has been published to date. Nevertheless The LAPTOP-HF trial is currently ongoing and when completed will provide important data for determining whether left atrial monitoring will similarly reduce hospitalization rates in heart failure.[95]

Theoretically, hemodynamic monitoring should reduce hospitalization rates to greater extents than usual care or telemonitoring if patients were offered appropriate advice to mitigate abnormal cardiac physiology, such as fluid overload or bradycardia, by altering medication regimens at home so that hospitalization would not be necessary. Our meta-analysis found that the risk reduction for hospitalization using hemodynamic monitoring was slightly higher at 40% compared to 27% using telemonitoring, but this was not significantly different. This meta-analysis provides data that less-invasive remote monitoring by telemedicine is equally effective as more invasive forms of hemodynamic monitoring. The former approach may be more cost-effective and yet able to prevent hospitalizations. Therefore, healthcare resources can be focused on the patients who do require hospital admission, who can be offered additional investigations such as quantification of blood biomarkers and echocardiography for guiding their management.[96,97]

4.1 Limitations

There are some limitations of this study that must be recognized. Firstly, we had observed a substantial heterogeneity for the HRs for the effects of telemonitoring on hospitalization rates. In our study, hazard ratios of randomized controlled trials and cohort studies, which are different study designs, were initially pooled together. A recent Cochrane review showed that there were no significant difference in the effective estimates between observational studies and randomized controlled trials, suggesting that factors other than study design are responsible for differences in outcomes.[98] However, in our subgroup analysis, we found that the pooled HR was significantly lower for cohort studies when compared to the HR for RCT. Therefore, meta-analysis should combine the effect estimates

separately based on trial design. Moreover, this subgroup analysis resulted in a reduction of I^2 to 72% for RCTs, suggesting that this contributed to the heterogeneity observed. Other sources, as assessed by our subgroup analyses, were the duration over which mortality was assessed (short-term versus long-term mortality) and whether the HRs were univariate or multivariate HRs. Secondly, we detected significant bias using both Begg and Mazumdar rank correlation test and Egger's test, in that the reported HRs skewed towards reduced hospitalization by telemonitoring. In other words, fewer HRs were from the studies reporting a lack of effect on hospitalization. Therefore, this may represent publication bias in which only positive findings were published by the journals, with negative results possibly not published. Thirdly, there were only four cohort studies that assessed hemodynamic monitoring. As only three RCTs with a limited number of subjects were conducted, future RCTs are needed for different types of hemodynamic monitoring systems, especially left atrial pressure monitoring, for which the HR was only available in one study and it was therefore not possible to conduct a subgroup analysis for this system. Finally, there is a lack of studies that directly compare hemodynamic monitoring to telemonitoring, which needs to be investigated in the future, especially given the invasive nature of hemodynamic monitoring systems.

4.2 Conclusions

This meta-analysis demonstrates that both telemonitoring and hemodynamic monitoring are equally effective approaches to reduce hospitalization rates in heart failure. Telemonitoring should be used more widely, since it is less invasive than hemodynamic monitoring and may be more cost-effective. However, direct comparisons between these modes of monitoring are needed in the future.

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Table 1S. Quality ratings for included case-control studies using the Newcastle-Ottawa quality assessment scale for telemonitoring.

Number	First Author	Selection (score)				Comparability (score)				Total Score
		Case definition	Representative of cases	Selections of controls	Definition of controls	Comparability of cases and controls on the basis of the design or analysis	Ascertainment of exposure	Same method ascertainment participants	Nonresponse rate	
1	Morguet 2008	-	1	1	1	2	-	-	1	6

Table 2S. Quality ratings for included cohort studies using the Newcastle-Ottawa quality assessment scale for telemonitoring.

Number	First Author	Selection (score)				Comparability (score)	Exposure (score)			Total Score
		Representative of exposed cohort	Selections of non-exposed cohort	Assessment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Ascertainment of outcome	Was follow-up long enough for outcomes to occur?	Adequacy of follow up of cohorts	
1	Kao 2016	1	1	1	0	0	1	1	1	6
2	Smolis-Bąk 2015	1	1	1	1	2 (age, comorbidities)	1	1	1	9
3	Kurtz 2011	1	1	1	1	2 (age, LVEF)	1	1	1	9
4	Hudson 2005	1	0	1	1	0	1	1	1	6
5	Schofield 2005	1	1	1	1	2	1	1	1	9
6	Roth 2004	1	1	1	1	2	-	1	1	8

LVEF: left ventricular ejection fraction.

Table 3S. Quality ratings for included case-control studies using the Newcastle-Ottawa quality assessment scale for hemodynamic monitoring.

Number	First Author	Selection (score)				Comparability (score)				Total Score
		Case definition	Representative of cases	Selections of controls	Definition of controls	Comparability of cases and controls on the basis of the design or analysis	Ascertainment of exposure	Same method ascertainment participants	Nonresponse rate	
1	Jermyn 2016	1	1	-	1	2	1	1	1	8
2	Abraham 2016	1	1	1	1	2	1	1	1	9
3	Raina 2015	1	1	-	1	2	1	1	1	8
4	Benza 2015	1	1	-	1	2	1	1	1	8
5	Abraham 2011	1	1	1	1	2	1	1	1	9

Table 4S. Quality ratings for included cohort studies using the Newcastle-Ottawa quality assessment scale for hemodynamic monitoring.

Number	First Author	Selection (score)				Comparability (score)	Exposure (score)			Total Score
		Representative of exposed cohort	Selections of non-exposed cohort	Assessment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Ascertainment of outcome	Was follow-up long enough for outcomes to occur?	Adequacy of follow up of cohorts	
1	Desai 2017	1	1	1	1	2	1	1	1	9
2	Ritzema 2010	-	1	1	1	2	1	1	1	8
3	Adamson 2003	1	1	1	1	2	1	1	1	9

Table 5S. Quality ratings for included randomized controlled trials using the Jadad quality assessment scale for telemonitoring.

Number	Study	Randomization	Allocation concealment	Double blinding	Withdrawals and dropouts	Total score
1	Gallagher 2017	2	1	1	1	5
2	Sardu 2016	2	2	2	0	6
3	Hale 2016	1	0	0	1	2
4	Ong 2016	2	2	2	1	7
5	Kraai 2016	2	1	1	1	5
6	Idris 2015	1	0	0	1	2
7	Pedone 2015	1	1	2	1	5
8	Bekelman 2015	2	0	0	1	3
9	Vuorinen 2014	1	0	0	1	2
10	Blum 2014	1	0	0	1	2
11	Giacomelli 2014	1	0	0	1	2
12	Martín-Lesende 2013	2	0	1	1	4
13	Krum 2013	1	1	1	1	4
14	Sabatier 2013	1	0	0	1	2
15	Boyne 2012	2	0	2	1	5
16	Lynga° 2012	1	1	2	1	5
17	Seto 2012	2	2	2	1	7
18	Dendale 2012	1	2	2	1	4
19	Koehler 2012	2	1	1	1	5
20	Wade 2011	1	0	0	1	2
21	Domingo 2011	1	0	0	1	2
22	Howlett 2011	1	0	0	1	2
23	Chaudhry 2010	2	2	2	1	7
24	Antonicelli 2010	1	0	0	1	2
25	Delaney 2010	1	0	0	1	2
26	Peters-Klimm 2010	2	2	2	1	7
27	Bowles 2009	1	2	2	1	6
28	Scherr 2009	1	0	2	1	4
29	Mortara 2009	2	2	2	1	7
30	Dar 2009	2	1	2	1	6
31	Goode 2009	1	0	0	1	2
32	Brown 2008	2	1	0	1	4
33	Soran 2008	1	1	2	1	5
34	Antonicelli 2008	1	0	0	1	2
35	Kashem 2008	2	0	0	1	3
36	Woodend 2008	1	0	0	1	2
37	Sisk 2006	2	2	2	1	7
38	Riegel 2006					
39	GESICA Investigators 2005	1	0	0	1	2
40	Dunagan 2005	2	0	0	1	3
41	Cleland 2005	1	1	2	1	5
42	Capomolla 2004	1	0	0	1	2
43	Galbreath 2004	1	0	0	1	2
44	DeBusk 2004	2	1	1	1	5
45	Goldberg 2003	1	0	0	1	2
46	Laramee 2003	2	1	2	1	6
47	McDonald 2002	1	1	2	1	5
48	Riegel 2002	1	2	2	1	6
49	Kasper 2002	1	0	1	1	3
50	Krumholz 2002	1	0	0	1	2
51	Jerant 2001	2	2	0	1	5
52	Blue 2001	1	1	1	1	4

Table 6S. Quality ratings for included randomized controlled trials using the Jadad quality assessment scale for hemodynamic monitoring.

Number	Study	Randomization	Allocation concealment	Double blinding	Withdrawals and dropouts	Total score
1	Adamson 2016	1	1	1	1	4
2	Adamson 2014	1	1	1	1	4
3	Adamson 2011	1	1	1	1	4
4	Bourge 2008	1	1	2	1	5

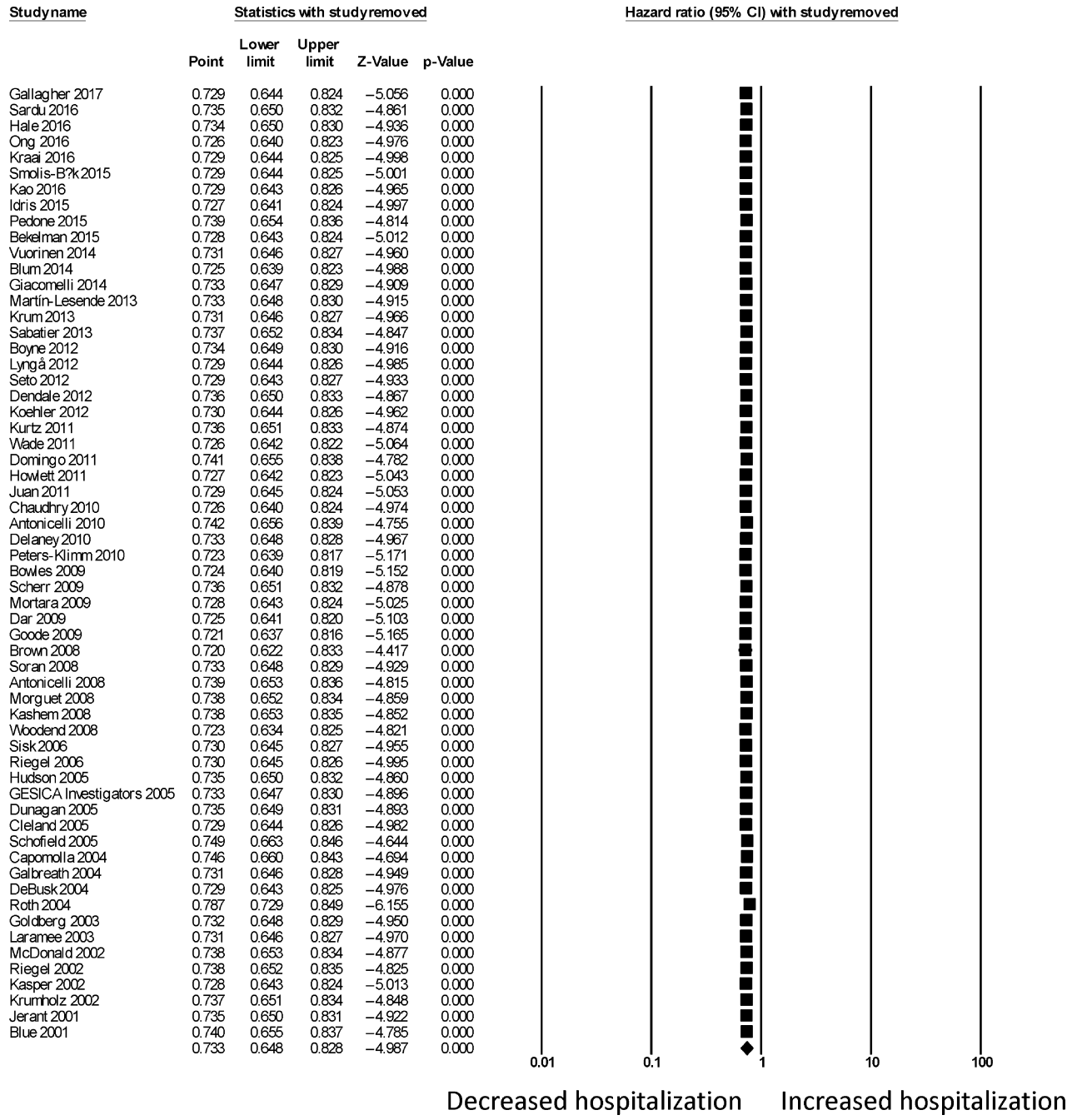


Figure 1S. Sensitivity analysis for hazard ratio on hospitalizations using telemonitoring.

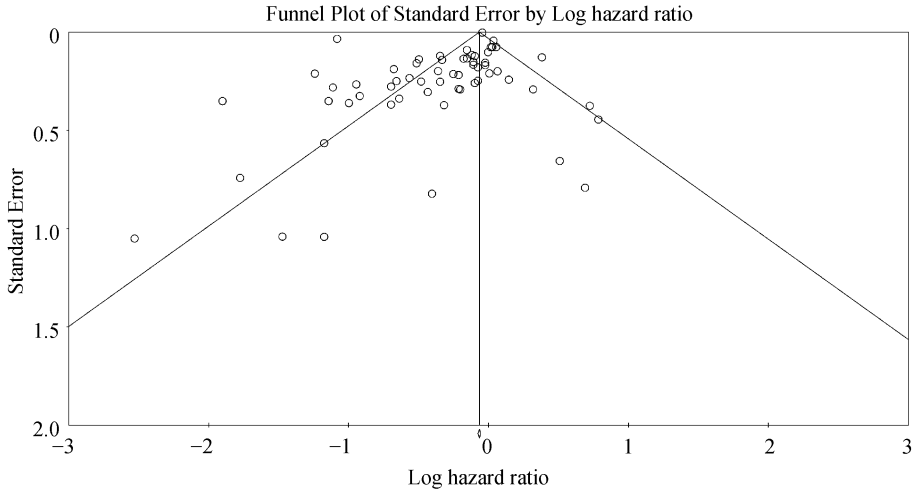


Figure 2S. Funnel plot of standard error against the logarithm of hazard ratio for hospitalizations using telemonitoring.

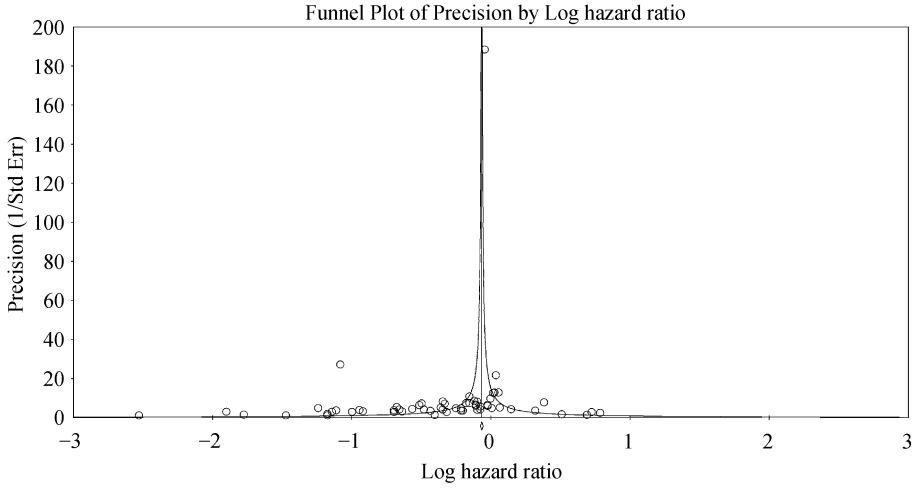
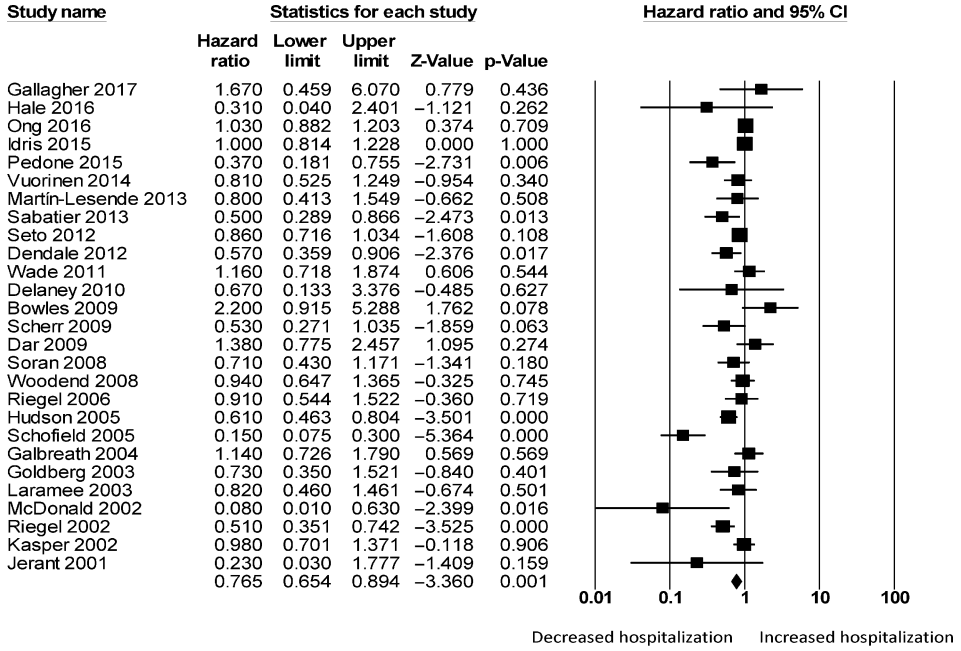


Figure 3S. Funnel plot of precision against the logarithm of hazard ratio for hospitalizations using telemonitoring.



Study name	Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value
Gallagher 2017	1.670	0.459	6.070	0.779	0.436
Hale 2016	0.310	0.040	2.401	−1.121	0.262
Ong 2016	1.030	0.882	1.203	0.374	0.709
Idris 2015	1.000	0.814	1.228	0.000	1.000
Pedone 2015	0.370	0.181	0.755	−2.731	0.006
Vuorinen 2014	0.810	0.525	1.249	−0.954	0.340
Martín-Lesende 2013	0.800	0.413	1.549	−0.662	0.508
Sabatier 2013	0.500	0.289	0.866	−2.473	0.013
Seto 2012	0.860	0.716	1.034	−1.608	0.108
Dendale 2012	0.570	0.359	0.906	−2.376	0.017
Wade 2011	1.160	0.718	1.874	0.606	0.544
Delaney 2010	0.670	0.133	3.376	−0.485	0.627
Bowles 2009	2.200	0.915	5.288	1.762	0.078
Scherr 2009	0.530	0.271	1.035	−1.859	0.063
Dar 2009	1.380	0.775	2.457	1.095	0.274
Soran 2008	0.710	0.430	1.171	−1.341	0.180
Woodend 2008	0.940	0.647	1.365	−0.325	0.745
Riegel 2006	0.910	0.544	1.522	−0.360	0.719
Hudson 2005	0.610	0.463	0.804	−3.501	0.000
Schofield 2005	0.150	0.075	0.300	−5.364	0.000
Galbreath 2004	1.140	0.726	1.790	0.569	0.569
Goldberg 2003	0.730	0.350	1.521	−0.840	0.401
Laramee 2003	0.820	0.460	1.461	−0.674	0.501
McDonald 2002	0.080	0.010	0.630	−2.399	0.016
Riegel 2002	0.510	0.351	0.742	−3.525	0.000
Kasper 2002	0.980	0.701	1.371	−0.118	0.906
Jerant 2001	0.230	0.030	1.777	−1.409	0.159
	0.765	0.654	0.894	−3.360	0.001

Figure 4S. Subgroup analysis for hazard ratio on short-term hospitalizations using telemonitoring.

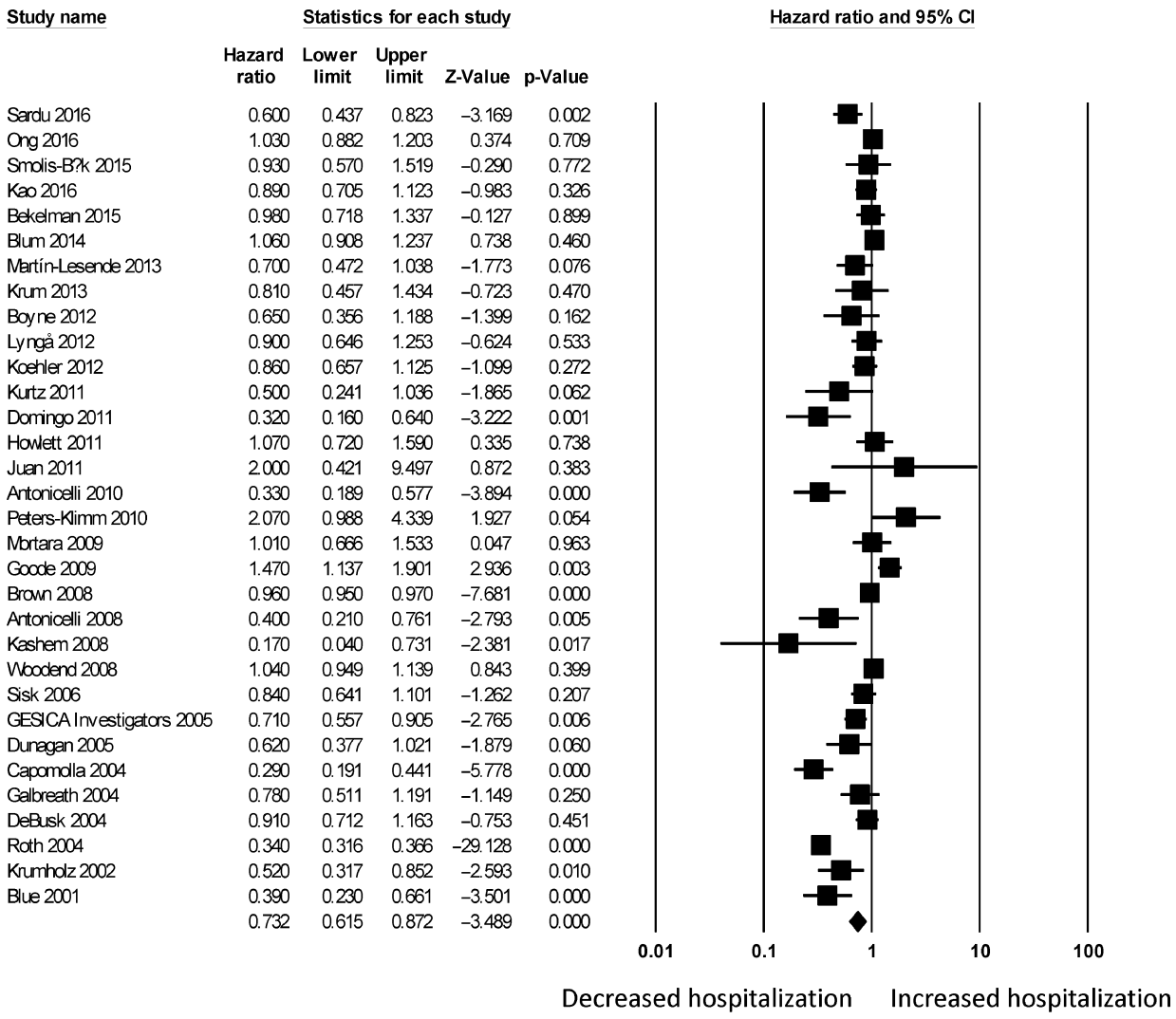


Figure 5S. Subgroup analysis for hazard ratio on long-term hospitalizations using telemonitoring.

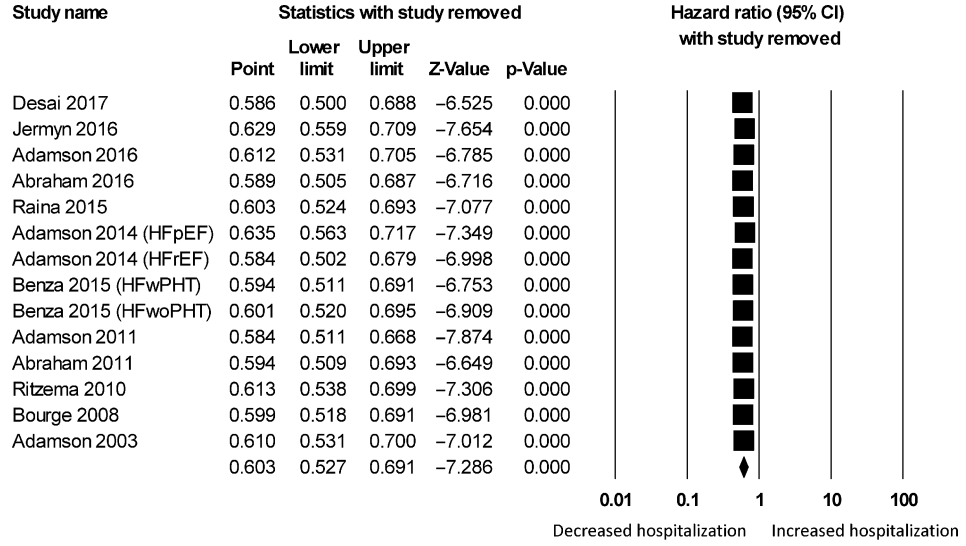


Figure 6S. Sensitivity analysis for hazard ratio on hospitalizations using heomdynamic monitoring.

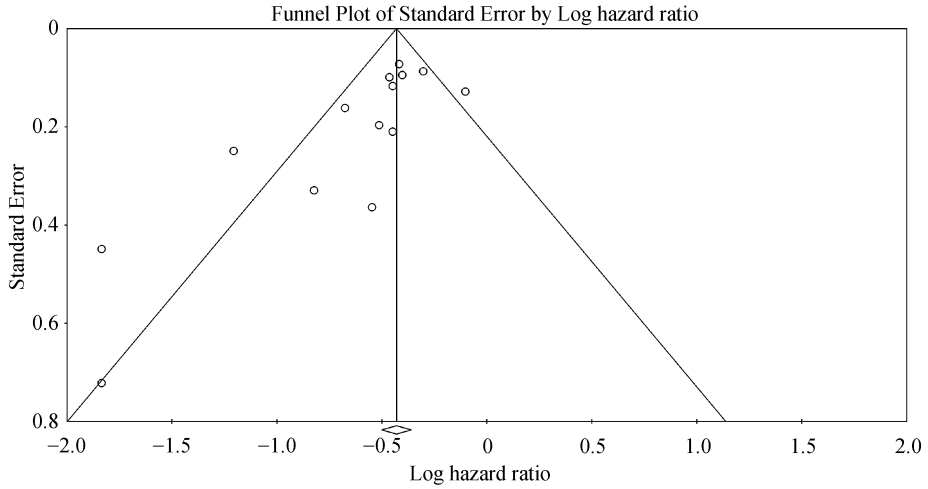


Figure 7S. Funnel plot of standard error against the logarithm of hazard ratio for hospitalizations using heomdynamic monitoring.

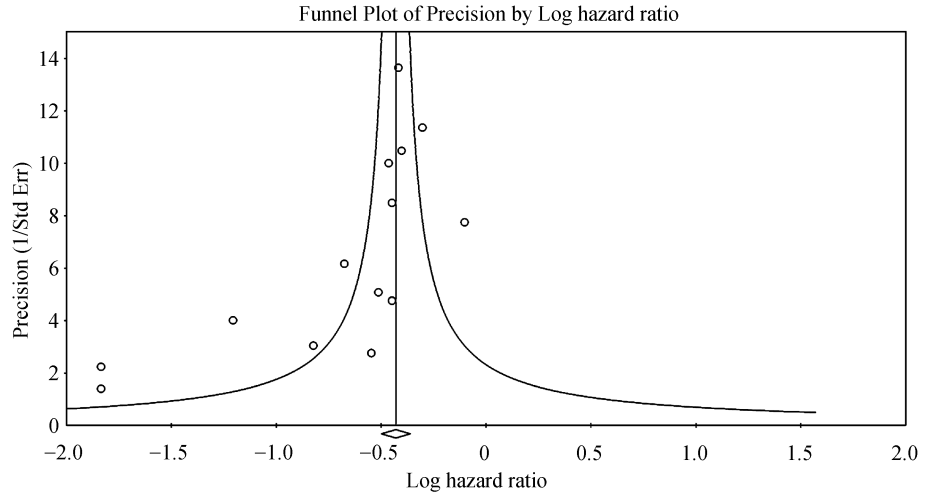


Figure 8S. Funnel plot of precision against the logarithm of hazard ratio for hospitalizations using heomdynamic monitoring.

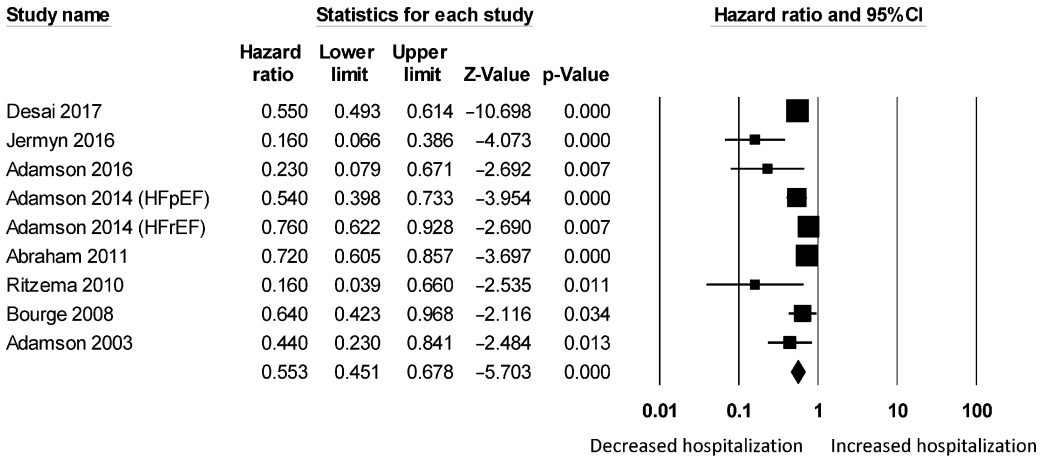


Figure 9S. Subgroup analysis for hazard ratio on short-term hospitalizations using heomdynamic monitoring.

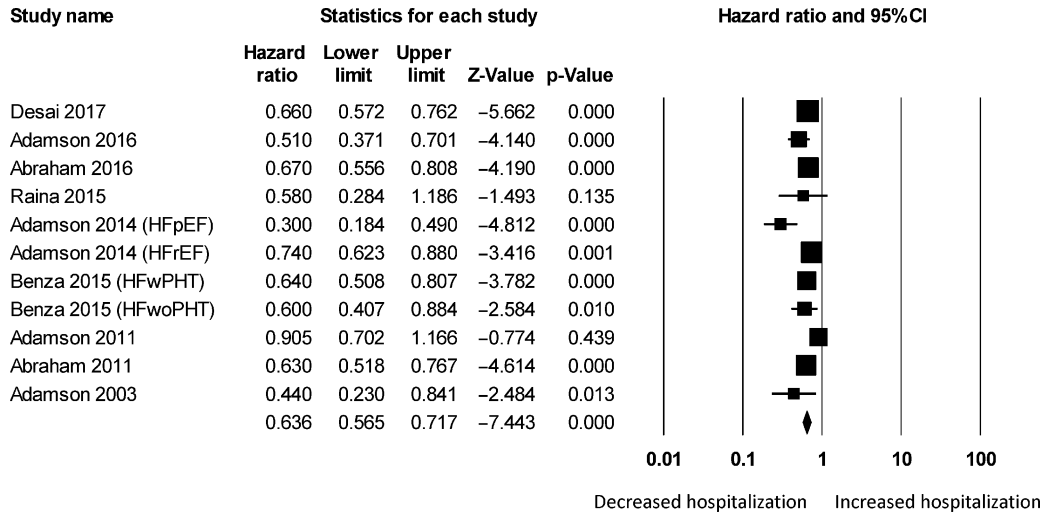


Figure 10S. Subgroup analysis for hazard ratio on long-term hospitalizations using heomdynamic monitoring.

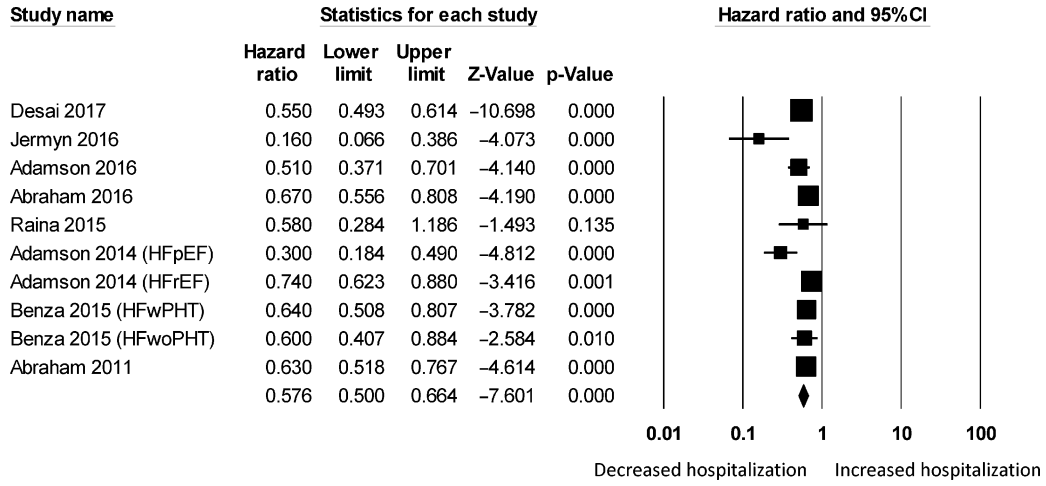


Figure 11S. Subgroup analysis for hazard ratio on long-term hospitalizations using pulmonary pressure monitoring.

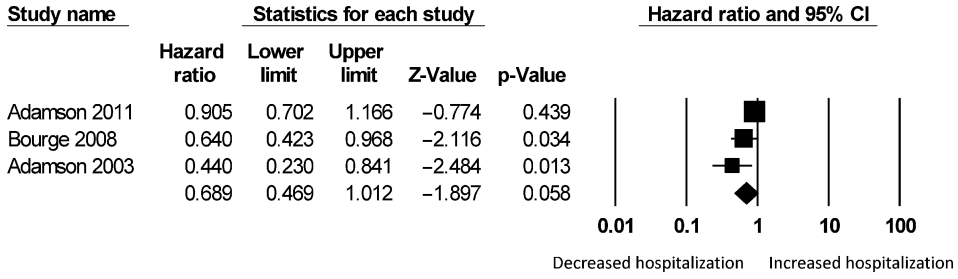


Figure 12S. Subgroup analysis for hazard ratio on long-term hospitalizations using right ventricular pressure monitoring.