THE ANATOLIAN JOURNAL OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Role of Telemedicine Intervention in the Treatment of Patients with Chronic Heart Failure: A Systematic Review and Meta-analysis

META-ANALYSIS

ABSTRACT

Backgound: Although telemedicine interventional therapy is an innovative method to reduce public medical burden and improve heart failure, its effectiveness is still controversial. This meta-analysis evaluates the role of telemedicine interventional therapy in the treatment of patients with chronic heart failure.

Methods: Relevant literature on telemedicine in chronic heart failure treatment was screened and extracted based on predefined criteria. Quality assessment used Cochrane Handbook 5.1.0 tool, and meta-analysis was conducted using R 4.2.2 software.

Results: Fifteen English-language articles were ultimately included in this meta-analysis. The risk bias evaluation determined that 4 articles were low-risk bias and 11 articles were unclear risk bias. The meta-analysis revealed that, compared to the routine intervention group, the all-cause hospitalization rate of patients in the telemedicine intervention group decreased [OR = 0.63, 95% CI (0.41; 0.96), P = .03], and the hospitalization rate of heart failure also decreased [OR = 0.70, 95% CI (0.48; 0.85), P < .01]. However, there were no differences in mortality [OR = 0.64, 95% CI (0.41; 1.01), P = .05], length of hospitalization [MD = −0.42, 95% CI (−1.22; 0.38), P = .31], number of emergency hospitalizations [MD = −0.09, 95% CI (−0.33; 0.15), P = .45], medication compliance [OR = 1.67, 95% CI (0.92; 3.02), P = .09], or MLHFQ scores [MD = −2.30, 95% CI (−6.16; 1.56), P = .24] among the patients.

Conclusion: This meta-analysis showed that telemedicine reduced overall and heart failure-related hospitalizations in chronic heart failure patients, suggesting its value in clinical management. However, it did not significantly affect mortality, hospital stay length, emergency visits, medication adherence, or quality of life. This suggests the need to optimize specific aspects of telemedicine, identify key components, and develop strategies for better treatment outcomes.

Keywords: Telemedicine, chronic heart failure, treatment, meta-analysis

INTRODUCTION

With the aging of the global population, the number of patients with chronic heart failure (CHF) is increasing rapidly. It is estimated that 26 million adults in the world suffer from chronic heart failure, and the total prevalence rate is about 1-2%.[1,2] Chronic heart failure becomes more common with age and stands as the most prevalent cause of death for patients over 65 years old.[3,4] CHF can lead to decreased life expectancy, impaired quality of life, and recurrent hospitalizations, imposing a considerable economic burden to society. Concurrently, the demand for health-care resources to manage heart failure is on the rise, necessitating innovative methods to alleviate this burden and mitigate the detrimental effects of heart failure. Previous studies on traditional remote monitoring of patients with heart failure have confirmed that remote monitoring may reduce mortality, hospitalization rate and cost, and improve the quality of life and the rating of New York Heart Association (aka NYHA).[5-7]

However, the outcomes of telemedicine interventions have been inconsistent due to variations in research interventions and designs. For instance, in studies by Koehler et al[8] and Hwang et al,[9] telemedicine intervention did not reduce the

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Received: September 20, 2023
Accepted: December 26, 2023
Available Online Date: February 27, 2024

Cite this article as: Wang C, Ba Y, Ni J, Huang R, Du X. Role of telemedicine intervention in the treatment of patients with chronic heart failure: A systematic review and meta-analysis. *Anatol J Cardiol.* 2024;28(4):177-186.

DOI:10.14744/AnatolJCardiol.2023.3873

all-cause hospitalization rate when compared with conventional treatment. Still, in research by Comín-Colet et al[10] and Jiménez-Marrero et al[6], telemedicine did lead to a reduction in this rate. Some meta-analyses have reported the effectiveness of telemedicine in reducing all-cause mortality and hospitalization rates and enhancing the quality of life in treating CHF.[11-13] However, considering that many literatures have been updated since these Meta-analyses, but not all the included literatures are RCTs, we decided to conduct the latest meta-analysis of the literatures on this subject. In this study, we primarily selected RCT publications to assess the role of telemedicine intervention in treating patients with chronic heart failure, thereby providing evidence-based medical support for the telemedicine care of CHF patients.

METHODS

Retrieval Strategy

In this study, the Chinese and English randomized controlled studies published from the database establishment to March 28th, 2023 were retrieved. The retrieval databases included PubMed, EMbase, Cochrane Library, Web of science, the EBSCO host, China National Knowledge Infrastructure (CNKI), VIP, and Wanfang Database, and the related literature about the role of telemedicine intervention in the treatment of patients with chronic heart failure were retrieved. The retrieval methods were subject words combined with free words. The search terms include telemedicine, Information system, Health monitoring, Telephone monitoring, phone support, internet via smart applications, IOT, video-conference monitoring, Chronic heart failure, Heart failure, Heart failure, Treatment, and Efficacy.

Inclusion and Exclusion Criteria

Inclusion Criteria

In this meta-analysis, our primary focus was on randomized controlled trials (RCTs). We recruited male and female patients aged 18 years and above who had a confirmed diagnosis of heart failure. The interventions tested in this study encompassed various telemedicine approaches, such as telemedicine management, cell phone teleintervention, telecontrol, and telemonitoring, for the experimental group, while the control group received conventional interventions. Our outcome measures consisted of several key metrics, including the rate of all-cause hospitalization, rate of heart failure-specific hospitalization, mortality rate, duration of hospitalization, number of emergency hospitalizations, medication adherence, and health-related quality of life assessed using the Minnesota Living with Heart Failure Questionnaire (MLHFQ).

Exclusion Criteria

Studies that were repeatedly published, those lacking comparability in baseline patient information, reports with unavailable raw data, and review articles were excluded from this meta-analysis. Additionally, literature from non-randomized controlled trials (non-RCTs) was also omitted from this analysis.

Literature Screening and Data Extraction

Two researchers independently searched and read the literature in the database according to the specified search terms, and screened and extracted the literature according to the inclusion and exclusion criteria. When there was disagreement between them, they discussed and ruled with the third researcher. Data extraction includes general information (such as the first author, publication time, age, sex ratio, and other baseline data) and the original data of outcome indicators. After data extraction, 2 researchers cross-checked.

Literature Quality Evaluation

Two researchers evaluated the quality of the included RCTs literature according to the Cochrane Handbook 5.1.0. If there were disagreements, they consulted with a third researcher. The evaluation content included: generation of random sequences; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; completeness of data; selective reporting; other biases. Each item was assessed as "low risk," "high risk," or "unclear." If the criteria were fully met, it was considered a "low risk of bias"; if partially met, it was deemed an "unclear risk of bias"; if not met at all, it was rated as a "high risk of bias."

Statistical Analysis

The software R 4.2.2 (Lucent Technologies, New Jersey, USA) was used for meta-analysis. In this study, the continuous variables were analyzed by Mean difference (MD) and its 95% confidence interval (CI), and the binary variables were analyzed by odds ratio (OR) and 95% CI. The chi-square test was used to determine the heterogeneity among the included studies. When $P < .1$ and/or $I^2 > 50\%$, there was heterogeneity among the included studies, and random effect model was used for analysis. On the other hand, there is no heterogeneity among the included studies, and the fixed effect model is used for meta-analysis, and the funnel plot is used to analyze whether there is publication bias in the included studies.

HIGHLIGHTS

- Compared with routine intervention, there is no difference in mortality, hospitalization days, emergency hospitalization times, drug compliance and MLHFQ of patients with chronic heart failure treated by telemedicine intervention.
- Compared with routine intervention, the all-cause hospitalization rate of patients decreased.
- Compared with routine intervention, the hospitalization rate of patients with heart failure decreased.
- An ideal telemedicine application should prioritize secure, user-friendly communication with real-time video capabilities and EHR integration. It should support remote monitoring, prescription management, and multilingual access. Establishing such an application requires needs assessment, technology selection, user-centered design, rigorous development and testing, compliance with regulations, deployment and training, and continuous improvement based on user feedback.

RESULTS

Literature Screening Results

As seen in Figure 1, a search of Chinese and English databases yielded 1893 articles, all of which were in English. After using Endnote reference management software to remove 122 duplicate articles, 1771 remained. Following an initial screening by reading the titles and abstracts according to the inclusion and exclusion criteria, 167 articles were left. Among these, 3 were unavailable in full text, 43 did not align with the experimental group's intervention method, 26 were missing key data, and 80 had no control group. Finally, 15 articles were included.[5-9,14-22]

Basic Characteristics and Quality Assessment of the Included Literature

A total of 15 articles were included in this study, all of which were in English, comprising 3737 patients in total, with 1863 patients in the experimental group and 1874 patients in the control group. Other basic characteristics of the included studies can be seen in Table 1. The patient information in the intervention group was shown in Supplementary Table 1. According to the Cochrane Handbook 5.1.0, 4 of the 12 articles were assessed as having a low risk of bias, and 8 were assessed as having an unclear risk of bias, as shown in Figure 2.

META-ANALYSIS RESULTS

All-Cause Hospitalization Rate

Nine studies compared the all-cause hospitalization rate between the telemedicine intervention group and the routine intervention group. The heterogeneity test results for the studies showed $P < .01$ and $I^2 = 65\%$, and the combined effect was analyzed by random effect model. Meta-analysis showed that compared with the routine intervention group, the all-cause hospitalization rate of patients in the telemedicine intervention group decreased [OR = 0.63, 95% CI (0.41; 0.96), $P = .03$], the difference was statistically significant, as shown in Figure 3.

Hospitalization Rate of Heart Failure

Eight studies compared the hospitalization rate of heart failure between telemedicine intervention group and routine

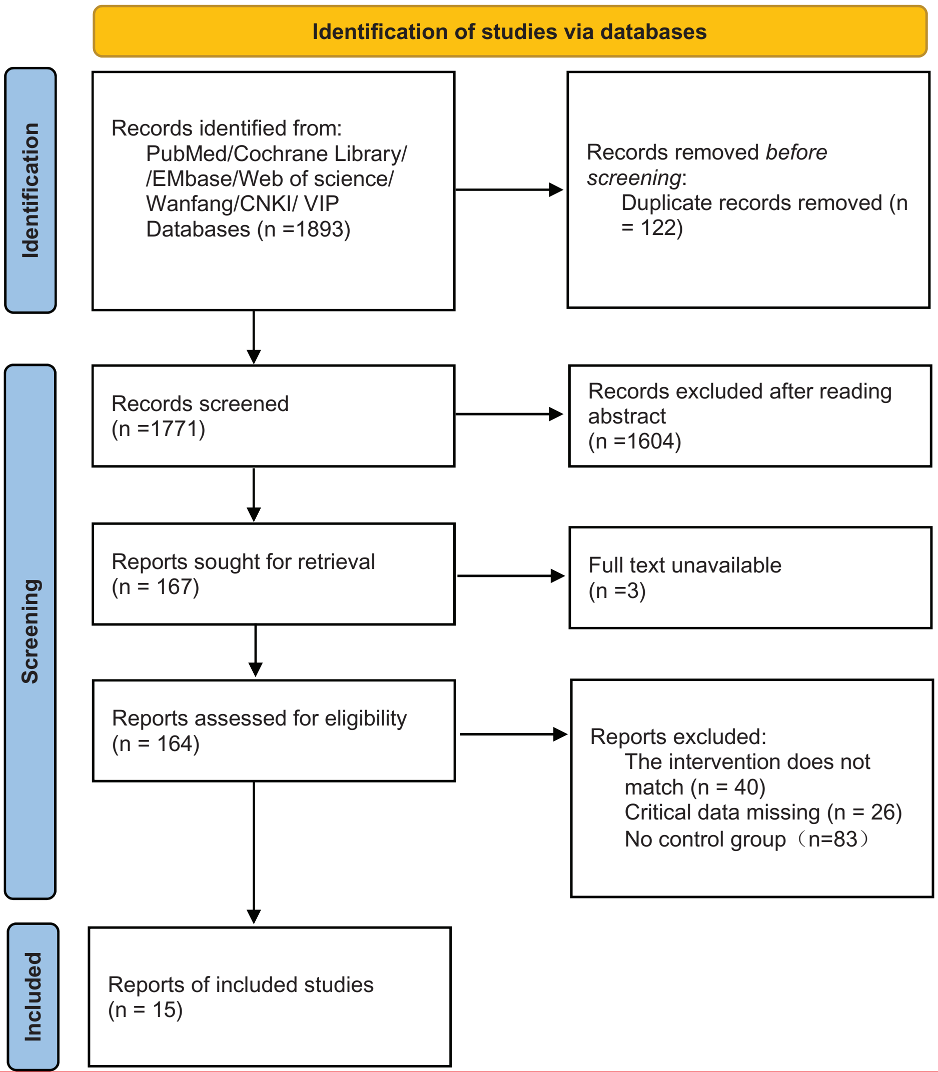

Figure 1. Document screening process and result chart.

Table 1. General Information of Included Literature

Author	Publication Year	Sample Size		Age (Years)		Male Proportion (%)		Left Ventricular Ejection Fraction (%)		Outcome Index of Intervention		Follow-up time	Outcome Index
		Experimental Group	Control Group	Experimental Group	Control Group	Experimental Group	Control Group	Experimental Group	Control Group	Experimental Group	Control Group		
Koehler[8]	2011	354	356	66.9 ± 10.8	66.9 ± 10.5	80.5	82	26.9 ± 5.7	27.0 ± 5.9	Telemedicine management	Routine nursing	24 months	①②③④
Seto[14]	2012	50	50	55.1 ± 13.7	52.3 ± 13.7	82	76	27.1 ± 7.8	27 ± 9.9	Mobile phone remote intervention	Routine intervention	/	⑤⑦
Comi´n-Colet[10]	2016	81	97	74 ± 11	75 ± 11	43	39	45 ± 16	49 ± 16	telemedicine	Routine intervention	6months	①②③④⑤
Hale[15]	2016	11	14	68.4 ± 11.8	74.4 ± 10.4	64	64	/	/	telemedicine	Routine intervention	/	①②④⑤⑥⑦
Hwang[19]	2017	24	29	68 ± 14	67 ± 11	79	72	36 ± 16	35 ± 17	Family-related remote rehabilitation	Routine intervention	6months	①③⑦
Frederix[16]	2019	80	80	76 ± 10	76 ± 10	64	67	35 ± 15	37 ± 15	remote control	Routine nursing	79months	③④
Bakitas[17]	2020	208	207	63.5 ± 8.0	64.1 ± 9.1	53.4	53.1	/	/	Telemedicine intervention	Routine nursing	9months	④⑤
Ding[18]	2020	49	51	69.2 ± 11.5	71.8 ± 13.0	78	77	29.0 ± 7.5	28.6 ± 7.9	Innovative remote monitoring	Routine intervention	6months	⑥
Jime´nez-Marrero[6]	2020	50	66	77 ± 11	78 ± 10	54	51	58 ± 10	56 ± 11	telemedicine	Routine intervention	6months	①②③
Galinier[5]	2020	482	455	70.0 ± 12.4	69.7 ± 12.5	73.4	71	39.3 ± 14.5	38.1 ± 15.2	Remote monitoring	Standard nursing	18months	①②③
Sahlin[19]	2022	58	60	80 ± 8	77 ± 11	67	53	/	/	telemedicine	Routine intervention	8months	①②③
Clays[7]	2021	34	22	61.8 ± 11.0	65.2 ± 9.6	76.5	77.3	32.7 ± 5.9	31.3 ± 6.9	telemedicine	Routine intervention	/	①⑦
Chen[20]	2019	255	260	62 ± 14	61 ± 15	54.5	57.3	42 ± 16	45 ± 17	message and phone	Routine intervention	6months	③
Dendale[21]	2012	80	80	75.9 ± 9.6	75.6 ± 9.8	62	67	34.9 ± 15.0	35.9 ± 15.1	telemedicine	Routine intervention	6 months	②③
Vuorinen[22]	2014	47	47	58.3 ± 11.6	57.9 ± 11.9	83	83	27.3 ± 4.9	28.6 ± 5.0	telemedicine	Routine intervention	6 months	④

Outcome indicators: ① All-cause hospitalization rate; ② Hospitalization rate of heart failure; ③ Mortality rate; ④ Days of hospitalization;⑤ Number of emergency hospitalizations; ⑥ Drug compliance; ⑦ Health-related quality of life(MLHFQ).

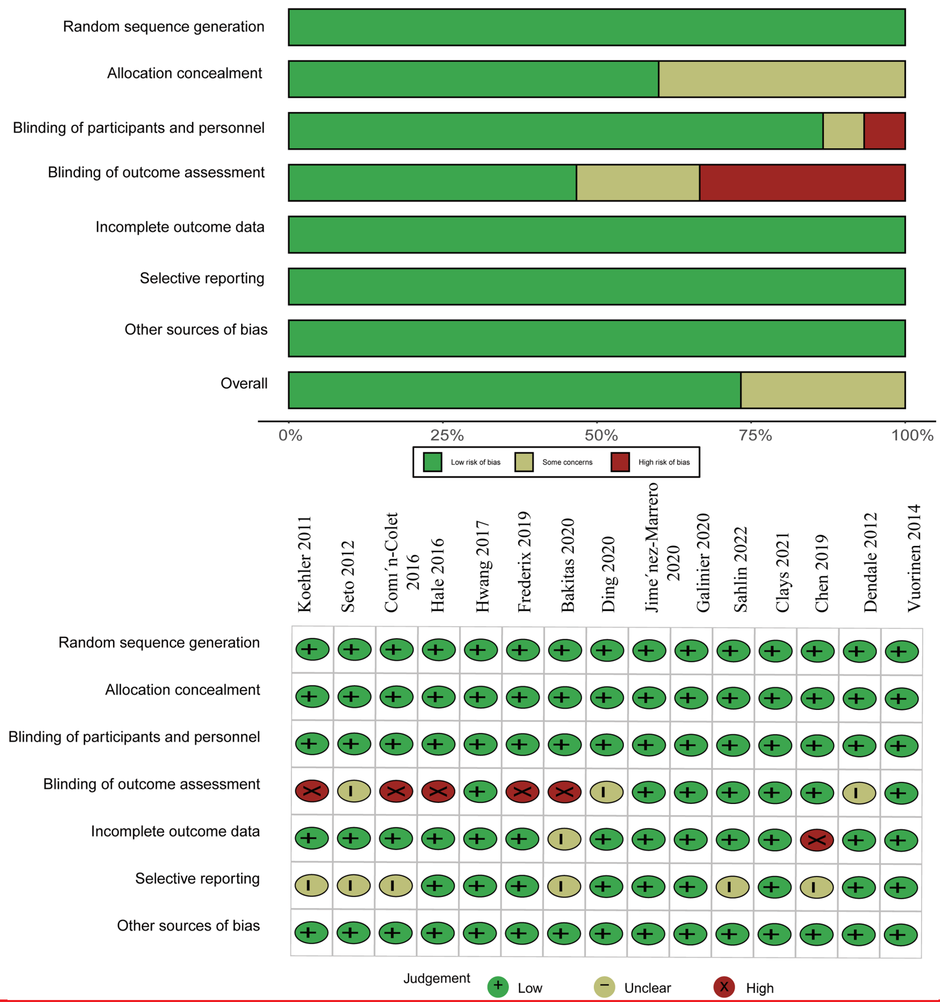

Figure 2. Document quality evaluation.

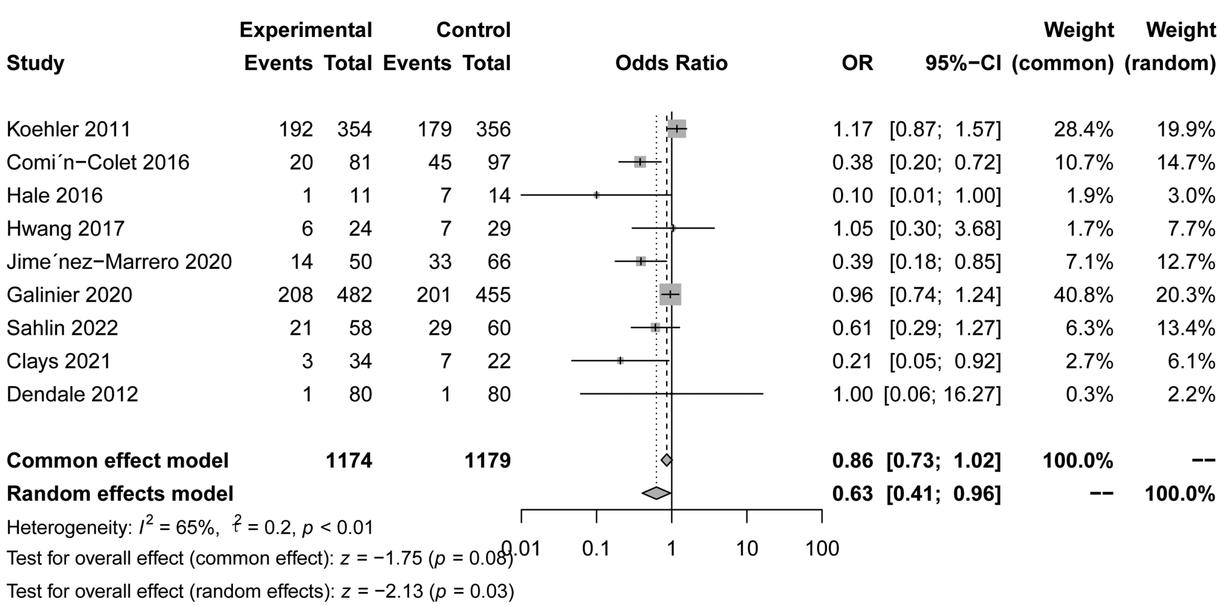

Figure 3. Forest map comparing all-cause hospitalization rates between the 2 groups.

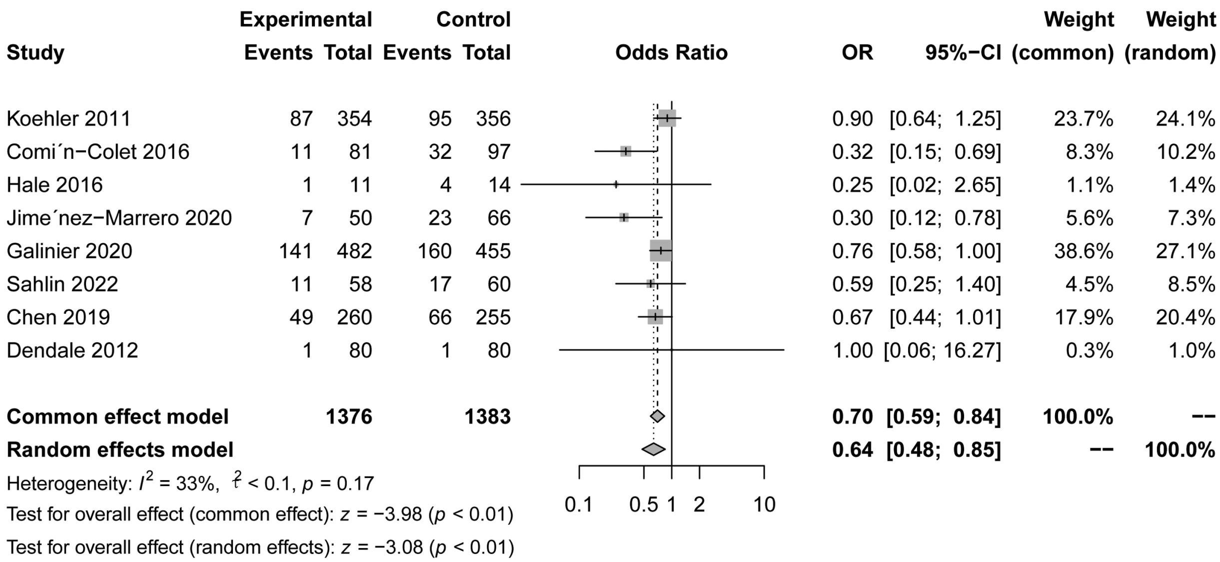

Figure 4. Forest map comparing hospitalization rate of heart failure between 2 groups.

intervention group. The results of heterogeneity test showed that P = .17 and I^2 = 33%, and the combined effect was analyzed by common effect model. Meta-analysis showed that compared with the routine intervention group, the hospitalization rate of heart failure in the telemedicine intervention group decreased [OR = 0.70, 95% CI (0.48; 0.85), P < .01], the difference was statistically significant, as shown in Figure 4.

Mortality Rate

Nine studies compared the mortality between the telemedicine intervention group and the routine intervention group. The results of heterogeneity test showed that P < .01 and I^2 = 68%, and the combined effect was analyzed by random effect model. Meta-analysis showed that there was no difference in mortality between the telemedicine intervention group and the routine intervention group [OR = 0.64, 95% CI (0.41; 1.01), P = .05], the difference was not statistically significant, as shown in Figure 5.

Days of Hospitalization

Five studies compared the length of stay between the telemedicine intervention group and the routine intervention group. The results of heterogeneity test showed that P = .21 and I^2 = 31%, and the combined effect was analyzed by common effect model. Meta-analysis showed that there was no difference in the length of stay between the telemedicine intervention group and the routine intervention group [MD = −0.42, 95% CI (−1.22; 0.38), P = .31], the difference was not statistically significant, as shown in Figure 6.

Emergency Hospitalization Times

Four studies compared the number of emergency hospitalizations between the telemedicine intervention group and

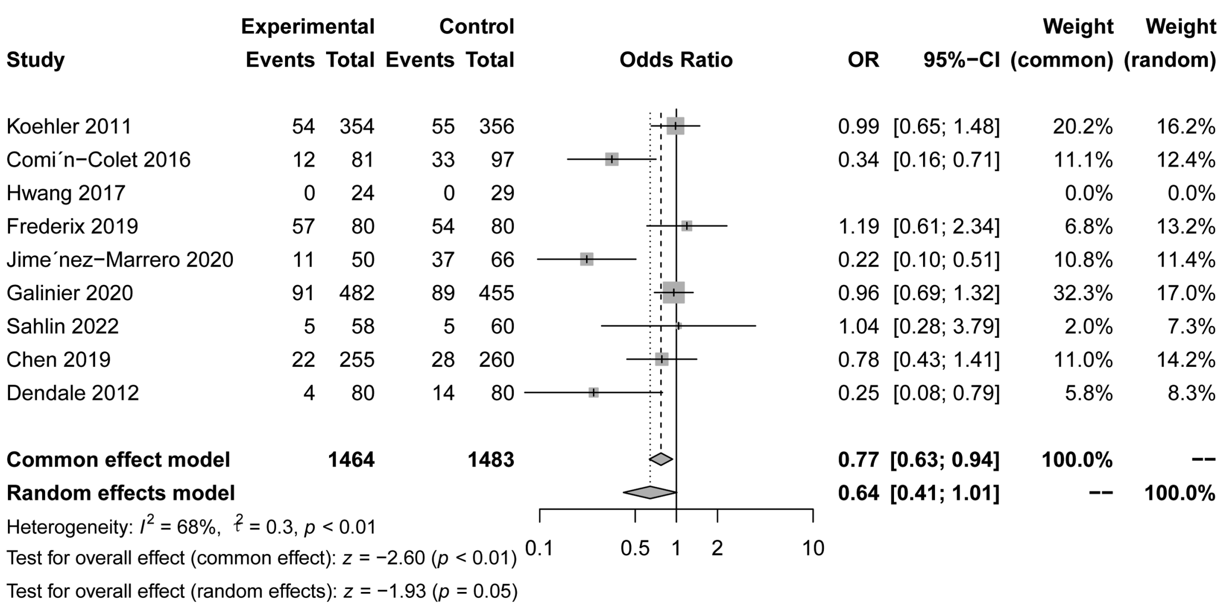

Figure 5. Forest map of mortality comparison between 2 groups.

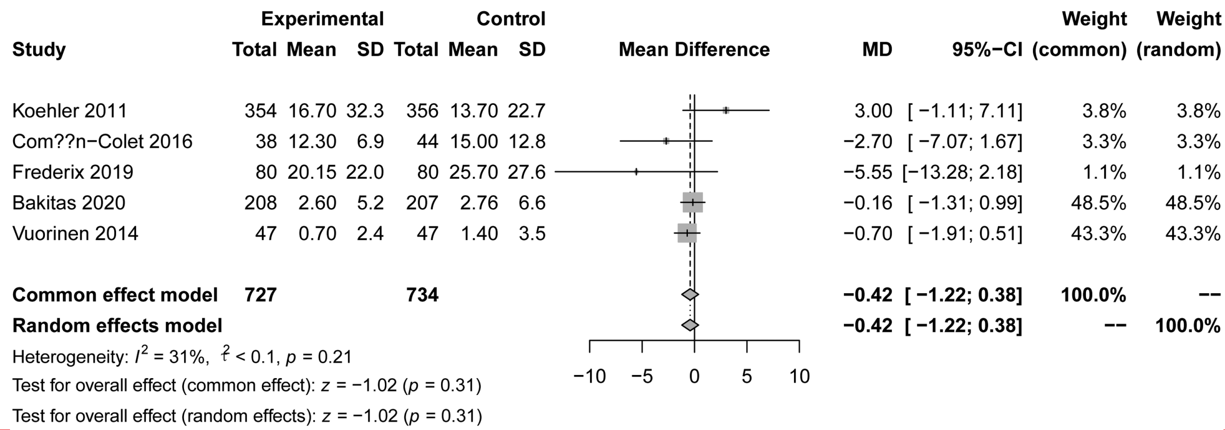

Figure 6. Forest map comparing hospitalization days between 2 groups.

the routine intervention group. The results of heterogeneity test showed that *P* = .05 and I^2 = 62%, and the combined effect was analyzed by random effect model. Meta-analysis showed that there was no difference in the number of emergency hospitalizations between the telemedicine intervention group and the routine intervention group [MD = −0.09, 95% CI (−0.33; 0.15), *P* = .45], the difference was not statistically significant, as shown in Figure 7.

Drug Compliance

Two studies compared the drug compliance between the telemedicine intervention group and the routine intervention group. The results of heterogeneity test showed that *P* = .69 and I^2 = 0%, and the combined effect was analyzed by fixed effect model. Meta-analysis showed that there was no difference in drug compliance between telemedicine intervention group and routine intervention group [OR = 1.67, 95% CI (0.92; 3.02), *P* = .09], the difference was not statistically significant, as shown in Figure 8.

Health-Related Quality of Life

Four studies compared the MLHFQ between the telemedicine intervention group and the routine intervention group. The results of heterogeneity test showed that *P* = 0.61 and

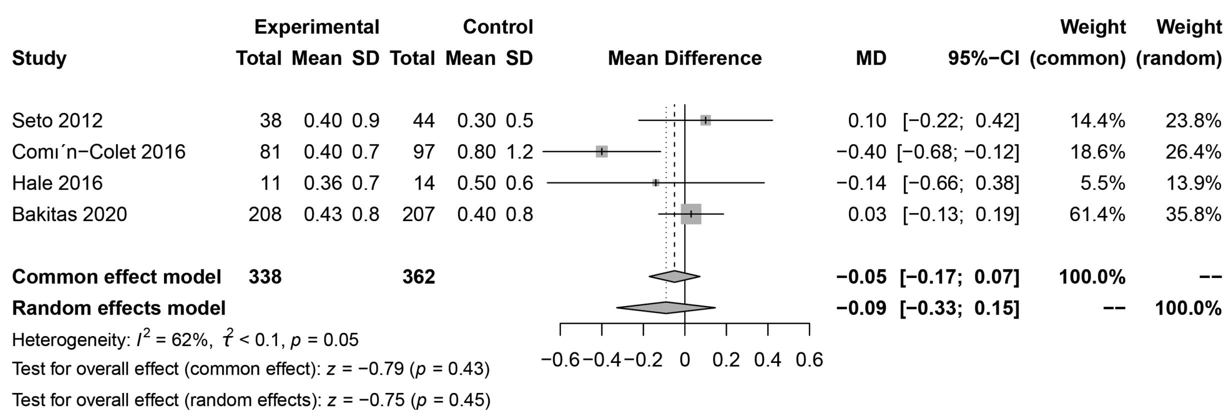

Figure 7. Forest map of comparison of emergency hospitalization times between 2 groups.

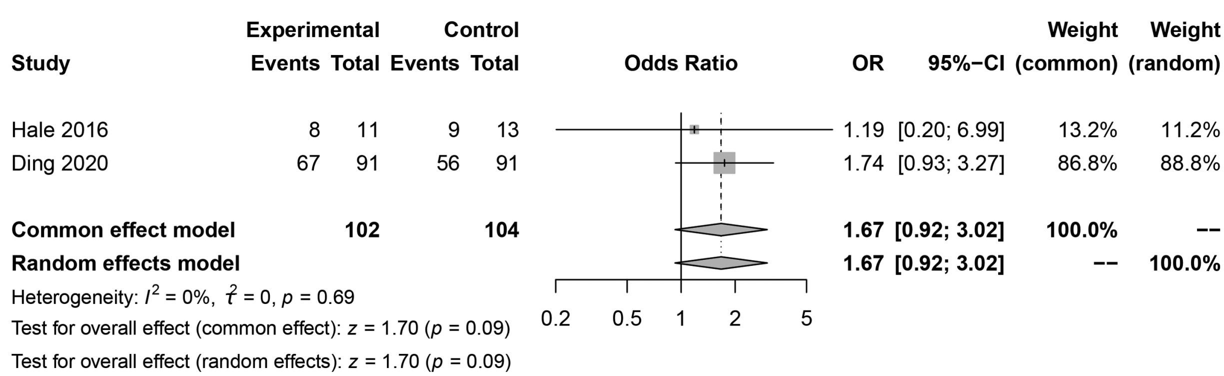

Figure 8. Forest diagram of drug compliance comparison between two groups.

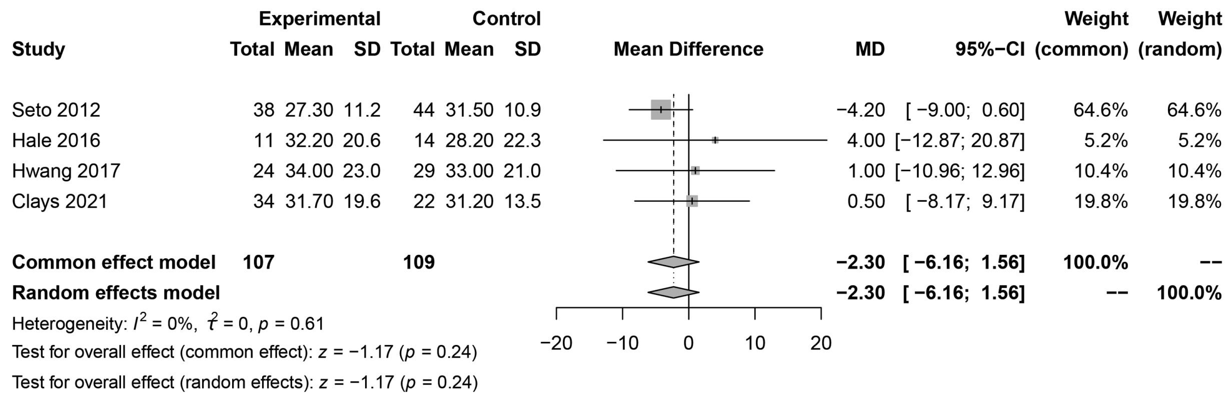

Figure 9. Forest map of health-related quality of life (MLHFQ) comparison between two groups.

$I^2 = 0\%$, and the combined effect was analyzed by fixed effect model. Meta-analysis showed that there was no difference in MLHFQ between telemedicine intervention group and routine intervention group [MD = −2.30, 95% CI (−6.16; 1.56), *P* = 0.24], the difference was not statistically significant, as shown in Figure 9.

Publication Bias and Sensitivity Analysis

The inverted funnel plot is used to analyze whether there is publication bias. Taking the all-cause hospitalization rate as an example, the results show that the research data is roughly symmetrically distributed in an inverted funnel shape, and there is no obvious publication bias. The sensitivity analysis by one-by-one elimination method found that the combined effect did not change significantly, indicating that the results of meta-analysis were basically stable, as shown in Figure 10.

DISCUSSION

Heart failure, a chronic condition that presents a significant challenge to both individual health and global health-care systems, not only compromises patients' quality of life but also contributes to a marked increase in repeat visits and hospitalizations, placing a substantial financial strain on health-care resources. In this background, the development and validation of effective patient management strategies are paramount. Telemedicine interventions, which transcend traditional health-care delivery by utilizing advanced remote monitoring and communication technologies to offer continuous patient monitoring and management, demonstrate considerable potential for enhancing chronic disease management.[7,23] To comprehensively evaluate the impact of telemedicine on heart failure patients, this meta-analysis systematically compiled and analyzed data from a series of randomized controlled trials (RCTs). These data encompass a broad spectrum of telemedicine intervention formats, including but not limited to telephone support and home telemonitoring systems, with the objective of elucidating the role of these interventions in reducing hospitalization frequency, influencing mortality rates, and enhancing overall patient quality of life.

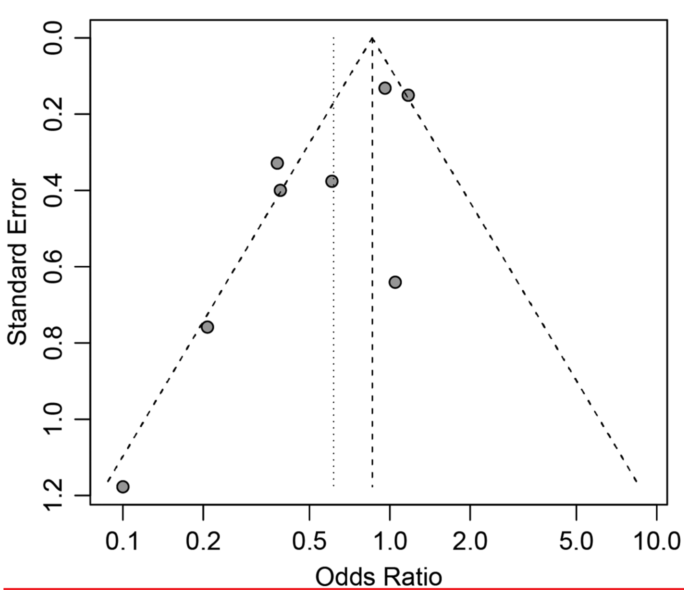

Figure 10. Funnel plot (all-cause hospitalization rate).

The structure of this meta-analysis reveals that telemedicine interventions significantly lower the risk of all-cause and heart failure-specific hospitalization in patients with heart failure. This indicates that telemedicine plays a role in reducing acute events associated with heart failure, potentially leading to decreased health-care costs. Notably, the reduction in heart failure-specific hospitalization risk was particularly prominent, providing empirical evidence for the positive effects of telemedicine and highlighting its potential value in heart failure management. However, our analysis did not find a significant improvement effect of telemedicine interventions in terms of mortality, duration of hospitalization, number of emergency hospitalizations, medication adherence, and health-related quality of life in heart failure patients. This may suggest variations in the impact of telemedicine interventions on different clinical outcomes or underscore the need for more tailored interventions and personalized treatment strategies. Nonetheless, these findings emphasize the potential usefulness of telemedicine interventions in reducing the risk of heart failure hospitalization. Future studies should prioritize optimizing telemedicine strategies to enhance overall patient well-being, particularly by improving medication adherence and enhancing quality of life. In the meantime, it is essential to design more refined randomized controlled trials to evaluate the impact of telemedicine on various clinical outcomes in heart failure patients and identify patient subgroups that can derive maximum benefit from the intervention.

It is worth delving deeper into the diversity of telemedicine interventions, as it may contribute to the heterogeneity of treatment outcomes.[24] Various means such as telephone follow-up, mobile health applications (mHealth apps), and remote sensing device monitoring exhibit differences in intervention complexity, patient compliance, and technological requirements. The varying modes of intervention directly influence the variability of study results, emphasizing the need to consider the specific form of intervention when interpreting these outcomes. Additionally, the selection of intervention modalities should account for individual patients' specific needs, preferences, and life circumstances to ensure optimal patient engagement and sustainability of the intervention. However, the literature we reviewed lacked nuanced insights on teleinterventions, and subgroup comparisons were not conducted.[7,14,16-18,20-22] Future studies should aim to evaluate the adaptability of personalized telemedicine programs for different patient groups and compare their effectiveness to optimize the practical application of telemedicine interventions and further their standardization in clinical practice.

Among the current strategies aimed at reducing the risk of hospitalization in patients with heart failure, a majority of studies have primarily focused on optimizing drug therapy. However, telemedicine interventions show promise in positively impacting the reduction of hospitalization risk by guiding patients to adhere to medication regimens recommended by treatment guidelines.[25,26] This is supported by previous meta-analyis.[26,27] Previous research has demonstrated that telemedicine interventions, through early identification of decompensation and timely therapeutic interventions, can help minimize the risk of re-hospitalization and potentially improve treatment adherence. However, there are some discrepancies between these findings and our own results. For instance, a 2009 meta-analysis examined the role of telemonitoring in congestive heart failure, and although patient quality of life and satisfaction were similar or better than usual care, there were no notable differences in other outcomes.[28] This contrasts somewhat with our conclusions, and the reasons behind this disparity are not immediately evident, possibly related to variances in baseline characteristics, such as comorbidities, among the patients included in the study. Based on the available evidence, we believe that telemedicine interventions offer certain benefits in reducing hospitalization risk for patients with chronic heart failure. Therefore, we encourage the implementation of telemedicine interventions in clinical practice for heart failure patients, taking into account individual patient conditions and resource feasibility.

There are also some limitations in this meta-analysis. Although we found that telemedicine intervention can reduce the hospitalization rate of patients with heart failure, the patient outcome indicators for all-cause mortality was not analyzed in groups, and the results of quality of life were contrary to some research results. This may be because we only used MLHFQ as a method of analysis. Heterogeneity between studies (I^2 of 50%-75%) may affect the validity of our conclusions, even though we used a random-effects model to analyze the data. The random-effects model assumes that the estimated effects differ across studies, so interpretation of these results must be cautiously understood considering various factors. In addition, the application of various technical methods in this meta-analysis has increased the complexity of sub-analysis, thereby limiting the analysis of technological differences from this meta-analysis. Considering these limitations, future research should focus on optimizing the analysis methods for overall mortality rates, which may include adopting multidimensional subgroup analysis to enhance the level of detail and transparency in the meta-analysis. Furthermore, the use of diversified tools for assessing quality of life should be considered to comprehensively capture and analyze changes in patient's quality of life.

CONCLUSION

Telemedicine intervention can reduce all-cause hospitalization rate and heart failure hospitalization rate of patients with chronic heart failure. It is advisable to adopt telemedicine interventions for CHF patients where feasible. However, considering the relatively small number of included studies in this meta-analysis and the presence of moderate heterogeneity in some results, further validation is still required through more high-quality research.

Data Access Statement

Data sharing is not applicable for this article, as no datasets were generated or analyzed during the current study.

Ethics Committee Approval: As this is a systematic review and meta-analysis based on previously published literature, ethical approval was not required.

Peer-review: Externally peer-reviewed.

Author contributions: Concept – W.C., B.Y.; Design – W.C., B.Y., N.J.; Supervision – H.R., D.X.; Resource – H.R., D.X.; Materials – W.C., B.Y., D.X.; Data Collection and/or Processing – W.C., B.Y., N.J.; Analysis and/or Interpretation – W.C., B.Y., N.J.; Literature Search – W.C., B.Y., N.J.; Writing – W.C., B.Y.; Critical Review – W.C., B.Y., N.J., H.R., D.X.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: The project was supported by Medical Health Science and Technology Project in Hangzhou City (A20200777) and Hangzhou Key Discipline—Department of Cardiovascular Medicine (OO20200121).

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Supplementary Table 1. Additional Table for Patient Information in the Intervention Group

Author	Publication Year	Causes of HF	Disease Course (year)	NYHA Classification				Intervention Methods
				I	II	III	IV	
Koehler	2011	Chronic heart failure	>2	0	176	178	0	Use portable devices for electrocardiogram (ECG), blood pressure, and weight measurements, and transmit encrypted data to remote medical centers through personal digital assistants (PDAs).
Seto	2012	/	4.8(7.8)	0	21	6	2	The patients in the remote monitoring group measured their weight and blood pressure daily for 6 months, performed a single lead electrocardiogram once a week, and answered daily symptom questions.
Comín-Colet	2016	Chronic heart failure	/	96		82		Monitor biometric data (weight, heart rate, and blood pressure); symptom reporting provides multi-channel services and patient tracking.
Hale	2016	/	/	12	10	2	0	The device provides visual cues and audio alerts to remind participants when to take their medication. If a dose is not taken within 30 minutes, a counselor at the monitoring center will call the participant.
Hwang	2017	Heart disease	/	3	9	12	0	Remote Rehabilitation Conference
Frederix	2019	/	/	/	/	/	/	/
Bakitas	2020	/	/	0	0	200	6	/
Ding	2020	Chronic heart failure	/	/	/	/	/	Remote weight monitoring, structured telephone support, and nurse-led collaborative care
Jiménez-Marrero	2020	/	/	60		56		/
Galinier	2020	/	/	29	210	182	54	Daily transmission of weight measurements and heart failure symptom records to a secure server
Sahlin	2022	/	/	4	57	51	4	The remote tool is based on a tablet connected wirelessly to a weight scale, combined with symptom monitoring, interactive education, and adjustment of diuretics for patients at home.
Clays	2021	/	/	0	46	7	0	/
Chen	2019	/	/	0	0	175		/
Dendale	2012	/	/	/	/	/	/	/
Vuorinen	2014	/	/	0	17	28	2	The patient configuration includes a weight scale, blood pressure monitor, mobile phone, and self-care instructions. The patient uses the mobile app to measure and report once a week, while evaluating symptoms.