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Melatonin as a Novel Drug to Improve Cardiac Function and Quality of Life in Heart Failure Patients: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Heart failure as an advanced cardiac disease has a high incidence and prevalence in all societies nowadays. Many drugs and treatment methods have been discovered for improving heart failure patients' conditions till now in this way melatonin therapy is one of the less-known methods rarely used by clinicians.

Methods: To investigate the positive effect of melatonin on heart failure development, we conducted a systematic review and meta-analysis by searching valid databases with keywords based on the protocol. Based on the eligible criteria, four articles were selected for data synthesis and analysis after scanning the title and/or abstract and reading full-text.

Results: As a result of analysis, increasing ejection fraction (Mean difference: 2.39 [−1.82, 6.59] $p = 0.27$), NYHA (New York Heart Association Functional Class) (Odds ratio: 4.84 [1.00, 23.44] $p = 0.05$), and significant elevation of quality of life (Mean difference: −5.95 [−9.54, −2.35] $p = 0.001$) were observed. As the effect of melatonin, fatigue, and NT-Pro BNP were reduced but on the contrary sleep quality, appetite, and FMD (Flow-Mediated Dilation) significantly increased.

Conclusion: Thus, melatonin, by increasing psychologic parameters and cardiac potency, could be advised as a novel drug for treatment and palliating heart failure patients.

1 | Introduction

HF (Heart Failure) is an advanced heart disease in which cardiac pumping function is significantly reduced in advanced conditions. This disease has a high prevalence in the world in this way 64.3 million people were estimated to have suffered in 2017, although its prevalence, incidence, and survival are variable in different countries [1, 2]. Despite lifetime risk of

developing HF in men and women being almost the same throughout life, its occurrence increases by old age in women more than in men [3, 4]. HF can occur as a result of myocardial ischemia, high blood pressure, infection, etc and the risk can be increased by many different parameters such as smoking, diabetes, obesity, and hypertension [5–11]. HF as a basic disease causes many secondary problems such as pulmonary edema, thromboembolism [11–13], impaired kidney

Abbreviations: BP, blood pressure; CI, confidence interval; EF, ejection fraction; FMD, flow-mediated dilation; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; MLHFQ, the minnesota living with heart failure questionnaire; NT-Pro BNP, N-Terminal pro-B-type Natriuretic Peptide; NYHA FC, New York Heart Association Functional Class; QoL, Quality of Life; RCT, randomized controlled trial; RevMan, review manager; SD, standard deviation; SV, stroke volume.

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or liver functions, respiratory distress, etc [14–17]. However, there are many treatment methods to improve and palliate primary and advanced-stage cardiac failure. Catheter ablation, gene therapy, hormone therapy, drug therapy, etc have been discovered till now, some are common methods but despite usefulness, other methods have been paid less attention [18–20]. Drug therapy as a classic method has significantly developed especially in recent years in this way many classes of drugs such as angiotensin-converting enzyme inhibitors, Beta-blockers, Mineralocorticoid receptor antagonists, Digoxin, and other stuff are used in the vast domain of *HF* patients [21]. Hormone therapy, as a less used method, can be used as a way of drug therapy for helping *HF* patients [19, 22, 23]. Melatonin therapy is a kind of hormone therapy in which melatonin or sleep hormone is used as a drug for cancer, myocardial infarction, depression, etc [24–27]. Melatonin, an indolamine hormone, is secreted more by epiphysis and less by the bone marrow, retina, skin, and gastrointestinal tract [28, 29]. This hormone regulates sleep rhythm naturally; however, it can be used as a drug for regulating insomnia and other sleep problems [30]. Furthermore, melatonin by antioxidant features protects the body from free radicals [31, 32] so it could be used for conditions such as cancer and myocardial ischemia-reperfusion injury, etc [24, 25]. With attention to sleep regulating, antioxidant, etc features of melatonin, it guesses that melatonin may be helpful for *HF* patients' *QoL* (Quality of Life) and cardiac potency. Thus, many studies have been performed to evaluate melatonin efficacy on psychological and cardiovascular parameters in *HF* patients [22, 23, 33–35]. However, the outcomes were invalid due to the low number of participants and scattered data in different studies; therefore, we conducted a systematic review and meta-analysis based on all related *RCTs* (randomized controlled trial) to resolve the mentioned problems.

2 | Methods

2.1 | Search Strategy

We (ASD and NG) searched PubMed, Scopus, Web of Science, and Cochrane Library on November 28, 2023. Based on protocol, mesh, and synonyms of *HF*, melatonin and outcomes (*QoL*, *NT-Pro BNP* (N-terminal pro-B-type natriuretic peptide) and Stroke volume) were searched in the mentioned databases for all articles that investigate the effect of melatonin on the improvement of *QoL* and heart function in *HF* patients. As a result of searching all fields in databases, 8013 manuscripts were found; including original articles, reviews, books, letters, etc. (Figure 1).

2.2 | Eligibility Criteria

We (NG and ASD) scanned the records that remained after the deletion of reviews, books, letters, duplicates, etc by reading the title and/or abstract, then differences between outcomes of scanning performed by NG and ASD; were found and solved by AH. Studies were selected for data synthesis and analysis exactly according to protocol.

The study protocol was designed based on PICOT framework, which includes participant, intervention, comparison, outcome, and type of study. Only *RCT* (randomized controlled trial) studies were selected for data synthesis and analysis. All eligible studies investigated the effect of oral melatonin tablets as an intervention compared to placebo tablets in heart failure patients classified as *NYHA* II and III. The main outcomes of the studies include psychological parameters (*QoL*), serum markers (*NT-Pro BNP*), and cardiovascular parameters (Stroke volume and *NYHA*).

As a result, 27 articles remained for reading full-text; Ultimately, four articles were selected for data synthesis, from which three articles were chosen for data analysis.

2.3 | Data Extraction

Data from residual records were extracted by ASD and NG, then any differences were investigated and resolved by AH. Extracted data include the first author's name, year of publication, type of study, participant characteristics (age, gender, and sample size), type of comparison, outcome (Stroke volume, *QoL*, *NYHA*, and *NT-Pro BNP*), and conclusion of the study.

2.4 | Risk of Bias Assessment

The risk of bias for selected studies was independently evaluated through Review Manager software (Version 5.4.1 The Cochrane Collaboration, 2020) by AH and NG. Biases, which consist of random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias (follow-up patients), were classified into three groups: low risk (green), high risk (red), unclear risk (yellow). Ultimately, any differences and disagreements are checked and resolved by ASD.

2.5 | Data Analysis and Synthesis

Data from eligible studies were analyzed with Review Manager software (Version 5.4.1 The Cochrane Collaboration, 2020). Outcomes were classified into three categories: a) *NYHA* b) *EF* (Ejection Fraction) c) *QoL*. Comparison of these outcomes was performed by considering the mean difference with 95% *CI* for analyzing data of *QoL* and *EF*, and also odds ratio with 95% *CI* for *NYHA* which all results were reported as forest plot graphs. Furthermore, the random effect analysis model and inverse variance statistical method were used to decrease heterogeneity and variance between the selected studies. *P* and *I*² values were used to show the validity and homogeneity of the results and studies. Analyzing *EF* and *QoL* was performed by using mean and SD (standard deviation). However, in studies in which SD hadn't been reported, SD was measured by using start and end *CI* with *RevMan* (Review Manager) calculator.

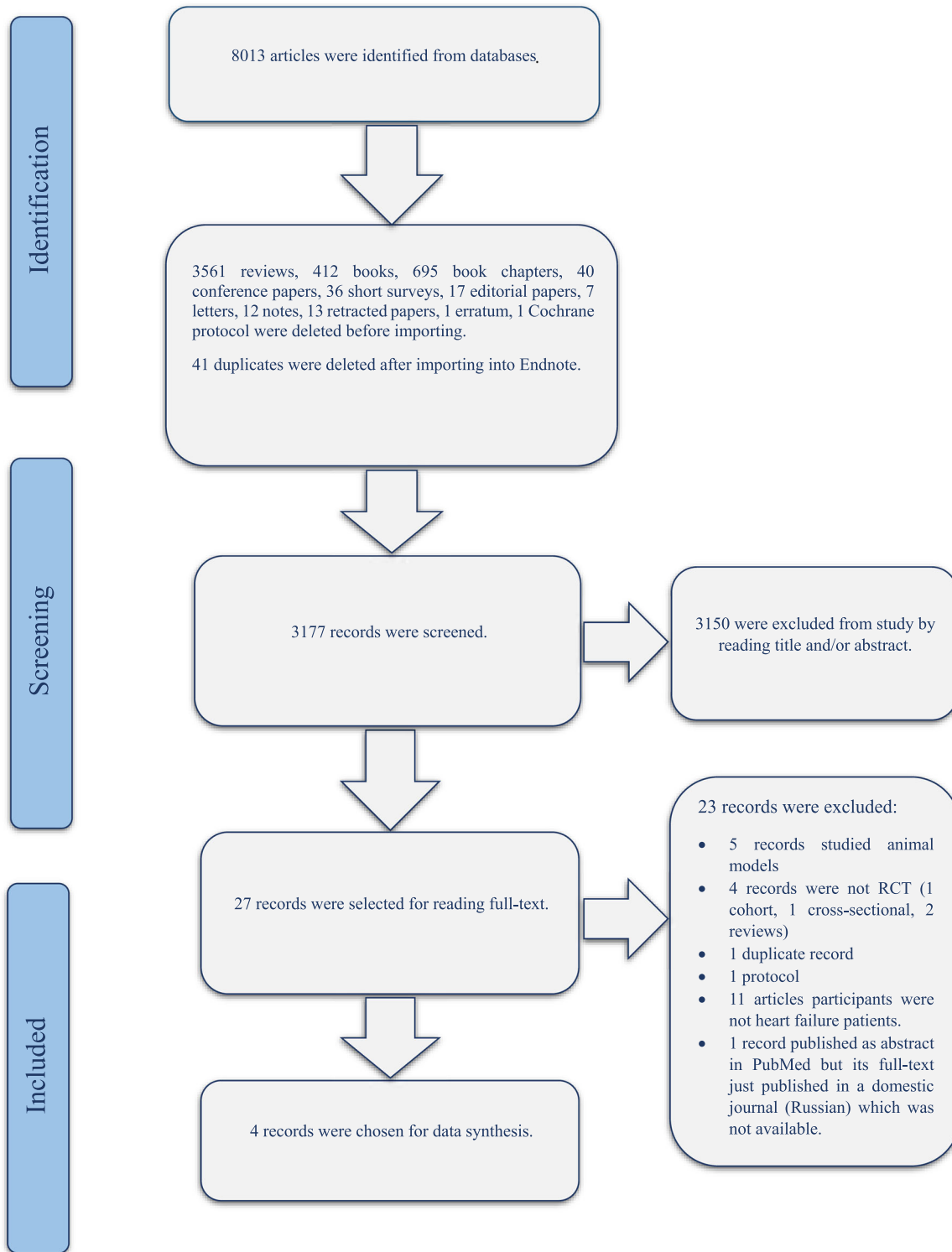


FIGURE 1 | Flow chart of study selection.

3 | Result

3.1 | Literature Search

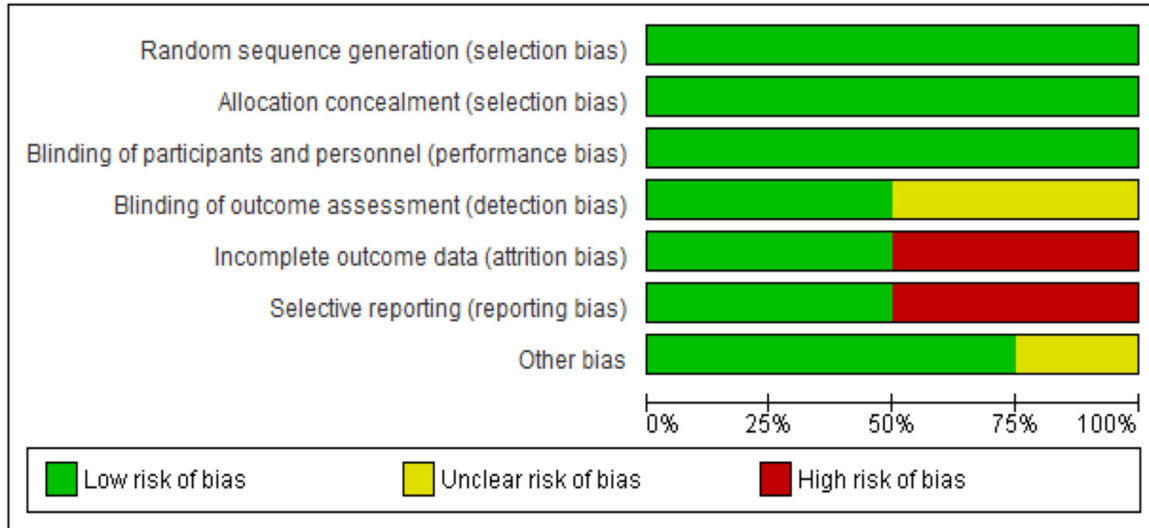
Scopus, PubMed, CENTRAL, and Web of Science databases were systematically searched with keywords (mesh and synonyms of (heart failure AND melatonin AND (QoL OR SV OR NT-Pro BNP))) based on protocol. 8013 records were found from which, 3561 reviews, 695 book chapters, 412 books, 41 duplicates, 40 conference papers, 36

short surveys, 17 editorial papers, 13 retracted papers, 12 notes, 7 letters, 1 erratum, 1 Cochrane protocol were excluded before screening. 3177 records were scanned by reading title and/or abstract from which 3150 records were excluded and 27 records remained for full-text screening. 23 manuscripts were excluded by full-text reading because 5 records studied animal models, 4 records were not RCT (1 cohort, 1 cross-sectional, 2 reviews), 1 duplicate record (published in double languages), 1 protocol, in 11 articles participants were not heart failure patients, 1 record published as

abstract in PubMed but its full-text just published in a domestic journal (Russian) which was not available. Ultimately, four articles were selected for data synthesis (*Jafari-Vayghan 2022* [23], *Hoseini 2022* [33], *Hoseini 2021* [22], and *Garakyaraghi 2012* [34]) from which three articles were used for data analysis. Actually, *Hoseini 2021 and 2022* manuscripts were common RCT studies (same population) and outcomes were published in two separate articles. *EF* and *NYHA* classes as outcomes of *Hoseini 2022* and *Garakyaraghi 2012* and *QoL* as the outcome of *Jafari-Vayghan 2022* and *Hoseini 2022* were separately analyzed.

3.2 | Quality Assessment

The quality assessment of the included studies was performed in the Cochrane scoring system by NG and AH. Disagreements and differences were resolved by discussion among the members. The overall risk of studies is shown in Figure 2. Selection and performance biases were completely low risk but 50% of detection, reporting, and attrition biases were unclear, high, and high risk, respectively. The other bias was low risk except for 25% which was unclear. The risk of bias for each study is demonstrated in Figure 2.



	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Garakyaraghi 2012	+	+	+	?	-	+	?
Hoseini 2021	+	+	+	+	+	-	+
Hoseini 2022	+	+	+	+	+	-	+
Jafari-Vayghan 2022	+	+	+	?	-	+	+

FIGURE 2 | The overall and summary of risk of bias.

3.3 | Literature Characteristics

3.3.1 | Participant

Four RCT studies were selected for systematic review in this way one was published in 2012 [34], one was published in 2021 [22], and two were published in 2022 [23, 33]. 166 people participated in the studies (132 men and 34 women) and the mean age of them ranged from 50.82 to 65.8. 83 and 76 people remained in melatonin and control groups, respectively after exclusion. All patients were categorized in II and III NYHA classification (Table 1).

3.3.2 | Intervention

Oral melatonin was used for intervention groups (3, 10, and 20 mg/d for 8, 24, and 24 weeks, respectively), and placebo was used for control groups (cellulose pills and cornstarch tablets) (Table 1).

3.4 | Data Synthesis

3.4.1 | Garakyaraghi 2012

Garakyaraghi et al. studied the effect of melatonin on left ventricular EF and NYHA changes in HF patients. Both parameters improved as a result of the intervention, in this way the baseline of EF in the intervention and control groups was 31.8 ± 7.8 and 34.1 ± 9.9 , also after intervention, this parameter was 37.6 ± 7.1 and 35.3 ± 6.9 for the mentioned groups, respectively. During the trial process, the development of EF for melatonin and control groups was 5.8 ± 6.3 and 1.1 ± 5.5 . Thus, the improvement of EF was more significant in the intervention group compared to control. Participants of the intervention group were classified in NYHA class II (20 patients) and III (3 patients), and the control group in NYHA class II (14 patients) and III (2 patients) before intervention. As the effect of melatonin therapy, improvement in 6 patients was observed (class I: 6 patients, class II: 14 patients, class III: 3 patients), the placebo effect also caused improvement in just a patient in the control group (class I: 1 patient, class II: 13 patients, class III: 2 patients).

3.4.2 | Hoseini 2021

Hoseini et al. measured the effect of melatonin therapy on BP (blood pressure) and FMD (flow-mediated dilation) parameters in HF patients. Covariance analysis was used for adjusting the baseline parameters of the study, therefore the difference in end-point data demonstrates the variation between intervention and control groups. Justified end-point systolic/diastolic BP for melatonin and control groups were 121.7/76.1 and 116/72.4, respectively. Although the development of BP was seen, there is no valid correlation between melatonin therapy and improvement of BP (systolic $p = 0.157$ and diastolic $p = 0.098$). Significant elevation of mean FMD, as a prognostic parameter, was seen in nondiabetic HF patients (4.65% [1.14, 7.88], $p = 0.006$)

but there is no significant change in mean FMD in diabetic HF patients (0.10% [-4.27, 4.06], $p = 0.960$).

3.4.3 | Hoseini 2022

The effect of melatonin on NT-Pro BNP, NYHA, EF (serum and cardiovascular parameters), and QoL (for measuring the development of life conditions) was studied by Hoseini et al. As mentioned, in Hoseini's study covariance analysis was used. NT-Pro BNP in intervention and comparison groups were 221.1 [148.9, 293.2] and 332.1 [253.5, 410.7] so cardiac stress was decreased as the effect of melatonin therapy ($p = 0.044$). Improvement of NYHA in four patients in the melatonin group and a patient in the control was observed, in this way NYHA class 4.42 [0.47, 41.31] times developed in intervention to control groups. However, Hoseini measured the NYHA's odds ratio, by considering the deterioration, 12.9 [1.6, 102.4] ($p = 0.015$) but we considered just the improvement of patients for adjusting to Garakyaraghi's study in data analysis. EF, according to the mean difference (0.40 [-2.51, 3.31]), doesn't have valid improvement. However, QoL development was observed but due to $p \geq 0.05$, the outcome was invalid.

3.4.4 | Jafari-Vayghan 2022

Jafari-Vayghan et al. studied the effect of melatonin on QoL (MLHFQ (The Minnesota Living with Heart Failure questionnaire)), fatigue (FSI (Fatigue Symptom Inventory)), appetite (SNAQ (Simplified Nutritional Appetite Questionnaire)), and NRI (nutritional risk index) in cardiac cachexic HF. As the effect of melatonin QoL ($p = 0.01$), appetite ($p = 0.004$), fatigue ($p = 0.002$), and NRI ($p = 0.015$) status significantly were improved. QoL had two dimensions (physical and emotional dimensions); despite that, the physical dimension was significantly improved ($p = 0.048$) in the melatonin group, but any valid changes weren't seen in the emotional dimension ($p = 0.495$).

3.5 | Data Analysis

3.5.1 | Effect of Melatonin on QoL

As selected studies, two records investigated the effect of melatonin on QoL in HF patients. The results of studies were reported by mean difference and the validity was reported by 95% CI, P, and I^2 -values. Both studies have demonstrated a positive effect of melatonin on HF, in this way -5.80 [-12.39, 0.79] improvement of QoL for Hoseini 2022 and -6.01 [-10.30, -1.72] for Jafari-Vayghan 2022. Hoseini 2022 adjusted the baseline data of the study by using covariance analysis; therefore, the difference in the ultimate result shows the variation of outcomes (QoL, EF, etc). These studies used MLHFQ for evaluating QoL in quantity. In this questionnaire, lower numbers report improvement in QoL. There is no heterogeneity between these studies ($p = 0.96$, $I^2 = 0\%$) and the overall result demonstrates a significant difference between melatonin and control groups (-5.95 [-9.54, -2.35], $p = 0.001$). Ultimately, the outcomes indicate the validity of QoL development in HF patients as the efficacy of melatonin (Figure 3).

TABLE 1 | Study characteristics.

Number	Author, Year	Study design	Sample size (Melatonin/Control)	Gender (Male/Female)	Age (Melatonin/Control)	Type of intervention	Type of comparison
1	Garakyaraghi et al. [34]	RCT	23/16	27/12	63.6 (±6.6)/65.8 (±12.5)	3 mg/day for 8 weeks	Placebo (cellulose pills)
2	Hoseini et al. [22]	RCT	42/43	80/12 ^a	62.7 (±10.3)/59.1 (±11.5) ^a	10 mg/day for 24 weeks	Placebo tablets
3	Hoseini et al. [33]	RCT	42/43	80/12 ^a	63.5 (±22.89)/58.5 (±15.15) ^a	10 mg/day for 24 weeks	Placebo tablets
4	Jafari-Vayghan et al. [23]	RCT	18/17	25/10	55.78 (±11.57)/50.82 (±11.22)	20 mg/day for 24 weeks	Placebo (cornstarch tablets)

Outcome

Number	QoL (Melatonin-Control)	EF (Melatonin-Control)	NYHA (Melatonin-Control)	Author conclusion
1	—	5.8 (±6.3) - 1.1 (±5.5)	6/23/1/16	The present study showed that melatonin may be an adjunctive option to improve <i>LVEF</i> (Left Ventricular Ejection Fraction) and functional class of patients with heart failure of different etiologies. However, larger studies would help to more clearly define its role in heart failure management.
2	—	—	—	Melatonin might be beneficial for the endothelial function in patients with <i>HFrEF</i> (Heart Failure with Reduced Ejection Fraction), and as a consequence, it could improve their outcome. Nevertheless, according to our results, this benefit in diabetic patients with <i>HFrEF</i> is debated and should be examined in a properly designed study.
3	22.2 (±15.4) - 28 (±15.59)	29.5 (±7.7016) - 29.1 (±5.8488)	4/42/1/43	Melatonin might lower serum <i>NT-Pro BNP</i> and improve disease-specific health-related quality of life in patients with <i>HFrEF</i> . Thus, it could be a valuable supplement for these patients. Further studies in subgroups of patients with <i>HF</i> , such as diabetic or hypertensive cardiomyopathic patients, and sensitive evaluation methods for cardiac function might provide new information in this regard.
4	4.89 (±7.15) - 1.12 (±5.74)	—	—	The findings of this study indicate that cosupplementation of <i>BCAAs</i> and melatonin for 8 weeks improved the <i>CC</i> outcomes such as <i>QoL</i> , fatigue status, and appetite in cachectic <i>HF</i> patients, but it could not affect <i>NRI</i> (nutritional risk index). Although separate supplementation with melatonin and <i>BCAAs</i> had positive effects on <i>QoL</i> , fatigue, and appetite of study participants, this study demonstrated that adding <i>BCAAs</i> to melatonin augmented these effects more than either of the 2 other supplements given alone.

^aData at the onset of study.

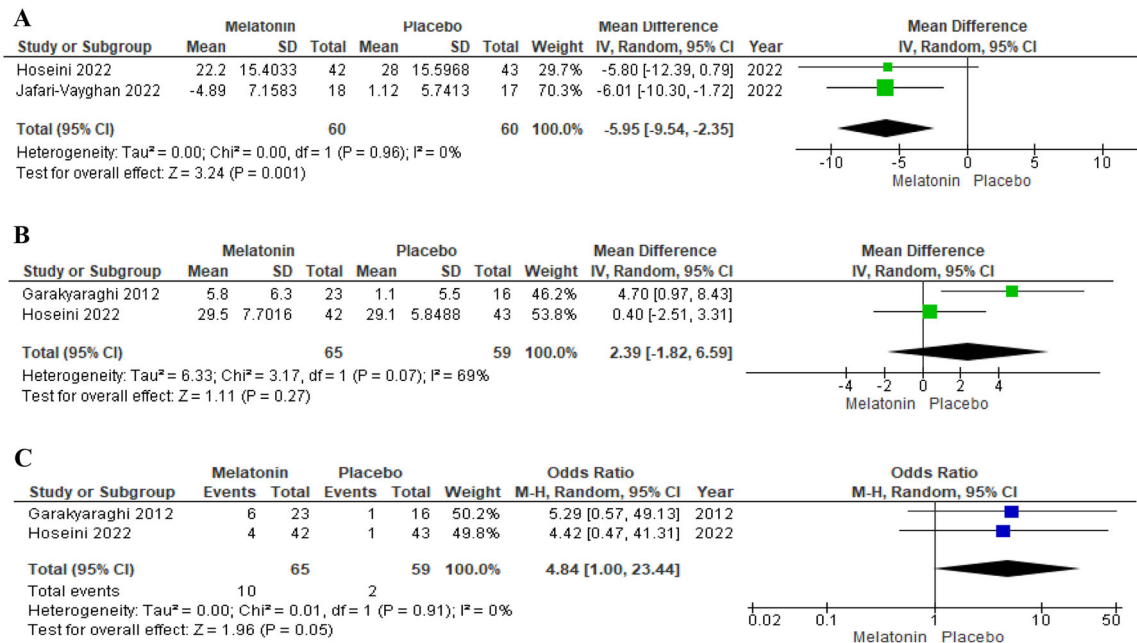


FIGURE 3 | (A) Effect of melatonin on QoL. (B) Effect of melatonin on EF. (C) Effect of melatonin on NYHA.

3.5.2 | Effect of Melatonin on EF

Garakyaraghi 2012 and Hoseini 2022 studied the effect of melatonin on EF in patients with HF. The results of the studies were reported using the mean difference with 95% CI, P, and I² values. There is no significant heterogeneity between studies (p = 0.07, I² = 69%); Hence, these studies were approximately homogenous. Both Garakyaraghi 2012 and Hoseini 2022 reported development in EF due to oral melatonin (mean difference with 95% CI: 4.70 [0.97, 8.43] and 0.40 [-2.51, 3.31], respectively). The change of EF in the Hoseini 2022 study was not significant based on the confidence interval. Overall, a 2.39 [-1.82, 6.59] increase in EF was observed in the melatonin group compared to control. However, due to p = 0.27, the result of the analysis was insufficient to support a positive effect of melatonin on EF (Figure 3).

3.5.3 | Effect of Melatonin on NYHA

The effect of melatonin on NYHA change was studied just by the homogenous Hoseini 2022 and Garakyaraghi 2012 studies (p = 0.91 and I² = 0%). Odds ratio with 95% CI, P, and I² values were used for comparison of the intervention and control groups. In Hoseini 2022 and Garakyaraghi 2012 studies, 4.42 [0.47, 41.31] and 5.29 [0.57, 49.13] times improvement in NYHA class in the melatonin group to control was seen, respectively. Ultimately, 4.84 [1.00, 23.44] times development in NYHA class in melatonin to control group was observed. Furthermore, p = 0.05 demonstrated approximate validity in the global society (Figure 3).

3.6 | Quality of Evidence

The effect of melatonin on EF, QoL, and NYHA in HF patients was investigated (Table 2). The certainty of evidence for EF and NYHA was low and QoL has moderate certainty of evidence.

Each investigation was performed on more than 120 patients and all analyzed studies were RCT.

4 | Discussion

This study is the first systematic review and meta-analysis article that investigated and analyzed the effect of melatonin therapy on psychological, serum, and cardiovascular parameters in HF patients. Outcomes demonstrate melatonin has significant efficacy for improvement of patient's QoL (p < 0.05). However, the evidence does not support the positive effect of melatonin on EF and NYHA due to p ≥ 0.05. NT-Pro BNP, BP, and FMD were investigated by Hoseini's studies [22, 33] which reported the significant effect of melatonin on NT-Pro BNP and FMD but the effect on BP was invalid. All selected studies for data analysis were RCT; in this way, three of them were published after 2020 [22, 23, 33]. Five studies were selected for data synthesis and analysis; the abstract of Zaslavskaya's study was published in PubMed database and its full-text was published only in Russian and a domestic (Russian) journal; We can't find the article by texting emails to the first and corresponding authors so this article was extracted from data synthesis and analysis [35]. All remaining studies were performed in I.R IRAN, so it's needed to perform more studies in this context and also in other countries to determine the validity of the effect of melatonin on other parameters. The effect of melatonin on HF teenagers and children (under 18 years old) hasn't been studied till now, therefore medical society needs to conduct trials to show the effect of melatonin on under 18 years old patients. The other observed problem was missing the extreme number of participants compared to all patients in one study [34]. Compliance of patients to taking drugs could also affect the results of studies; fortunately, taking drugs by patients was checked in all selected studies. The side effects of melatonin in HF patients weren't recognized completely so more epidemic studies are needed to detect them. despite positive melatonin efficacy, it

TABLE 2 | Quality of evidence.

Outcome	Predicted absolute effects		Mean difference (first two) odds ratio (the last) with 95% CI	Number of participants	GRADE; Certainty of the evidence
	Improvement with melatonin	Improvement in control			
EF	—	—	2.39 [−1.82, 6.59]	124 (2 RCTs)	⊕⊕○○ ^{b,c}
QoL	—	—	−5.95 [−9.54, −2.35]	120 (2 RCTs)	⊕⊕⊕○ ^b
NYHA	15 per 100	3 per 100	4.84 [1.00, 23.44]	124 (2 RCTs)	⊕⊕○○ ^{b,c}

Note: Studies that related to the efficacy of melatonin on EF, QoL, and NYHA. Population: HF patients, Intervention: Oral melatonin, Comparison: Placebo tablets.

GRADE: Working Group Grades of Evidence

HIGH: There is complete confidence that the true effect is close to the estimate of the effect. ⊕⊕⊕⊕

MODERATE: The effect of the estimate is moderately confided: Despite the true effect is likely close to the effect estimate, it could be substantially different from the effect estimate. ⊕⊕⊕○

LOW: The validity of the effect estimate is low: The true effect may be substantially different from the estimate of the effect. ⊕⊕○○

VERY LOW: Very little confidence exists in the effect estimate: The true effect is probably different from the effect estimate. ⊕○○○

a) Low participant (one downgrade for imprecision)

b) Studies report data incompletely or incorrectly (one downgrade for risk of bias)

c) Studies missed more than 12.5% of participants to the outcome (one downgrade for risk of bias)

d) Studies were not RCT (one downgrade for risk of bias)

isn't prescribed by treatment staff so it is hoped that after publishing this article, an increase in the melatonin use for HF will be observed.

5 | Conclusion

We conducted a systematic review and meta-analysis to confirm the positive effect of melatonin on HF patients' development. Four articles were appropriate to protocol criteria from which three were used for data analysis. As a result of this study, melatonin therapy can be introduced as a new method for treating and palliating HF patients. After the melatonin intervention, a significant improvement in QoL was observed. However, no significant development in EF and NYHA class was observed in the final analysis. Furthermore, as effect of melatonin NT-Pro BNP and fatigue were decreased but elevation of sleep quality, appetite, and FMD were seen.

Acknowledgments

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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