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Review

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The Effect of Omega-3 Supplementation on Heart Failure Outcome: A Meta-Analysis of Randomized Clinical Trial

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ABSTRACT

The effect of omega-3 supplementation on cardiovascular (CV) disease has been widely studied in several large clinical trials. However, the evidence of the effect of omega-3 supplementation in patients with heart failure (HF) remains controversial. This meta-analysis investigated the effects of omega-3 supplementation on patients with HF. We conducted a literature search on MEDLINE, Embase, and Cochrane databases for clinical trials and preprints of relevant articles. Following a literature search and critical appraisal, 5 studies were included in the meta-analysis. The pooling of the result of the studies shows that there were no significant association between omega-3 supplementation and CV mortality (odds ratio [OR], 0.94; 95% confidence interval [CI], 0.84–1.05, p=0.16) nor hospitalization due to HF (OR, 0.94; 95% CI, 0.88–1.02; p=0.13). Our systematic review and meta-analysis showed that omega-3 supplementation has no beneficial effect in patients with HF.

Keywords: Atherosclerosis; Cardiovascular disease; Omega-3 fatty acid; Secondary prevention

INTRODUCTION

Recently, the effect of omega-3 supplementation on cardiovascular (CV) health have been widely investigated. The omega-3 effect on CV research dates back to an original study that observed that the Inuit people in Greenland have a significantly lower rate of acute myocardial infarction than Western participants.[1] Since then, there has been much research, both clinical and molecular, on the effect of omega-3 on CV health.

Despite extensive clinical trials and research, the evidence for the omega-3 supplementation on CV health is inconclusive. The most recent large-scale randomized clinical trial of omega-3, Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial, showed that high dose omega-3 supplementation (4 g of icosapent ethyl) significantly reduced the risk of ischemic events, including CV death.[2] However, another trial, The Risk and Prevention Study, shows that 1 g omega-3 supplementation did not significantly reduce CV morbidity and mortality.[3]

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Conflict of Interest
The authors have no conflicts of interest to declare.

Data Availability Statement
The datasets analyzed during this study are available from the corresponding author upon reasonable request.

Author Contributions
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Clinical trials on the effect of omega-3 supplementation on heart failure (HF) are small and inconclusive. The results of the Vitamin D and Omega-3 Trial-Heart Failure (VITAL-HF) trial[4] shows a significant reduction in HF rehospitalization with marine omega-3 supplementation. It has also been postulated that the beneficial effects of omega-3 supplementation on these diseases are dose-dependent. Research has shown that high-dose omega-3 supplementation significantly improves inflammatory biomarker levels in patients with HF.[5] Therefore, we conducted a meta-analysis to study the effect of omega-3 supplementation on HF-related mortality and hospitalization and whether the effect was dose-dependent.

MATERIALS AND METHODS

We searched the literature for eligible trials from three peer-reviewed databases (MEDLINE, Embase, and Cochrane Library for Clinical Trials) and grey literature from 2 pre-prints databases (medRxiv and SSRN), and ClinicalTrials.gov for unfinished clinical trials. For the peer-reviewed databases, we used keywords as stated in **Supplementary Table 1**. For the pre-print databases and ClinicalTrials.gov, we used the search terms "randomized controlled trials," "heart failure," and "omega-3." Two authors (BD and AMA) independently screened the studies eligible for inclusion in the review. Disagreements were resolved through discussion after both authors completed their preliminary search, and when necessary, deliberation was conducted with a third author (AS). We included studies written in English, randomized controlled trials conducted in patients with HF, using omega-3 as an intervention, and reporting at least one of our primary outcomes: mortality, hospitalization, or rehospitalization.

After a preliminary search, we extracted data from the full-paper articles regarding Trial Name, Author, Year, Country, Study design, study population, sample size, follow-up duration, primary outcome, and secondary outcomes. The data are presented in **Table 1** and **Supplementary Fig. 1**.

After extraction, we conducted a risk-of-bias assessment using the Cochrane risk-of-bias assessment for randomized controlled trials. The risk of bias was assessed based on 6 domains: 1) adequate sequence generation, 2) allocation concealment, 3) blinding, 4) incomplete outcome data, 5) selective reporting of outcomes, and 6) any other bias. The risk of bias was classified as good, poor, or fair, depending on the thresholds for converting the Cochrane risk-of-bias tool to Agency for Healthcare Research and Quality Standards. The risk of bias is summarized in the risk of bias table, available in **Supplementary Fig. 2**.

A meta-analysis was performed using RStudio version 2022.02.0. As there are differences in the omega-3 dose, we conducted a meta-analysis using the random effects model, as we expected different true effect sizes for different doses of omega-3. To pool the overall effect size, we weighted each study by sample size using the Mantel-Haenszel method. We then calculated the between-study heterogeneity using I^2 statistics. When I^2 was >50%, subgroup analysis was conducted to investigate the source of heterogeneity (**Supplementary Fig. 3**).

We planned a subgroup analysis of studies that separated eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) treatments, but we did not find such a study. Additionally, the included studies did not separate the types of HF; therefore, a preplanned subgroup analysis for different types of HF was not conducted.

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Table 1. Trials characteristics

No	Trial	Author	Year	Country	Design	Study population	Intervention				Sample size		Follow up duration	Primary outcome
							Omega-3			Placebo	Omega-3	Placebo		
							EPA	DHA	Total					
1	GISSI-HF	GISSI-HF investigators	2008	Italy	Randomized controlled trial	Men and women aged 18 years or older, with clinical evidence of heart failure of any cause that was classified according to the ESC guidelines as NYHA class II–IV			1 g of omega-3	1 g of olive oil	3,494	3,481	3.9 years (IQR, 3.0–4.5)	- Patients admitted for HF (omega-3 vs. placebo; 978 [28·0%] vs. 995 [28·6%]; HR, 0·94; 95% CI, 0·86–1·02; *p*=0·147) - Cardiovascular mortality (omega-3 vs. placebo: 712 [20·4%] vs. 765 [22·0%]; HR, 0·90; 95% CI, 0·81–0·99; *p*=0·045) - Patients admitted (omega-3 vs. placebo: 1,986 [56·8%] vs. 2,028 [58·3%]; HR, 0·94; 95% CI, 0·88–1·00; *p*=0·049
2	ORIGIN	ORIGIN Trial Collaborator	2012	Multinational	Randomized controlled trial	Participants aged 50 years old or older with history of MI, stroke, or revascularization; angina with documented ischemia; a ratio of urinary albumin to creatinine of more than 30 mg per gram; LV hypertrophy; 50% or more stenosis of a coronary, carotid, or lower-limb artery on angiography; or an ankle–brachial index of less than 0.9.	465 mg	375 mg	1 g of omega-3	1 g of olive oil	6,281	6,255	6.2 years	- Hospitalization for HF (omega-3 vs. placebo: 331 [5.3%] vs. 320 [5.1%]; HR, 1.02; 95% CI, 0.88–1.19; *p*=0.76) - Death from CV cause (omega-3 vs. placebo: 574 [9.1%] vs. 581 [9.3%]; HR, 0.98; 95% CI, 0.87–1.10; *p*=0.72)
3	VITAL-HF	Djousse L	2019	United States	Randomized controlled trial	Men who were 50 years of age or older and women who were 55 years of age or older with confirmed HF case	460 mg	380 mg	1 g of omega-3		12,933	12,938	5.3 years	- Hospitalization for HF (omega-3 vs. placebo: 244 vs. 255; HR, 0.96; 95% CI, 0.80–1.14; *p*=0.61) - Recurrent HF hospitalization (omega-3 vs. placebo; 326 vs. 379; HR, 0.86; 95% CI, 0.74–0.998; *p*=0.048)
4	-	Kojuri J	2013	Iran	Randomized controlled trial	Patients with class II or III CHF resulting from underlying ischemic heart disease	N/A	N/A	2,000 mg of omega-3	Placebo capsule containing water	38	32	6 months	- Mortality (2 [4.2%] vs. 1 [3.6%]; *p*=0.73)
5	-	Nodari S	2010	Italy	Randomized controlled trial	Patients aged between 18 and 75 years with a diagnosis of NICM, LV systolic dysfunction	318 mg	531 mg	1,000 mg of omega-3	1,000 mg of olive oil	67	66	12 months	- Hospitalization for HF (omega-3 vs. placebo: 4 [5.9%] vs. 20 [30.3%]; *p*=0.0002)

EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; GISSI-HF, Gruppo Italiano per lo Studio della Sopravvivenza nella Insufficienza Cardiaca-Heart Failure; ESC, European Society of Cardiology; NYHA, New York Heart Association; IQR, interquartile range; HF, heart failure; HR, hazard ratio; CI, confidence interval; ORIGIN, Outcome Reduction with an Initial Glargine Intervention; MI, myocardial infarction; LV, left ventricular; CV, cardiovascular; VITAL-HF, Vitamin D and Omega-3 Trial-Heart Failure; CHF, congestive heart failure; N/A, not applicable; NICM, non-ischemic dilated cardiomyopathy.

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RESULTS

We identified 259 records from the databases and 8 records from ClinicalTrials.gov. After deduplication, 186 abstract records were screened for eligibility. A total of 177 articles were excluded, and nine full-text articles were retrieved. Two of the research datasets were not available because the principal investigator was uncontactable (n=1), and no interim data were available for ongoing clinical trials (n=1). One study was not a randomized controlled trial and was therefore excluded.[6] Another research was excluded because it did not meet the inclusion criteria.[7] Finally, five trials were included in this systematic review and meta-analysis. The included studies are summarized in **Table 1**. Critical analysis results showed low bias in three studies,[4,8,9] moderate bias in one study,[10] and high bias in one study.[11] A summary of the critical analysis is provided in the **Supplementary Table 1** and **Supplementary Figs. 1-3**.

The result from Gruppo Italiano per lo Studio della Sopravvivenza nella Insufficienza Cardiaca-Heart Failure (GISSI-HF) trial shows that in New York Heart Association (NYHA) class II–IV patients, omega-3 supplementation resulted in reduction in CV mortality (hazard ratio [HR], 0.90; 95% confidence interval [CI], 0.81–0.99; p=0.045) and hospitalization (HR, 0.94; 95% CI, 0.88–1.00; p=0.049), but not in hospitalization for HF (HR, 0.94; 95% CI, 0.86–1.02; p=0.14). VITAL-HF trial also reported lower recurrent hospitalization for HF (HR, 0.86; 95% CI, 0.74–0.998; p=0.048), but not for single episode of HF hospitalization (HR, 0.96; 95% CI, 0.80–1.14; p=0.61). Another trial that reported significant results was by Nodari et al.,[10] showing that omega-3 supplementation significantly reduced hospitalization for HF (omega-3 vs. placebo: 4 [5.9%] vs. 20 [30.3%]; p=0.0002). However, the Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial[8] and Kojuri et al.[11] reported null results for CV mortality and hospitalization due to HF. Meta-analysis results show no significant difference in CV mortality in patients with HF (odds ratio [OR], 0.94; 95% CI, 0.84–1.05; p=0.16). **Fig. 1** shows forest plots for the included studies. There was no significant heterogeneity among the studies (I^2=0%; p=0.59).

Omega-3 supplementation also did not decrease the risk of hospitalization for patients with HF (OR, 0.94; 95% CI, 0.88–1.02; p=0.13). There was significant heterogeneity in our study (I^2=78%), which stemmed from a small trial[10] that has a significantly larger effect size for hospitalization. When the study was omitted, the heterogeneity was reduced to low (I^2=4%), while the effect size remained insignificant. A forest plot of hospitalizations is shown in **Fig. 2**.

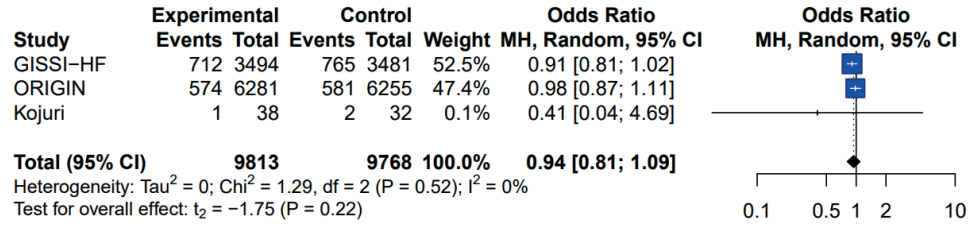

Fig. 1. Mortality rate omega-3 compared with control.
GISSI-HF, Gruppo Italiano per lo Studio della Sopravvivenza nella Insufficienza Cardiaca-Heart Failure; ORIGIN, Outcome Reduction with an Initial Glargine Intervention; MH, Mantel-Haenszel; CI, confidence interval.

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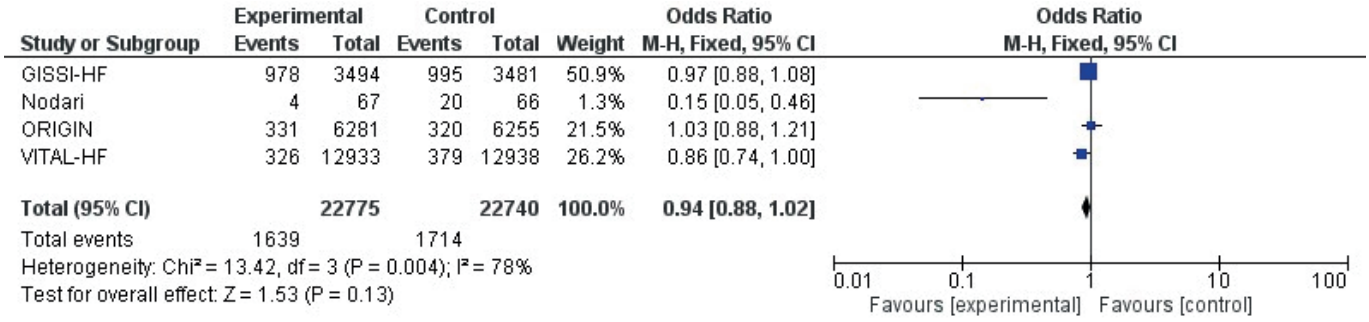

Fig. 2. Hospitalization rate receiving omega 3 compared to control.
MH, Mantel-Haenszel; CI, confidence interval; GISSI-HF, Gruppo Italiano per lo Studio della Sopravvivenza nella Insufficienza Cardiaca-Heart Failure; ORIGIN, Outcome Reduction with an Initial Glargine Intervention; VITAL-HF, Vitamin D and Omega-3 Trial-Heart Failure.

DISCUSSION

The aim of the present systematic review and meta-analysis was to analyze the effect of omega-3 supplementation in patients with HF. Our meta-analysis results show that omega-3 supplementation did not significantly affect the CV mortality and hospitalization rate of patients with HF. We included three large trials on this subject: the GISSI-HF, ORIGIN, and VITAL-HF trials. One trial[9] reported a lower mortality in the omega-3 group, whereas another[8] reported no difference in mortality. There was no source of heterogeneity in our meta-analysis, indicating that the null effect size was similar across the studies.

The null result of our study can be explained by the mechanism of action of omega-3 in CV disease. The most well-known effect of omega-3 is its triglyceride-lowering activity. Elevated serum triglyceride levels are linked to inflammation, potentially affecting circulation in the small blood vessels of the heart, which in turn may increase the likelihood of HF and contribute to the development of plaques in the coronary arteries. Additionally, high triglyceride levels are associated with being overweight or obese as well as diabetes, both recognized as risk factors for ischemic heart disease and heart attacks, often resulting in HF with a reduced ejection fraction.[12] The ORIGIN Trial[8] showed that, despite no effect on mortality and hospitalization in patients with HF, omega-3 supplementation significantly lowered triglyceride levels in patients with HF. This does not necessarily reduce mortality in patients with HF, as previous research has shown that triglycerides do not even have an inverse correlation with HF mortality.[13]

Additionally, the evidence for omega-3 as an antiarrhythmic agent remains conflicting. Existing evidence indicates that omega-3 polyunsaturated fatty acids (PUFAs) exhibit antiarrhythmic effects by enhancing autonomic function, improving endothelial function, decreasing blood pressure, exerting anti-inflammatory actions, regulating blood lipid levels, reducing oxidative stress, and managing calcium overload and abnormal cardiac remodeling (fibrosis). Nonetheless, the available data suggest that the therapeutic range of omega-3 PUFAs in countering arrhythmias is narrow. A recent meta-analysis of the effect of omega-3 on the prevention of atrial fibrillation shows that omega-3 supplementation increased the risk of atrial fibrillation in a dose-dependent manner. This may explain the net zero effect on mortality in patients with HF, as atrial fibrillation has been shown to increase the mortality rate of patients with HF in previous studies.[14]

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A meta-analysis conducted by Wang et al. also revealed the effectiveness of omega-3 in reducing brain natriuretic peptide (BNP) and serum norepinephrine in patients with HF. HF is characterized by an overactive sympathetic nervous system and increased synthesis and release of cardiac BNP. Elevated norepinephrine levels are known to correlate with higher mortality rates in patients with HF. Furthermore, BNP levels are associated with increased stress on the ventricular walls, and lower BNP levels are known to reduce wall stress, which aligns with improvements in diastolic function. In addition, the plasma BNP or N-terminal prohormone of brain natriuretic peptide (NT-proBNP) concentration serves as an indicator of HF severity, increasing exponentially as the cardiac condition worsens. Wang et al.[15] and Linssen et al.[16] demonstrated that doubling the NT-proBNP level is associated with a 22% increase in all-cause mortality and a 16% increase in CV events.[15,16]

In terms of hospitalization, VITAL-HF[4] showed a lower rate of hospitalization for HF, while other trials show there was no difference in hospitalization. The pooled effect size for our meta-analysis showed a null effect of omega-3 supplementation on hospitalization risk. However, it must be noted that the analysis of hospitalization due to HF in this study was an ancillary analysis, meaning that the study might not have been designed to properly detect such an effect size, which warrants further research in the field.

One excluded study[6] was a non-randomized controlled trial of 1,800 mg EPA in patients with HF. The study results showed that EPA supplementation significantly improved the left ventricular ejection fraction and increased event-free survival. However, it must be noted that EPA supplementation in this study was only administered to patients with dyslipidemia, subsequently causing differences in the baseline, which might have biased the study. Therefore, further studies of EPA supplementation alone in patients with HF is warranted.

To the best of our knowledge, our study is the first to analyze the effect of omega-3 in patients with HF. One meta-analysis examined the effect of omega-3 supplementation on HF.[17] However, this meta-analysis included studies in which outcomes were associated with HF in different diseases, such as acute coronary syndromes and cardiomyopathies, and not exclusively in patients with HF. The meta-analysis showed that, although there was no reduction in hospitalization and mortality rates, there was a lower rehospitalization rate for HF. By contrast, our meta-analysis included studies conducted only on patients with HF. However, the results of our meta-analysis were in accordance with those of a previous meta-analysis, with no differences in hospitalization and mortality due to HF. It is also important to note that our analysis on the risk of hospitalization does not specify whether it pertains to first-time or recurrent hospitalization or whether it is caused by HF or other factors, as only one trial differentiates between these categories.

This systematic review and meta-analysis had several limitations. First, there are not enough studies with different doses of omega-3 to conduct a meta-regression, which could be beneficial for understanding the dose-effect of omega-3 in patients with HF. Second, we could not find any grey literature, which may have increased publication bias. However, the trials included in our study had several null results, indicating that publication bias was unlikely to influence our results. In conclusion, omega-3 supplementation at lower and higher doses did not reduce mortality or hospitalization in patients with HF, and its usage is not recommended. Future studies using higher doses of omega-3 supplementation in patients with HF are warranted.

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BD, AS, AMA, and DRD contributed to the study protocols. Study selection, data extraction, and critical appraisal were performed using the BD, AS, AMA, and DRD. AS contributed to the deliberation as a third party. BSP, AS, and BR assisted in the interpretation and discussion of the results. BAW and SF created the forest and funnel plots and proofread the manuscript for conciseness and grammatical errors. All authors have read and agreed to the contents of the manuscript.

SUPPLEMENTARY MATERIALS

Supplementary Table 1
Preliminary search of studies

Supplementary Fig. 1
PRISMA diagram.

Supplementary Fig. 2
Risk of bias assessment.

Supplementary Fig. 3
Funnel plot.

REFERENCES

1. O'Keefe JH Jr, Harris WS. From Inuit to implementation: omega-3 fatty acids come of age. Mayo Clin Proc 2000;75:607-614. PUBMED | CROSSREF
2. Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB, et al. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. N Engl J Med 2019;380:11-22. PUBMED | CROSSREF
3. Risk and Prevention Study Collaborative Group, Roncaglioni MC, Tombesi M, Avanzini F, Barlera S, Caimi V, et al. n-3 fatty acids in patients with multiple cardiovascular risk factors. N Engl J Med 2013;368:1800-1808. PUBMED | CROSSREF
4. Djoussé L, Cook NR, Kim E, Bodar V, Walter J, Bubes V, et al. Supplementation with vitamin D and omega-3 fatty acids and incidence of heart failure hospitalization: VITAL-Heart Failure. Circulation 2020;141:784-786. PUBMED | CROSSREF
5. Mehra MR, Lavie CJ, Ventura HO, Milani RV. Fish oils produce anti-inflammatory effects and improve body weight in severe heart failure. J Heart Lung Transplant 2006;25:834-838. PUBMED | CROSSREF
6. Kohashi K, Nakagomi A, Saiki Y, Morisawa T, Kosugi M, Kusama Y, et al. Effects of eicosapentaenoic acid on the levels of inflammatory markers, cardiac function and long-term prognosis in chronic heart failure patients with dyslipidemia. J Atheroscler Thromb 2014;21:712-729. PUBMED | CROSSREF
7. Kalstad AA, Myhre PL, Laake K, Tveit SH, Schmidt EB, Smith P, et al. Effects of n-3 fatty acid supplements in elderly patients after myocardial infarction: a randomized, controlled trial. Circulation 2021;143:528-539. PUBMED | CROSSREF
8. ORIGIN Trial Investigators, Bosch J, Gerstein HC, Dagenais GR, Díaz R, Dyal L, et al. n-3 fatty acids and cardiovascular outcomes in patients with dysglycemia. N Engl J Med 2012;367:309-318. PUBMED | CROSSREF
9. Tavazzi L, Maggioni AP, Marchioli R, Barlera S, Franzosi MG, Latini R, et al. Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. Lancet 2008;372:1223-1230. PUBMED | CROSSREF

10. Nodari S, Triggiani M, Campia U, Manerba A, Milesi G, Cesana BM, et al. Effects of n-3 polyunsaturated fatty acids on left ventricular function and functional capacity in patients with dilated cardiomyopathy. J Am Coll Cardiol 2011;57:870-879. PUBMED | CROSSREF
11. Kojuri J, Ostovan MA, Rezaian GR, Archin Dialameh P, Zamiri N, Sharifkazemi MB, et al. Effect of omega-3 on brain natriuretic peptide and echocardiographic findings in heart failure: double-blind placebo-controlled randomized trial. J Cardiovasc Dis Res 2013;4:20-24. PUBMED | CROSSREF
12. Welty FK. How do elevated triglycerides and low HDL-cholesterol affect inflammation and atherothrombosis? Curr Cardiol Rep 2013;15:400. PUBMED | CROSSREF
13. Greene SJ, Vaduganathan M, Lupi L, Ambrosy AP, Mentz RJ, Konstam MA, et al. Prognostic significance of serum total cholesterol and triglyceride levels in patients hospitalized for heart failure with reduced ejection fraction (from the EVEREST Trial). Am J Cardiol 2013;111:574-581. PUBMED | CROSSREF
14. Tribulova N, Szeiffova Bacova B, Egan Benova T, Knezl V, Barancik M, Slezak J. Omega-3 index and anti-arrhythmic potential of omega-3 PUFAs. Nutrients 2017;9:1191. PUBMED | CROSSREF
15. Wang C, Xiong B, Huang J. The role of omega-3 polyunsaturated fatty acids in heart failure: a meta-analysis of randomised controlled trials. Nutrients 2016;9:18. PUBMED | CROSSREF
16. Linssen GC, Bakker SJ, Voors AA, Gansevoort RT, Hillege HL, de Jong PE, et al. N-terminal pro-B-type natriuretic peptide is an independent predictor of cardiovascular morbidity and mortality in the general population. Eur Heart J 2010;31:120-127. PUBMED | CROSSREF
17. Barbarawi M, Lakshman H, Barbarawi O, Alabdouh A, Al Kasasbeh M, Djousse L, et al. Omega-3 supplementation and heart failure: a meta-analysis of 12 trials including 81,364 participants. Contemp Clin Trials 2021;107:106458. PUBMED | CROSSREF