Research Square

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Effects of cardiomyopeptidin on myocardial injury in ICU patients: a prospective randomized controlled pilot study

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Abstract

Background

Cardiomyopeptidin (CMP) is a peptide-based drug derived from the ventricular muscle of healthy young pigs. As a peptide mixture, it has been suggested to target myocardial cells, potentially aiding in the repair of damaged myocardium, reducing myocardial oxygen consumption, and improving cardiac function, as indicated by preliminary studies. This study aims to investigate whether CMP could improve clinical outcomes in critically ill patients with myocardial injury.

Methods

A randomized, placebo-controlled pilot study was conducted among patients with myocardial injury from Nanfang Hospital in China. Patients were enrolled from March 2024 to October 2024; the last date of follow-up was December 11th, 2024. Patients were randomized 1:1 to receive either CMP (1 mg/kg/day based on ideal body weight, dissolved in 50 mL 0.9% NaCl) or placebo (50 mL 0.9% NaCl). The primary end point was major adverse cardiac events (MACE) to 90 days. Secondary endpoints included 28-day all-cause death, 90-day all-cause death and changes in cardiac biomarkers (hsTnT, MB, NT-proBNP, LDH, α-HBDH, CK, and CK-MB), LVEF and APACHE II score. Changes in cardiac biomarkers over time and differences between groups were analyzed using generalized estimating equations (GEE), and differences in the rates of mortality and adverse cardiac events between the two groups were compared.

Results

A total of 234 patients were randomized and included in the primary analysis (CMP group n = 117, placebo group n = 117). A total of 19 (8.1%) patients experienced MACE during the study period, and lower incidence of MACE in the CMP with statistical significance (11.1% vs. 5.1%; HR = 0.47; *P* = 0.045). In addition, CMP had an effect on reducing creatine kinase-MB and N-terminal Pro B-type Natriuretic Peptide.

Conclusion

The findings of this trial demonstrate preliminary evidence suggesting CMP has a trend toward reducing MACE in patients with myocardial injury. Additionally, CMP may reduce cardiac biomarkers, which warrants investigation to explore its further therapeutic benefits in these patients.

Trial registration

ClinicalTrials.gov, NCT06117046. Registered 14 September 2023.

Introduction

Myocardial injury is common among ICU patients with conditions such as sepsis, respiratory failure, shock, or pulmonary embolism. The Fourth Edition of the Universal Definition of Myocardial Infarction (2018) defines myocardial injury as an elevation in cardiac troponin (cTn) levels that exceeds the 99th percentile of healthy adults, in the absence of myocardial ischemia[1]. Studies indicate that approximately 50% of critically ill ICU patients admitted for non-cardiac reasons experience myocardial injury and/or infarction, which is strongly associated with higher in-hospital mortality and is independently predictive of poor prognosis[2, 3]. Currently, the management of myocardial injury in the ICU primarily relies on supportive care and the improvement of cardiac function, with insufficient evidence for targeted therapeutic strategies.

Cardiomyopeptidin (CMP), a peptide drug extracted from the ventricular muscle of healthy young pigs, is suggested to target myocardial cells. It facilitates the repair of damaged myocardium, reduces myocardial oxygen consumption, and improves cardiac function as a peptide-based drug[4–6]. Animal pharmacokinetic studies have shown that CMP follows a two-compartment model after intravenous injection, with a rapid distribution phase and a slower elimination phase. It is widely distributed in tissues, with the highest concentrations in kidneys, followed by liver, heart, muscle, and brain, and it does not easily cross the blood-brain barrier. Main excretion is through urine, with a total clearance of approximately 82.7% of the administered dose. High-resolution mass spectrometry (HRMS) was used to identify the peptides in CMP, and it was found that CMP contains 799 peptides derived from 70 proteins. Among these, 10 peptides with a PeptideRanker score ≥ 0.80 were identified as having significant bioactivities, including angiotensin-converting enzyme inhibition (ACEi), dipeptidyl peptidase-4 inhibition (DPP4i), and antioxidant activity (AO), which support the rationale for its use in cardiac care. Chinese scholars have conducted several studies on the efficacy of CMP, and preliminary results suggest that it may improve cardiac function in patients with myocardial infarction and myocardial injury. A previous cohort study shows that the use of CMP was associated with lower in-hospital mortality and fewer major adverse cardiac events, particularly among those with elevated high-sensitivity troponin T (hsTnT) levels and lower Acute Physiology and Chronic Health Evaluation II (APACHE II) scores. Notably, a stronger correlation was observed in patients without pre-existing heart disease[7]. However, systematic research on CMP is still insufficient at present. Its long-term efficacy, mechanism of action, and applicability in different patient populations need further verification.

This study aims to preliminarily investigate the cardioprotective effects of CMP in ICU patients with myocardial injury through a prospective, single-blind, randomized controlled trial. The research seeks to provide evidence-based guidance for the clinical application of CMP and assess their potential to improve patient outcomes.

Materials and Methods

Study Design

This single-center, single-blind, randomized controlled pilot study. The study adhered to medical ethical standards and has been approved by the hospital ethics committee (NFEC-2023-060). This study was conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. No

important changes were made to the eligibility criteria, intervention, prespecified outcomes, or statistical analyses after trial commencement. The study has been registered on ClinicalTrials.gov (NCT06117046). This trial was reported in accordance with the CONSORT guidelines.

Study Population

Patients were recruited in the ICU and screened to determine whether they met the following criteria: age over 18 years, hsTnT greater than 0.014 ng/mL on the first measurement after ICU admission, and during the ICU stay, the patients or their legal representative voluntarily signed the informed consent form. Considering that the protective effect of CMP was more pronounced in the subgroup of patients without underlying heart disease in the retrospective study, various types of organic heart diseases that may have caused chronic myocardial injury in the past were excluded. Additionally, since myocardial injury is diagnosed based on troponin levels, patients with acute ischemic stroke or chronic kidney disease were excluded to avoid confounding factors that could elevate troponin levels due to non-cardiac causes. The other exclusion criteria consisted of: (1) Patients with an expected ICU length of stay (LOS) of less than 48 hours; (2) Patients previously diagnosed with acute coronary syndrome, chronic cardiomyopathy, cor pulmonale, acute myocarditis, cardiac tamponade, or other conditions known to cause chronic myocardial injury; (3) Patients who underwent cardiopulmonary resuscitation and/or defibrillation before admission; (4) Patients diagnosed with acute myocardial infarction; (5) Patients diagnosed with acute ischemic stroke; (6) Patients diagnosed with stage 5 chronic kidney disease; (7) Pregnant or breastfeeding patients; (8) Participation in other interventional studies.

Randomization, Blinding and Intervention

Using R version 4.2.1 statistical software, we generated a block randomization protocol with a block size of 8 and randomly assigned eligible participants (1:1) to receive either CMP or matched placebo. The allocation sequence was placed in sequentially numbered, opaque, sealed envelopes by a research coordinator who was not involved in participant recruitment or outcome assessment. After eligibility was confirmed and written informed consent was obtained, the next envelope in sequence was opened to assign the participant to the intervention or placebo group. This study employs a single-blind design, where only the participants and their families are unaware of the treatment assignments. Investigators and clinical healthcare providers will be informed of the treatment allocations. Given the pilot nature of this single-center trial and the absence of stratified randomization, chance imbalances in baseline characteristics were anticipated.

Following randomization, participants in the trial group will receive CMP treatment. The dosing regimen follows the recommended dosage of 1 mg/kg/day as outlined in the product manual, with doses calculated based on the ideal body weight. The drug will be dissolved in 50 mL of 0.9% NaCl solution and administered via infusion at a rate of 1 to 2 mL per minute, once daily for 3 consecutive days. The placebo group will receive 50 mL of 0.9% NaCl.

Regarding the reproducibility of CMP batches, although different batches of CMP were used for the patients in the study, the manufacturer provided testing reports for all the batches used during the research period. These reports confirmed that the peptide content was stable across the different batches. The chromatographic profiles obtained through liquid chromatography indicated that the peptide composition remained consistent across batches.

Outcomes

The primary efficacy outcome was major adverse cardiac events (MACE)[8], defined as new-onset of myocardial infarction, heart failure, cardiac arrest and cardiac death, within 90 days. MACEs were adjudicated by multiple doctors from the research team, who were aware of treatment assignments.

Secondary endpoints included in-hospital mortality, 28-day all-cause mortality, 90-day all-cause mortality, duration of ICU and hospital stays, changes in the Left Ventricular Ejection Fraction (LVEF) and APACHE II score on day 7. LVEF was determined using the Simpson method[9]. Exploratory outcomes included change in Myoglobin (MB), hsTnT, N-terminal Pro B-type Natriuretic Peptide (NT-Pro BNP), Lactate (Lac), Lactate Dehydrogenase (LDH), Alpha-Hydroxybutyrate Dehydrogenase (α-HBDH), Creatine Kinase (CK), Creatine Kinase-MB (CKMB) at 3, 7 and 14 days, compared with baseline values obtained at screening.

Sample size

This study was designed as a single-center randomized pilot trial to evaluate feasibility and to obtain preliminary estimates of event rates and effect sizes to inform the design of a future definitive, adequately powered multicenter trial[10]. Because reliable prior data on the primary endpoint incidence and the expected effect size of CMP in ICU patients with myocardial injury were unavailable, a conventional a priori sample size calculation would have relied on highly uncertain assumptions and was considered unsuitable for this pilot design. Therefore, we planned to enroll approximately 200 participants within the prespecified recruitment window based on site feasibility and the precision required to estimate key parameters.

Statistical analyses

All participants who were grouped after randomization were included in the analysis according to the intention-to-treat (ITT) principle, serving as the primary analysis set for this study. Categorical variables are presented as frequencies and percentages, continuous variables as medians (IQR). No imputation was needed for the primary outcome as no data were missing. Missing data for other outcomes were replaced using the Last Observation Carried Forward (LOCF) method. MACE and mortality were analyzed using a Cox model. The prespecified adjusted model included baseline age, APACHE II score, and baseline hsTnT. Furthermore, potential bias factors were corrected for using multivariate analysis, ensuring the robustness of the results. And generalized estimating equations (GEE) models were applied for dynamic marker changes. Sensitivity analysis of primary outcome for participants lost to follow-up was conducted using both best-case and worst-case imputation methods. Per-protocol analyses, including only those who fully

adhered to the protocol, were also conducted. A two-sided *P*-value < 0.05 was statistically significant. Analyses were performed in R (Version 4.3.3). The trial protocol is available from the corresponding author upon reasonable request. No separate statistical analysis plan was publicly deposited; the prespecified statistical methods are described in the trial protocol and in the Statistical analyses section of this manuscript.

Results

Baseline Characteristics

This study was conducted at Nanfang Hospital, Southern Medical University in China, with screening and enrollment spanning from March 2024 to October 2024. During this study, a total of 646 patients developed myocardial injury, of which 589 met the inclusion criteria. Ultimately, 234 patients entered the randomization phase. These 234 participants were included in the intention-to-treat analysis set (ITT), with 117 receiving CMP and 117 receiving standard treatment (Fig. 1). During the study, one participant in the placebo group experienced an acute myocardial infarction and subsequently received CMP. A total of 212 participants who did not have any major protocol violations and completed all follow-ups were included in the per-protocol (PP) analysis set (Table S1).

The personal and clinical characteristics were generally balanced between the two groups at baseline (Table 1), although some differences, such as baseline hsTnT and heart failure prevalence. The median age was 61years (interquartile range (IQR) 49–73) and 72.2% of participants (n = 169) were men. The median APACHE II score was 14 (IQR 10–18), indicating disease severity. 37.2%(n = 87) of the participants suffered from hypertension, and 17.5% (n = 41) of the participants had heart failure when they were admitted to the ICU (Table 1). All these patients were acute heart failure.

Table 1
Patient characteristics before enrollment and treatment during ICU in each group (ITT population).

Characteristics	Overall (n = 234)	CMP group (n = 117)	Placebo group (n = 117)	*P*-value
Age	61.0[49.0,73.0]	62.0[51.0,74.0]	60.0[49.0,70.0]	0.469
Gender (Male)	169(72.2)	84(71.8)	85(72.6)	1.000
Co-morbidities, n (%)				
Hypertension	87(37.2)	36(30.8)	51(43.6)	0.058
Diabetes	69(29.5)	36(30.8)	33(28.2)	0.774
Heart failure	41(17.5)	29(24.8)	12(10.3)	0.006
Arrhythmia	33(14.1)	20(17.1)	13(11.1)	0.260
Chronic pulmonary	50(21.4)	20(17.1)	30(25.6)	0.151
Acute kidney injury	24(10.3)	16(13.7)	8(6.8)	0.131
Chronic liver disease	37(15.8)	18(15.4)	19(16.2)	1.000
Cerebrovascular disease	52(22.2)	29(24.8)	23(19.7)	0.432
Malignant tumor	54(23.1)	24(20.5)	30(25.6)	0.438
Smoking	82(35.0)	40(34.2)	42(35.9)	0.891
Vital Signs				
HR	91.0[76.0,105.0]	91.0[75.0,105.0]	91.0[77.0,105.0]	0.976
SBP (mmHg)	131.0[114.0,147.0]	129.0[112.0,144.0]	132.0[118.0,149.0]	0.126
DBP (mmHg)	65.0[58.0,74.0]	64.0[57.0,72.0]	68.0[59.0,77.0]	0.076
MAP (mmHg)	88.0[78.0,97.0]	84.0[77.0,94.0]	91.0[78.0,99.0]	0.027
RR	17.0[15.0,22.0]	18.0[15.0,23.0]	17.0[15.0,21.0]	0.170

All variables are summarized in the intention-to-treat (ITT) population (all randomized participants).

HR: Heart Rate. SBP: Systolic Blood Pressure. DBP: Diastolic Blood Pressure. MAP: Mean Arterial Pressure. RR: Respiratory Rate. APACHE II: Acute Physiology and Chronic Health Evaluation II. SPO2: Peripheral Capillary Oxygen Saturation. PaO2: Partial Pressure of Oxygen in Arterial Blood. PaCO2: Partial Pressure of Carbon Dioxide in Arterial Blood. P/F: PaO2 to FiO2 Ratio. Lac: Lactate. WBC: White Blood Cell Count. HGB: Hemoglobin. PLT: Platelet. SCr: Serum Creatinine. BUN: Blood Urea Nitrogen. ALT: Alanine Aminotransferase. AST: Aspartate Aminotransferase. hsTnT: High-sensitivity Troponin T. MB: Myoglobin. NT-ProBNP: N-terminal Pro B-type Natriuretic Peptide. LDH: Lactate Dehydrogenase. α-HBDH: Alpha-Hydroxybutyrate Dehydrogenase. CK: Creatine Kinase. CKMB: Creatine Kinase-MB. LVEF: Left Ventricular Ejection Fractio.

Characteristics	Overall (n = 234)	CMP group (n = 117)	Placebo group (n = 117)	*P*-value
APACHE II	14.0[10.3,18.0]	15.0[10.0,19.0]	14.0[11.0,17.0]	0.405
Laboratory Data				
SPO_2 (%)	100.0[99.0,100.0]	100.0[99.0,100.0]	100.0[98.0,100.0]	0.132
PaO_2 (mmHg)	121.5[92.9,158.0]	133.0[98.7,165.0]	115.0[90.1,151.0]	0.029
$PaCO_2$ (mmHg)	37.2[33.4,41.8]	37.8[34.2,42.1]	36.6[32.4,41.7]	0.173
P/F (mmHg)	299.0[214.0,404.0]	326.0[224.0,404.0]	288.0[210.0,398.0]	0.421
Lac (mmol/L)	1.2[0.8,1.9]	1.1[0.8,1.8]	1.3 [0.8,2.1]	0.291
WBC ($*10^9$/L)	10.94[7.25,15.27]	11.79[8.49,15.95]	9.35[6.58,14.13]	0.010
HGB (g/L)	85.0[67.0,105.0]	89.0[70.0,104.0]	78.0[65.0,106.0]	0.196
PLT ($*10^9$)	160.5[74.5,247.0]	159.0[87.0,274.0]	163.0[66.0,230.0]	0.090
SCr (mg/dL)	94.0[66.0,156.8]	97.0[65.0,159.0]	93.0[66.0,150.0]	0.689
BUN (mmol/L)	9.4[6.2,16.1]	9.8[6.7,17.1]	9.1[5.8,15.9]	0.373
ALT (U/L)	35.5[22.0,70.8]	36.0[24.0,71.0]	35.0[20.0,63.0]	0.618
AST (U/L)	28.0[13.3,66.8]	29.0[13.0,78.0]	27.0[14.0,55.0]	0.852
Cardiac Biomarkers				
hsTnT (ng/mL)	0.05[0.03,0.10]	0.06[0.03,0.16]	0.04[0.02,0.07]	0.001
MB (ng/mL)	154.5[66.2,416.8]	174.0[76.5,401.0]	135.0[46.7,446.0]	0.303
NT-ProBNP (pg/mL)	1231.5[331.3,4087.8]	1435.0[384.0,4382.0]	799.0[304.0,3305.0]	0.224
LDH (U/L)	274.0[191.3,446.0]	283.0[200.0,410.0]	262.0[184.0,485.0]	0.846
αHBDH (U/L)	200.0[141.5,305.8]	210.0[155.0,300.0]	188.0[136.0,310.0]	0.442
CK (U/L)	115.0[41.0,367.8]	108.0[35.0,398.0]	123.0[44.0,309.0]	0.771

All variables are summarized in the intention-to-treat (ITT) population (all randomized participants).

HR: Heart Rate. SBP: Systolic Blood Pressure. DBP: Diastolic Blood Pressure. MAP: Mean Arterial Pressure. RR: Respiratory Rate. APACHE II: Acute Physiology and Chronic Health Evaluation II. SPO2: Peripheral Capillary Oxygen Saturation. PaO2: Partial Pressure of Oxygen in Arterial Blood. PaCO2: Partial Pressure of Carbon Dioxide in Arterial Blood. P/F: PaO2 to FiO2 Ratio. Lac: Lactate. WBC: White Blood Cell Count. HGB: Hemoglobin. PLT: Platelet. SCr: Serum Creatinine. BUN: Blood Urea Nitrogen. ALT: Alanine Aminotransferase. AST: Aspartate Aminotransferase. hsTnT: High-sensitivity Troponin T. MB: Myoglobin. NT-ProBNP: N-terminal Pro B-type Natriuretic Peptide. LDH: Lactate Dehydrogenase. α-HBDH: Alpha-Hydroxybutyrate Dehydrogenase. CK: Creatine Kinase. CKMB: Creatine Kinase-MB. LVEF: Left Ventricular Ejection Fractio.

Characteristics	Overall (n = 234)	CMP group (n = 117)	Placebo group (n = 117)	*P*-value
CKMB (U/L)	13.0[9.0,21.0]	13.0[9.0,21.0]	12.0[9.0,20.0]	0.919
LVEF (%)	55.0[49.8,60.0]	55.0[50.0,60.0]	55.0[48.6,60.0]	0.372
All variables are summarized in the intention-to-treat (ITT) population (all randomized participants).				
HR: Heart Rate. SBP: Systolic Blood Pressure. DBP: Diastolic Blood Pressure. MAP: Mean Arterial Pressure. RR: Respiratory Rate. APACHE II: Acute Physiology and Chronic Health Evaluation II. SPO2: Peripheral Capillary Oxygen Saturation. PaO2: Partial Pressure of Oxygen in Arterial Blood. PaCO2: Partial Pressure of Carbon Dioxide in Arterial Blood. P/F: PaO2 to FiO2 Ratio. Lac: Lactate. WBC: White Blood Cell Count. HGB: Hemoglobin. PLT: Platelet. SCr: Serum Creatinine. BUN: Blood Urea Nitrogen. ALT: Alanine Aminotransferase. AST: Aspartate Aminotransferase. hsTnT: High-sensitivity Troponin T. MB: Myoglobin. NT-ProBNP: N-terminal Pro B-type Natriuretic Peptide. LDH: Lactate Dehydrogenase. α-HBDH: Alpha-Hydroxybutyrate Dehydrogenase. CK: Creatine Kinase. CKMB: Creatine Kinase-MB. LVEF: Left Ventricular Ejection Fractio.				

After randomization, 30.8% (n = 72) participants received continuous renal replacement therapy (CRRT), and 2.1% (n = 5) participants received extracorporeal membrane oxygenation (ECMO) support during their ICU stay (Table 2). The average fluid therapy administered to the participants was a positive fluid balance of 291.3mL (IQR − 65.7-674.7) per day. The total dose of norepinephrine bitartrate administered to the participants was 33.9 mg (IQR 2.1-134.57).

Table 2
Care Management of the Study Population in each group (ITT population).

Characteristics	Overall (n = 234)	CMP group (n = 117)	Placebo group (n = 117)	*P*-value
CRRT, n(%)	72(30.8)	41(35.0)	31(26.5)	0.202
ECMO, n(%)	5(2.1)	4(3.4)	1(0.9)	0.366
Input (ml/day)	2878.0[2200.8,3603.4]	3110.8[2398.5,3702.2]	2709.4[1951.1,3372.4]	0.004
Output (ml/day)	2614.2[1873.7,3230.6]	2697.4[2078.1,3262.0]	2508.2[1535.2,3137.1]	0.022
Volume (ml/day)	291.3[-65.7,674.7]	312.1[40.4,678.5]	235.5[-164.1,665.1]	0.002
rhBNP (mg)	0.2[0.0,6.6]	2.0[0.0, 8.0]	0.0[0.0,4.6]	0.008
Phosphocreatine, n(%)	5(2.1)	4(3.4)	1(0.9)	0.171
Coenzyme Q10, n(%)	3(1.3)	2(1.7)	1(0.9)	0.562
Equivalent Norepinephrine Base (mg)	33.9[2.1, 134.57]	40.0[4.7, 137.8]	33.1[0.0, 112.3]	0.141
ACEI, n(%)	1 (0.4)	1 (0.9)	0 (0.0)	NA

CRRT: Continuous Renal Replacement Therapy. ECMO: Extracorporeal Membrane Oxygenation. rhBNP: Recombinant Human Brain Natriuretic Peptide. NA indicates no variation in either group; statistical test not applicable.

Primary Outcome

In the primary outcome of MACE, a statistically significant reduction was observed with CMP treatment. Within the ITT population, the overall incidence of 90-day MACE was significantly lower in the CMP group (5.1%) compared to the placebo group (11.1%), with a hazard ratio (HR) of 0.47 (95% CI: 0.16–0.92; p = 0.045). Individual components of the primary end point, including cardiac death (CMP vs placebo: 1.7% vs 5.1%), myocardial infarction (1.7% vs 2.6%), heart failure (1.7% vs 7.7%), cardiac arrest (1.7% vs 1.7%). Arrhythmia (6.0% vs 7.7%) was analyzed and reported separately as an exploratory cardiovascular event. Similar results were also found in the per-protocol analyses (supplementary appendix table S1). Figure 3 illustrate the correlation between CMP use and the primary study outcome across each subgroup. The treatment effect was generally consistent with the primary ITT result across most subgroups. In comparison to subjects with an APACHE II score over 15, those with lower scores exhibited a more pronounced correlation trend between CMP use and reductions in MACE incidence. Additionally, in the sepsis-related myocardial injury subgroup, CMP demonstrated a trend toward a reduction in MACE (HR = 0.14, P = 0.006), which warrants further exploration in larger studies.

Secondary Outcomes

In-hospital mortality occurred in 10 participants (8.5%) in the CMP group and 16 (13.7%) in the placebo group (HR = 0.52, 95% CI 0.21–1.31, *P* = 0.170) (Table 3). There were no significant differences in all-cause mortality between the CMP group and placebo group at 28 days (HR: 1.10, 95% CI: 0.68–1.80, *P* = 0.690) and 90 days (HR: 0.98, 95% CI: 0.64–1.51, *P* = 0.930) after randomization (Table 3 &Table S2). The CMP group had a longer ICU stay but a shorter total hospital stay compared to the placebo group. A linear regression model suggested a potential association between CMP use and reduced total hospital stay (β = 0.05, *P* = 0.602), but this result was not significant. No CMP-related adverse events were observed, and detailed results are provided in Table S4.

Table 3
Clinical outcome and the association between cardiomyopeptidin and outcomes in ITT

Clinical outcome	Group		Effect Size (95% CI)	*P*-value
	CMP group (n = 117)	Placebo group (n = 117)		
Primary Outcomes				
MACE[b]	6 (5.1)	13 (11.1)	0.47(0.16,0.92)	0.045
Secondary Outcomes				
Cardiac death[b]	2 (1.7)	6 (5.1)	0.31(0.01,2.33)	0.631
Myocardial infarction[b]	2 (1.7)	3 (2.6)	0.57(0.09,3.12)	0.523
Heart failure[b]	2 (1.7)	9 (7.7)	0.25(0.02,1.30)	0.148
Cardiac arrest[b]	2 (1.7)	2 (1.7)	1.17(0.21,6.61)	0.852
Arrhythmia[b]	7 (6.0)	9 (7.7)	0.81(0.28,2.30)	0.699
In-hospital mortality[a]	10 (8.5)	16 (13.7)	0.52(0.21,1.31)	0.170
28-day mortality[a]	34 (29.1)	35 (29.9)	1.10(0.68,1.80)	0.690
90-day mortality[a]	41 (35.0)	43 (36.8)	0.98(0.64,1.51)	0.930
ICU LOS, (days)[c]	11.5[5.4,19.0]	8.3[4.8,14.0]	1.46(0.33,6.39)	0.168
Hospital LOS, (days)[c]	17.9[11.0,32.9]	19.2[9.9,28.5]	0.05(0.01,6.52)	0.278

[a] Data are expressed as No. (%) of patients. The effect value of mortality is HR value.

[b] Data are expressed as No. (%) of patients. The effect value of MACE and various adverse cardiac events is HR value. Hazard ratios and 95% confidence intervals for 90-day MACE and mortality were estimated using Cox proportional hazards models. The prespecified adjusted model included baseline age, APACHE II score, and baseline hsTnT.

[c] The effect value of total hospital stays and ICU stays is β value.

Cardiac Biomarkers

Exploratory analyses of cardiac markers showed that after treatment both study arms showed a similar change in MB, NT-proBNP, LDH, α-HBDH, CK, and CK-MB (Fig. 4). Within 14 days of enrollment, hsTnT levels in both the placebo and CMP groups remained stable compared to baseline, with no significant differences

observed between the groups at each time point (Table S3 and Fig. 4). As for longitudinal dynamic change of these markers, an ancillary finding was a significant improvement in LVEF over the 14-day follow-up period and showed differences between CMP and placebo.

Discussion

This study employed a randomized controlled pilot study design to investigate the cardioprotective effects of CMP in ICU patients with myocardial injury. The results demonstrated that CMP was associated with a lower incidence of MACE within 90 days compared with the placebo group. Additionally, the study revealed a trend toward decreased levels of specific cardiac biomarkers, including NT-ProBNP and CKMB.

CMP is widely used as an adjunctive therapy in the perioperative management of cardiac surgery patients with myocardial injury in China. Using the BIOPEP-UWM database tool, 10 peptides with a Peptide Ranker score of ≥ 0.80 were predicted in CMP. These peptides are rich in amino acid sequences with ACEI activity, dipeptidyl peptidase-4 inhibitory (DPP-4i) activity, and antioxidant activity. Previous studies have shown that ACEI drugs can improve long-term survival in MI patients[11, 12], and DPP-4i drugs can reduce the incidence of MACE in type 2 diabetes patients[13]. It is speculated that CMP may exert its cardioprotective effects through multiple pathways targeting various causes of myocardial injury in critical patients. However, it is acknowledged that "myocardial injury" in the ICU is a broad umbrella term encompassing acute or chronic insults of cardiac or non-cardiac origin (ischemic or non-ischemic). This heterogeneity presents a challenge in precisely defining the target population and interpreting the consistency of treatment effects, which is an inherent limitation of this exploratory study design.

This study further investigates the cardioprotective role of CMP in critically ill patients. One key exploratory finding was a statistically significant 6% numerical reduction in the incidence of MACE in the experimental group compared to the placebo group. Among the various cardiovascular events, heart failure showed the most pronounced difference between the two groups. Heart failure is a common complication in critically ill patients and a leading cause of morbidity and mortality in cardiovascular disease[14, 15]. It is closely linked to poor prognosis in ICU patients. In this study, a numerically lower incidence of heart failure (6%) was observed in the experimental group, and NT-ProBNP, a biomarker strongly associated with heart failure, decreased more significantly in this group. This observed trend towards reduced heart failure may be associated with the numerically lower mortality in the CMP group, although causality cannot be inferred given the non-significant differences. The experimental group showed a numerical 5.2% reduction in in-hospital mortality versus the placebo group, a difference not statistically significant. Subgroup analysis suggested CMP might be more beneficial for patients with sepsis. Regarding hospital and ICU stay duration, the CMP group had a longer ICU stay but a shorter total hospital stay compared to the placebo group. This may reflect a trend towards faster recovery after the ICU phase, though these differences were not statistically significant.

In this study, hsTnT was used as the diagnostic biomarker, and hsTnT, along with other cardiac biomarkers, was monitored at four time points over 13 days. HsTnT showed no significant changes in either group, possibly due to persistent systemic infection or shock in ICU patients. Apart from cTn, CK, CKMB, and LDH

are also biomarkers associated with myocardial injury[16, 17]. Elevated levels of CK, CKMB, and LDH are linked to higher risks of severe disease or ICU admission, and LDH also serves as a prognostic marker for mortality[18]. In this study, CK, CKMB, and LDH levels decreased over 13 days, with a more pronounced reduction in the experimental group. The study also explored the effects of CMP on left ventricular ejection fraction (LVEF) and found that CMP was associated with improved heart function in participants, supporting the need for further investigation into its clinical utility. While LVEF showed a favorable trend in the CMP group, these findings should be interpreted cautiously because single-time-point echocardiographic measures in ICU patients are influenced by loading conditions, hemodynamic support, and measurement variability.

The study was not powered for mechanistic inference or for most exploratory endpoints. As a pilot trial, the study was not designed to provide definitive evidence regarding the biological mechanism of CMP. Accordingly, we present the MACE result as a preliminary clinical signal and the biomarker/function results as exploratory and inconclusive, warranting confirmation in a larger, adequately powered trial with more rigorous cardiac phenotyping and endpoint adjudication.

Limitations

The single-blind design (blinding only patients) is a limitation, potentially introducing assessment bias in evaluating cardiovascular events, including MACE, as well as LVEF measurements. MACE events were adjudicated by multiple doctors from the research team who were aware of treatment assignments, which could have influenced the interpretation of these outcomes. Although standardized clinical diagnostic criteria were used and discussions among doctors were held to ensure accuracy, the lack of an independent adjudication committee for MACE events introduces the potential for assessment bias and performance bias. This ICU -setting feasible design, though practical, may introduce bias. Additionally, the lack of formal sample size calculation and the inclusion of 234 patients limited the statistical robustness, resulting in non-significant trends in mortality. A post-hoc power analysis revealed that the study had a power value of 0.39460, indicating that the study was underpowered to detect clinically meaningful differences in the primary endpoints. The effective and safe CMP dosage for ICU patients is unclear. The study used the minimum label dose without dose-finding exploration, which may be one of the reasons why some outcomes did not reach statistical significance. Moreover, multiple secondary and exploratory endpoints were analyzed without correction for multiple comparisons, increasing the risk of false-positive findings. This limitation should be acknowledged, and the secondary/exploratory findings require confirmation in future studies.

Conclusion

This study investigated the cardioprotective effects of CMP in ICU patients with myocardial injury not related to organic heart disease. The results indicated that CMP could reduce MACE in patients with myocardial injury. Although CMP showed a tendency to decrease in-hospital mortality and the incidence of heart failure, these findings were not statistically significant. And CMP could reduce levels of cardiac

biomarkers, such as NT-proBNP and CK-MB. The conclusions of this study require further validation through large-scale, double-blind, randomized controlled trials.

Abbreviations

PaO2	arterial oxygen partial pressure
PaCO2	arterial carbon dioxide partial pressure
P/F	Oxygenation Index
Lac	lactic acid
WBC	White Blood Cell Count
HGB	hemoglobin
PLT	platelet count
SCr	serum creatinine
BUN	Blood Urea Nitrogen
ALT	alanine aminotransferase
AST	aspartate aminotransferase
LDH	Lactate Dehydrogenase
α-HBDH	α Hydroxybutyrate dehydrogenase
CK	Creatine Kinase
CK-MB	creatine kinase isoenzymes
MB	myoglobin
NT-ProBNP	N-terminal pro-B-type natriuretic peptide
hsTnT	high sensitive troponin T
ICU	Intensive Care Unit
PCI	percutaneous coronary intervention
HR	Hazard Ratio
CI	Confidence Interval

CMP Cardiomyopeptidin

MACE major adverse cardiovascular event

LOS length of stay

GEE generalised estimating equations

cTn cardiac troponin

ECMO extracorporeal membrane oxygenation

rhBNP human brain natriuretic peptide

ARDS Acute Respiratory Distress Syndrome

PMI Perioperative myocardial infarction/injury

CRRT Continuous Renal Replacement Therapy

ITT intention-to-treat

LOCF Last Observation Carries Forward

GEE Generalized Estimating Equations

MCID minimal clinically important diffwerence

SVA Supraventricular arrhythmias

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Commission of Nanfang Hospital (No. NFEC-2023-060).

Consent for publication

Not applicable.

Availability of data and material

The datasets used in the present study are available from the first author and corresponding authors on reasonable request.

Competing interests

Not applicable.

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Authors' contributions:

L.J., H.H., C.Z. and Z.Z. designed the study and contributed to writing this manuscript. L.J., Q.Y., B.J., G.B., C.L.and Y.Y. collected data and L.J. analyzed data. Y.Y. and Y.J. provided critical revision of the article. All the authors provided final approval of the version submitted for publication.

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Figures

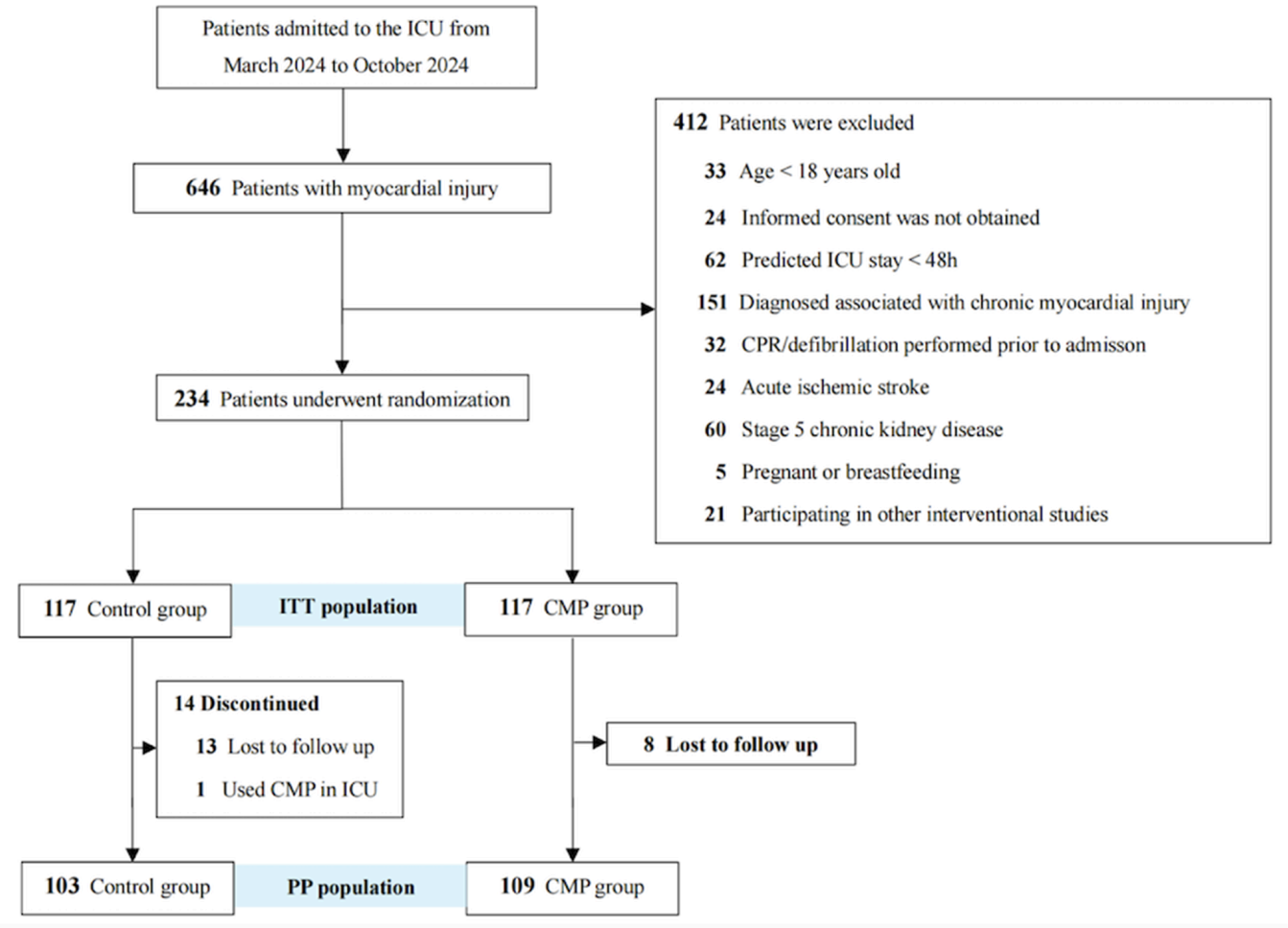


Figure 1. Flowchart of Study.

Figure 1

See image above for figure legend.

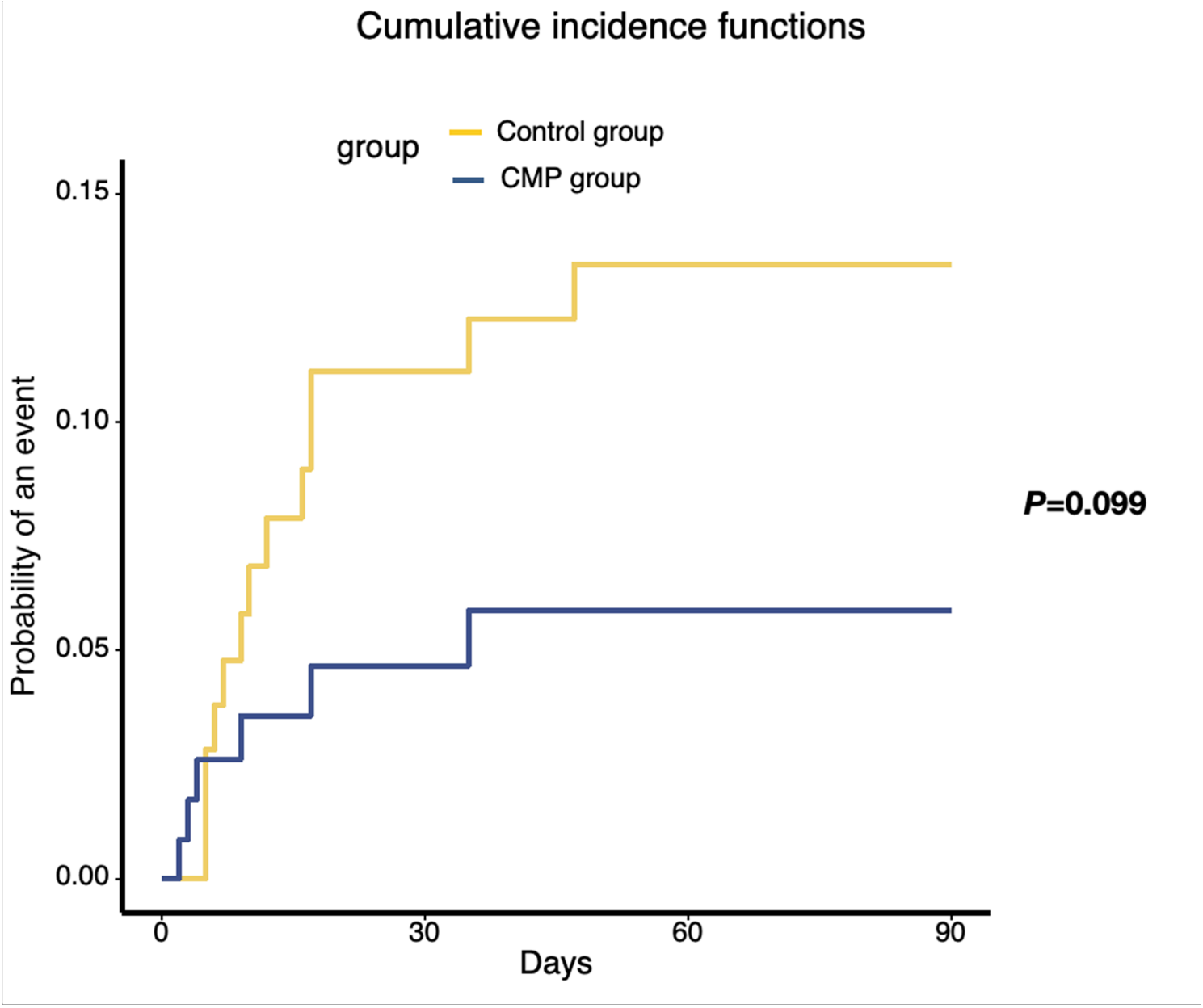


Figure 2

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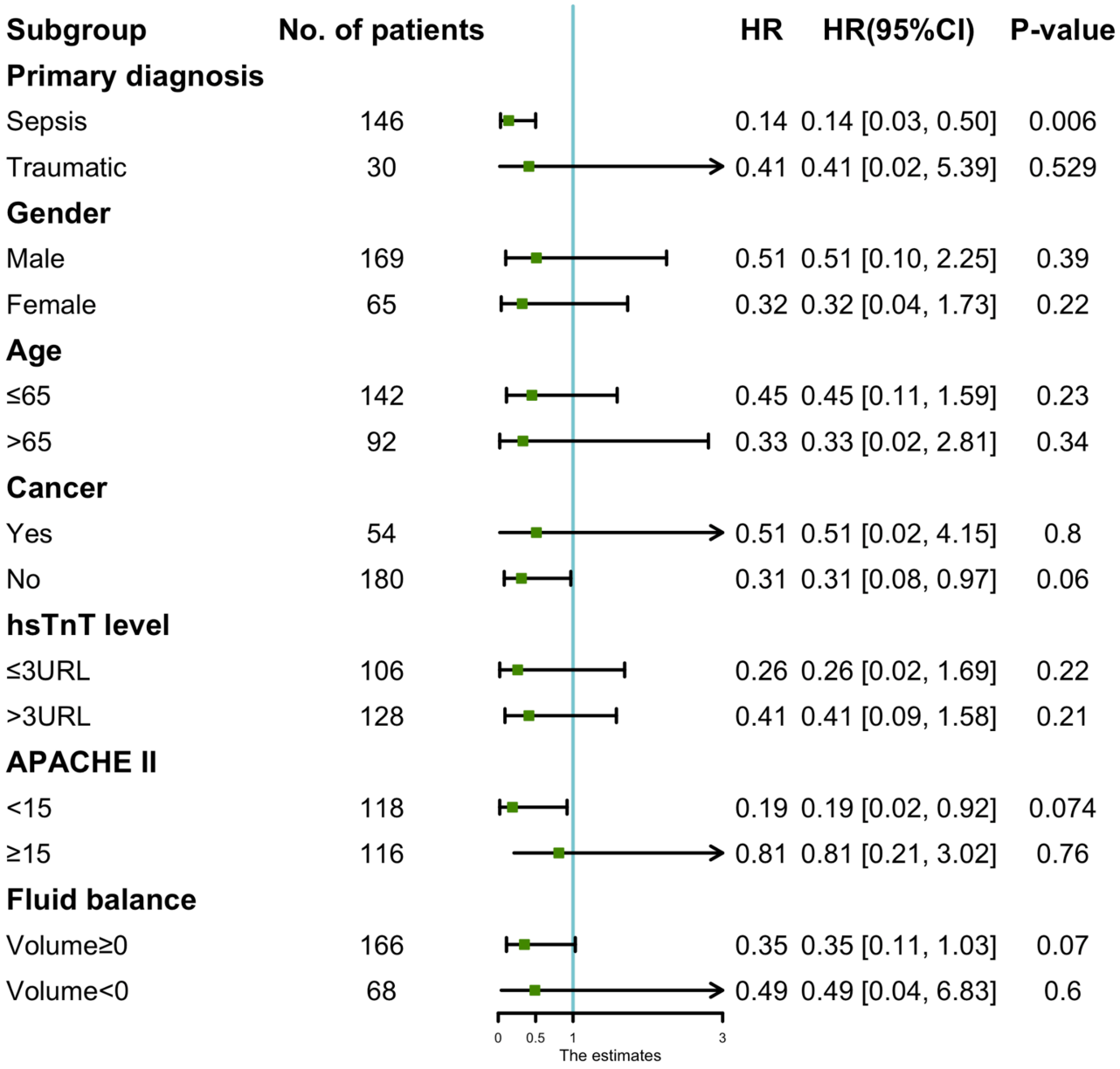


Figure 3

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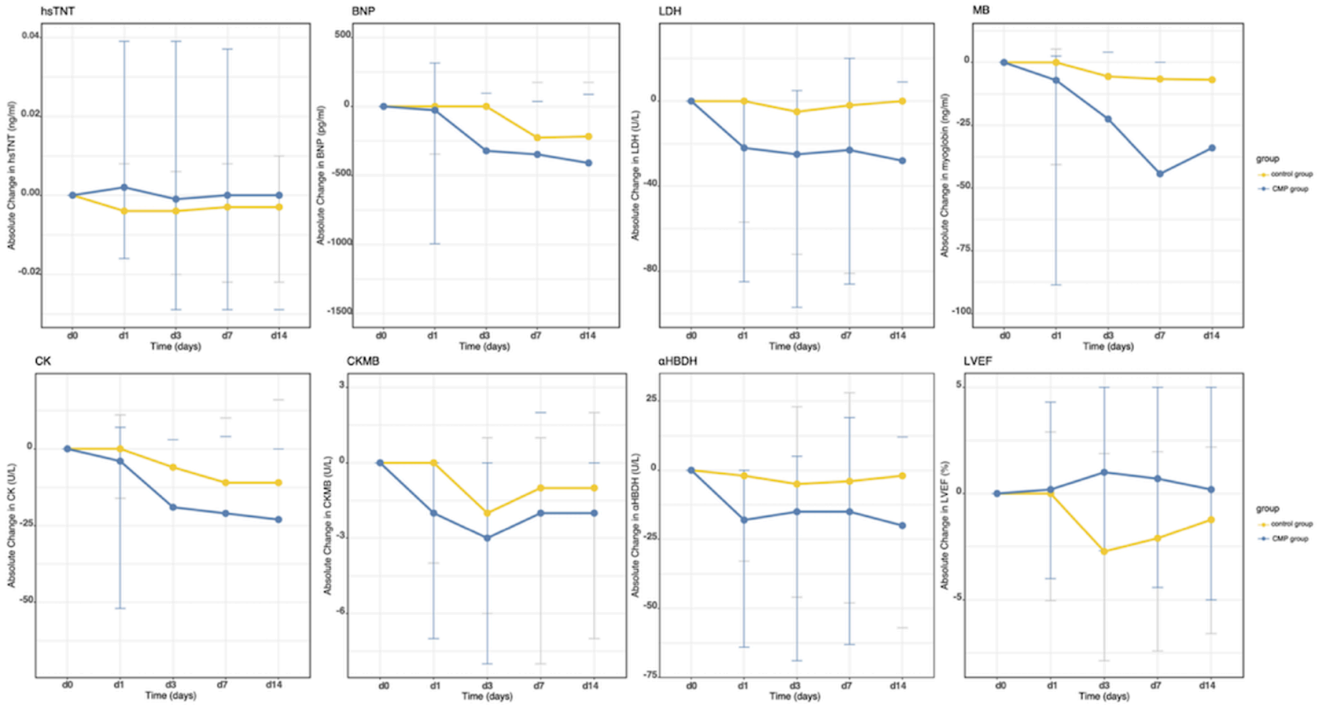


Figure 4. The variation trend of repeated measurement variables in each group

Figure 4

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