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Causal Association Between Heart Failure and Sepsis: Insights from Mendelian Randomization and Observational Studies

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Purpose: We aimed to identify the association between heart failure (HF) with sepsis and its mortality through Mendelian randomization (MR) and observational studies.

Patients and Methods: In MR study, we utilized public summary statistics from genome-wide association studies (GWAS). We conducted univariable, multivariable and network MR analyses to investigate causal relationships between HF and sepsis, and mediating roles of cytokines and growth factors. We performed an observational analysis using the MIMIC-IV database. Propensity score matching (PSM) and logistic regression models were employed to explore causal relationships between HF and sepsis, besides short-, medium-, and long-term mortality associated with sepsis.

Results: In univariable MR analysis, there was a causal relationship between genetically predicted HF (OR = 1.15, 95% CI = 1.02–1.29, P = 0.025) and sepsis. In multivariable and network MR analyses, βNGF was independently associated with sepsis. And it mediated 17.6% (95% CI 2.45–30.72%) of HF effect on sepsis. In the real-world observational study, acute on chronic diastolic (congestive) heart failure (DCHF) (OR = 1.59, 95% CI = 1.31–1.93, P < 0.001), acute DCHF (OR = 2.52, 95% CI = 1.61–3.95, P = 0.010), and acute diastolic heart failure (DHF) (OR = 1.52, 95% CI = 1.06–2.19, P = 0.024) after PSM were associated with occurrence of sepsis. Chronic systolic (congestive) heart failure (SCHF) was associated with increased 28-day (OR = 1.75, 95% CI = 1.06–2.91, P = 0.030), 1-year (OR = 1.80, 95% CI = 1.08–3.00, P = 0.023), and 2-year (OR = 1.86, 95% CI = 1.12–3.10, P = 0.018) mortality in sepsis.

Conclusion: Observational and MR analyses showed a causal relationship between HF and sepsis. Chronic SCHF was related to increased short/long-term mortality in sepsis. Our study indicated βNGF a key factor in HF-induced sepsis.

Keywords: βNGF, MIMIC-IV, PSM, GWAS

Introduction

Sepsis describes life-threatening organ dysfunction resulting from a dysregulated host response to infection. It is a global health priority affecting 55 million people worldwide and causing 11 million deaths annually,[1,2] placing a significant burden on global health systems. While sepsis can often be effectively prevented by identifying the causative pathogen and site of infection, in 30% to 70% of cases, the pathogen and its source remain unknown.[3–5] This uncertainty complicates the development of specific prevention strategies.

Heart failure (HF) is a clinical syndrome caused by structural or functional abnormalities of the heart, leading to the heart's inability to pump sufficient blood to meet the body's metabolic demands. Its clinical manifestations typically include shortness of breath, fatigue, and fluid retention (such as peripheral edema).[6] The pathophysiological process of

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HF is often accompanied by secondary damage to organ systems, including impaired intestinal barrier function and associated bacterial translocation.[7–9] These mechanisms make HF patients more susceptible to infections and sepsis. Additionally, cardiac remodeling in HF promotes a vicious pathophysiological cycle, with many HF-related deaths attributed to sepsis.[10,11] The global prevalence of HF increased by 29% between 2010 and 2019, with the highest prevalence observed in East Asia, North America and Western Europe. This has led to the widespread belief that the risk of pathogenic infections may increase in HF patients, highlighting the need for greater attention to infection prevention to reduce fatal outcomes.[12]

Previous studies have shown that HF patients are more likely to develop sepsis, experiencing higher rates of sepsis-related hospitalizations and deaths.[10,13] However, the majority of these studies are observational in nature, employing multivariate regression analyses and Cox proportional hazards models. Potential confounders and selection bias remain significant concerns that have not been adequately addressed.[14] Given these challenges, more rigorous methods such as propensity score matching (PSM) and Mendelian randomization are needed to clarify the relationship between HF and sepsis.

PSM creates matched sets of study and control groups with similar propensity scores, thereby improving the reliability of the results.[15] As a tool for balancing, PSM aims to improve the comparability of baseline covariates between the treatment and control groups through an appropriate PS model and effective adjustment or matching strategy. In our study, PSM was applied to match the sepsis group with the non-sepsis group, specifically to balance baseline characteristics and reduce the influence of confounding factors. Moreover, the causal relationship between HF and sepsis has not been fully elucidated. In recent years, MR has become a popular approach for making causal inferences, using single nucleotide polymorphisms (SNPs) as instrumental variables (IVs).[16,17] As genetic variants are randomly assigned during meiosis, they are generally unaffected by environmental factors and precede the onset of disease phenotypes.[18] When randomized controlled trials (RCTs) are impractical, MR can significantly reduce confounding and reverse causality to strengthen causal inference.[16,19,20] Therefore, we conducted MR analysis to further improve the robustness of our findings. In addition, previous studies have demonstrated correlations among circulating cytokines, growth factors, and inflammatory diseases. Inflammatory responses are typical features of both HF and sepsis.[21,22] Thus, we also applied network MR to investigate whether HF might promote sepsis via these mediating factors.

Through MR and observational analyses, our study aims to assess the causal relationship between HF and sepsis, as well as the short-, medium-, and long-term mortality associated with sepsis. Additionally, network mediation analysis was used to examine whether HF increases sepsis risk through intermediary factors. To further reduce confounding and strengthen the validity of our findings, we conducted a multivariable MR analysis focusing on exposures with potential causal relationships to the outcome.

Methods

Ethics Approval

This study utilized human data from publicly available databases, including GWAS data and the MIMIC-IV database, both of which had received ethical approval. The study was also reviewed and approved by the Institutional Review Board (IRB) of the First Affiliated Hospital of Harbin Medical University (IRB Approval Number: IRB-AF/SC-04/02.0).

Mendelian Randomization

The Design for Study

The design for MR study is depicted in Figure 1. We used GWAS datasets with a two-sample MR analysis for causality between HF and sepsis. We then investigated the causality among HF, cytokines, growth factors, and sepsis to find positive factors caused by HF or inducing sepsis. Furthermore, we performed multivariable MR (MVMR) analysis on HF and positive factors potentially associated with sepsis, which indicated the direct causality of HF and positive factors on sepsis. In addition, we used network MR to assess the causal relationships between HF and sepsis mediated by βNGF. Finally, sensitivity analyses were performed to validate the stability of our results.

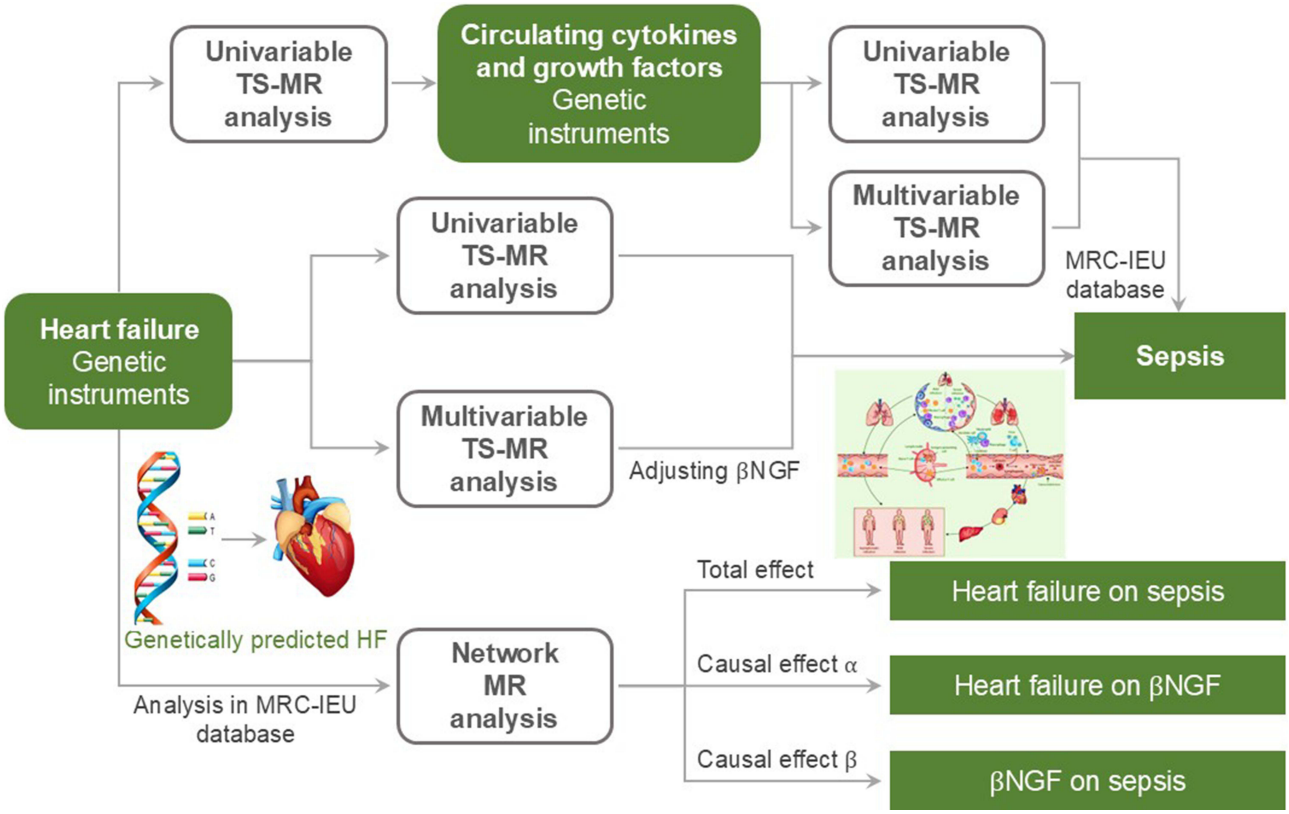

Figure 1 Flowchart of the Mendelian randomization study design.

GWAS Data Sources for Exposures, Mediators and Outcomes

Exposures

From the MRC-IEU database, we identified genetic instruments for HF (ID: ebi-a-GCST009541), The relevant detailed dataset information can be found in the study by Shah S et al.[23] This dataset encompasses 47,309 cases and 930,014 European ancestry controls from 26 studies within the (HERMES) Consortium. The population included cohorts aged 34 to 80 (17 studies, 38,780 hF cases, 893,657 controls) and case-control samples (9 studies, 8,529 cases, 36,357 controls). The case group included all participants clinically diagnosed with HF. Since the included studies involve multiple independent datasets, the definition of HF and the inclusion criteria for participants vary. For detailed inclusion criteria and HF definitions in each study, please refer to the work by Shah et al.[23] Detailed HF sources can be found in Supplementary Table S1

Mediators

Cytokines and growth factors GWAS data are sourced from the study by Ahola-Olli et al[24] and are available from the MRC-IEU. The study measured the concentrations of 41 cytokines and growth factors in 8,293 Finns and conducted a genome-wide association study (GWAS). This study utilized data from the Young Finns Study (YFS) and the FINRISK Study. Participants in the YFS were randomly selected in 1980 from five major cities in Finland and their surrounding rural areas, with 2,019 unrelated individuals from the 2007 follow-up included in the present analysis. The FINRISK Study participants were randomly selected individuals aged 25 to 74 years from five geographic regions of Finland, and this analysis used data from the 1997 and 2002 surveys. All participants were randomly selected and provided written informed consent. Detailed cytokines and growth factors sources can be found in Supplementary Table S1.

Outcomes

The GWAS summary data for the sepsis cohort were obtained from the MRC-IEU Open Database (Dataset ID: ieu-

b-4980), which is based on resources from the UK Biobank. This dataset encompasses 11,643 cases and 474,841 controls. The UK Biobank is a population-based cohort study covering the entire United Kingdom, with biological samples from over 500,000 individuals. Sepsis cases were identified through the Hospital Episode Statistics (HES) coding system, based on the International Classification of Diseases, 10th Revision (ICD-10) codes commonly used in clinical practice. Code A40 represents "Streptococcal sepsis", while code A41 refers to "Other sepsis".

Genetic Instrument Selection

For valid causal inference using MR, three key assumptions must be met: (1) the IVs must have a strong association with the exposure; (2) the IVs must not be correlated with any confounding factors; and (3) the IVs must influence the outcome solely through their effect on the exposure. Genetic tools (SNPs) for HF, cytokines, growth factors, and sepsis were selected based on genome-wide significance threshold ($P < 5E-6$). To identify independent SNPs, we conducted linkage disequilibrium (LD) pruning for each trait. This analysis was performed using the one thousand Genomes LD reference panel, with a particular focus on individuals of European descent. The LD threshold was established at $r^2 < 0.01$, with a clumping window of larger than 5000 kb. To derive accurate causal estimates from MR analysis, it is essential that the effects of SNPs on both outcomes and exposures are aligned with respect to the same allele. Therefore, we employed the "TwoSampleMR" R package to perform variant harmonization. This facilitated the identification and exclusion of palindromic SNPs where the correct orientation of the allele was difficult to ascertain. In order to mitigate confounding effects, Our study excluded SNPs significantly associated with outcome ($P < 5E-6$). Additionally, we evaluated the strength of the IVs by calculating the F-statistic ($beta^2/se^2$), with values below 10 indicating weakly powered IVs.[25] We quantified the extent to which the full set of SNPs contributed to phenotypic variation. R^2 was computed using the formula $beta^2 / [beta^2 + se^2*(N-2)]$, where N is the sample size, and the genetic variance attributable to each SNP was also calculated.[26]

Statistical Analyses

Analyses of main Mendelian randomization

We applied the random-effects inverse variance weighted (IVW) method as the primary analysis in our study. The IVW approach enables robust causal inference even when horizontal pleiotropy is present due to the fact that it combines causal estimates from each IV using a weighted regression method.[27] In addition, we applied the MR-Egger, weighted median, simple mode, and weighted mode methods as validations and complements to the IVW methods. The weighted median model calculates the weighted median value of IV-specific causal estimates. It can produce consistent causal estimates. This depends on valid instrumental variables accounting for more than half of the analysis weight. Meanwhile, the weighted mode-based estimation method typically shows low bias and minimal inflation of the Type 1 error rate, even with up to 40 invalid instruments. However, this method has limited power in detecting a causal effect.[28,29] We also performed multivariable Mendelian randomization (MVMR) analysis to investigate the direct effects of HF, cytokines, and growth factors on sepsis.

Analyses of network Mendelian randomization

We conducted network MR analyses to explore the possible mediation effect of βNGF in the causality between HF and sepsis. The analyses comprised three estimates: (1) the causality of HF on sepsis, (2) the causality of HF on βNGF (denoted as α), (3) the causality of βNGF on sepsis (denoted as β). We used the following formula to calculate the mediation effect: mediation effect = $\alpha \times \beta$.[30] Furthermore, we estimated the mediated effect fraction by taking the ratio of the mediation effect to the total causal effect of HF on sepsis.

Analyses of sensitivity

To ensure the validity of the core assumptions in univariate MR analysis, sensitivity tests were conducted using MR-Egger regression, MR- Pleiotropy Residual Sum, and Outlier (MR-PRESSO). Additionally, we performed multivariable MR-Egger regression to identify pleiotropy in multivariable MR analyses.[31] MR-PRESSO distortion tests reveal differences in estimates before and after outlier elimination.[32] We employed the Cochran's Q test method to evaluate heterogeneity among exposure-related SNPs. This method was also used to verify the alignment between MR

assumptions and the analyses. In light of the MR estimates and sensitivity analysis methods previously discussed, we established that valid causal inferences should satisfy the following criteria: (1) the results of MR estimation and sensitivity analyses demonstrated consistent directional concordance across the three methods; (2) the MR-Egger intercept test indicated the absence of horizontal pleiotropy. Additionally, F-statistics were computed to assess the strength of instrumental variables (IVs) in the univariable MR analysis. The "MVMR" R package was used to compute the two-sample conditional F-statistic (FTS) and assess the robustness of IVs in multivariable MR analysis.[33,34] A strong instrumental variable is indicated by an F-statistic greater than 10.[35] All of the above were done in R 4.3.1.[36] R packages "TwoSampleMR", "MRPRESSO" and "MendelianRandomization" were utilized for MR and sensitivity analyses.[32,37,38]

Analyses for Real-World Observations

The Description of Data Source

This study used version 1.0 of the MIMIC-IV database, an open-access electronic health record system, to collect observational data.[39] MIMIC-IV comprises comprehensive inpatient data from 523,740 patient admissions at the Beth Israel Deaconess Medical Center, Boston, over the years 2008 to 2019. Among these admissions, 76,540 were ICU cases. The database, a collaborative effort by the Massachusetts Institute of Technology, Philips Healthcare, and Beth Israel Deaconess Medical Center, contains vital signs, lab results, demographic data, imaging data, and clinical outcomes.[40]

The Description of Patient Population

Patients meeting the Sepsis 3.0 criteria for sepsis diagnosis in the MIMIC-IV ICU will be included in the study. Any patient whose age is under 18 or over 80 years will be excluded. Moreover, we also exclude patients with Sequential Organ Failure Assessment (SOFA) score < 2 or ICU length of stay < 24 hours. Finally, we identified 6224 patients with HF based on the ICD code and discharge summaries in the database, with exclusion criteria including (1) age under 18 or over 80 years and (2) ICU length of stay < 24 hours. We selected the last ICU admission for each patient meeting these criteria.[14] We extracted various confounders from MIMIC-IV, including age, sex, race, SOFA score, average heart rate during the ICU stay, diuretics, diabetes, chronic obstructive pulmonary disease (COPD), and ischaemic aetiology. The SOFA score evaluates various functions including respiratory, urinary, and cardiovascular systems in patients. Furthermore, the score is widely regarded as a crucial prognostic tool in ICU settings. The principal outcomes analyzed

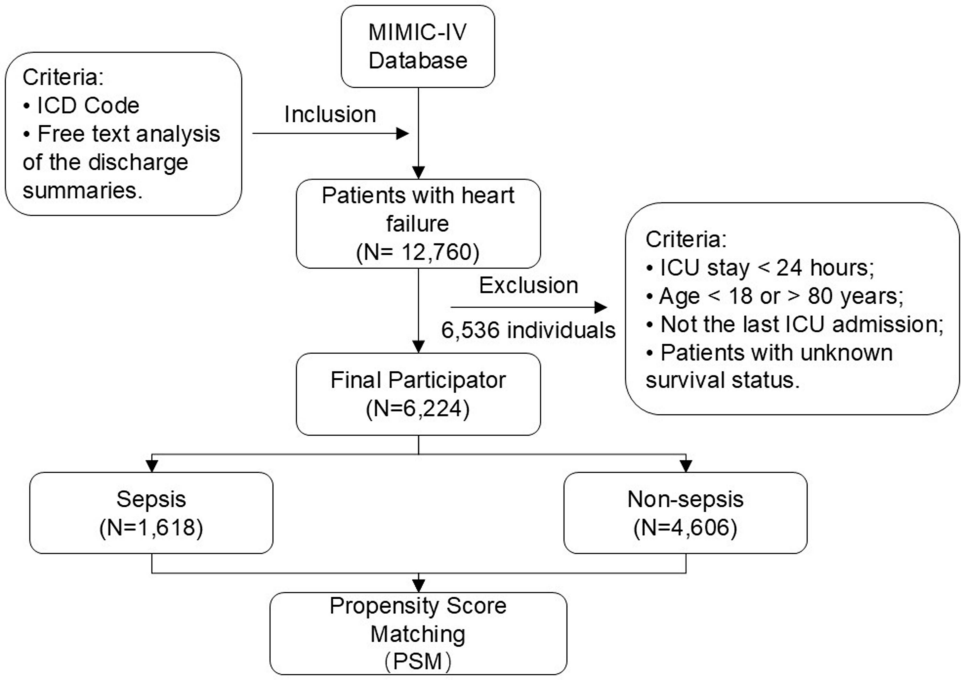

Figure 2 Flowchart of patients' inclusion and exclusion.

in this research are the incidence of sepsis and the associated short- and long-term mortality rates among these patients. Short-term and long-term mortality refers to patient mortality within 7 days, 28 days, 90 days, one year, and two years after discharge. The patient enrolment process for this study is depicted in Figure 2.

Propensity Score Matching (PSM)

We installed the R packages "tableone", "MatchIt", "lmtest", "sandwich", and 'gtools'. We then calculated the standardized mean differences (SMD), which was greater than 0.1, and p-values for most confounders. The SMD (>0.1) and significant p-values indicated differences in confounders between the comparison groups. The confounders in this study included gender, age, race, SOFA score, Charlson score, heart rate, use of Ramipril, diabetes, COPD, and ischemic etiology. Thus, we adjusted for these confounders using the propensity score method, aiming to achieve an equivalent distribution of all variables incorporated in the propensity score model between the sepsis and non-sepsis groups at each level of the estimated propensity score. Achieving this balance allows us to estimate the impact of HF by comparing outcomes between the sepsis groups across the different values of the estimated propensity score, assuming that all relevant confounders have been accounted for in the propensity score model.[41] In the PSM analysis conducted using MatchIt, we constructed matched groups of sepsis and non-sepsis individuals with closely aligned estimated propensity scores. We selected the matched cohorts using 1:2 nearest neighbor matching with a caliper constraint of 0.2, which involves selecting two unexposed matches for each exposed individual and removing 98% of the bias due to measured covariates.[42] After PSM, we used a logistic regression model to calculate the causal effect of different types of HF on sepsis and its short-, medium-, and long-term mortality.

Statistical Analyses

We assessed continuous variables between the sepsis and non-sepsis groups using ANOVA or the Mann–Whitney *U*-test. The choice of test was based on the normality of their distribution, while we evaluated categorical variables using the X^2 test. For multi-category variables, we applied the multi-group X^2 test. We used mean ± standard deviation to present the continuous baseline characteristics and expressed categorical variables using percentages. A logistic regression model was used to assess the relative risks between sepsis and non-sepsis patients, and the results were presented as odds ratios (ORs) with corresponding 95% confidence intervals (CIs).[43] We adjusted ORs for potential confounders, which included race, SOFA score, heart rate, use of diuretics, diabetes, COPD, and ischemic etiology. After balancing confounders through PSM, we analyzed the relationship between HF and sepsis and its mortality using logistic regression models. Furthermore, we conducted statistical analyses in this study using SPSS software (IBM Corp, version 29).

Results

Mendelian Randomization

Genetic Instruments

38 independent SNPs were ultimately identified as IVs for HF. 7, 14, and 5 SNPs were chosen as IVs for βNGF, MCP-1, and FGFB, respectively. The chosen IVs collectively explained 0.1% of the variance in HF and 4.76% of the variance in the cytokine βNGF. All IVs used in this MR analysis had F-statistics > 10, which indicates a strong instrumental variable. (Supplementary Table S2)

Causality of HF on Sepsis

Univariate MR analysis provided robust evidence that HF was related to a higher risk of sepsis (IVW: OR = 1.15, 95% CI = 1.02–1.29, P = 0.02) (details shown in Figure 3). The direction of causal estimates remained consistent across sensitivity analysis, and the MR-Egger intercept test showed no evidence of horizontal pleiotropy (P > 0.05). (Supplementary Table S3).

Causality of HF on Cytokines and Growth Factors

MR analysis demonstrated a causal relationship between HF and seven cytokines/growth factors: βNGF (OR = 1.22, 95% CI = 1.01–1.46, P = 0.038), RANTES, interleukin-13 (IL-13), interleukin-9 (IL-9), interleukin-4 (IL-4), interferon-

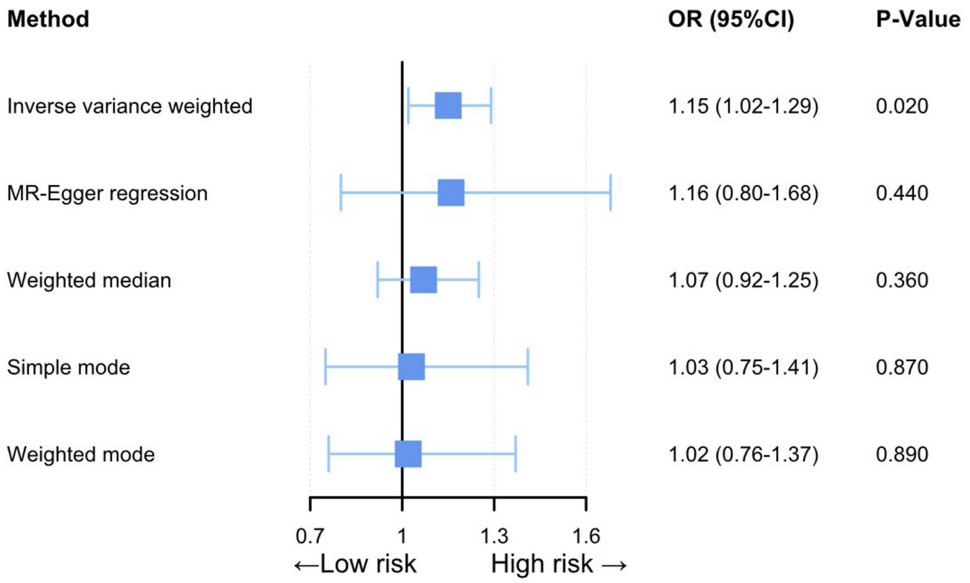

Figure 3 Forest plot illustrating the causal relationship between HF and sepsis by applying MR analysis.

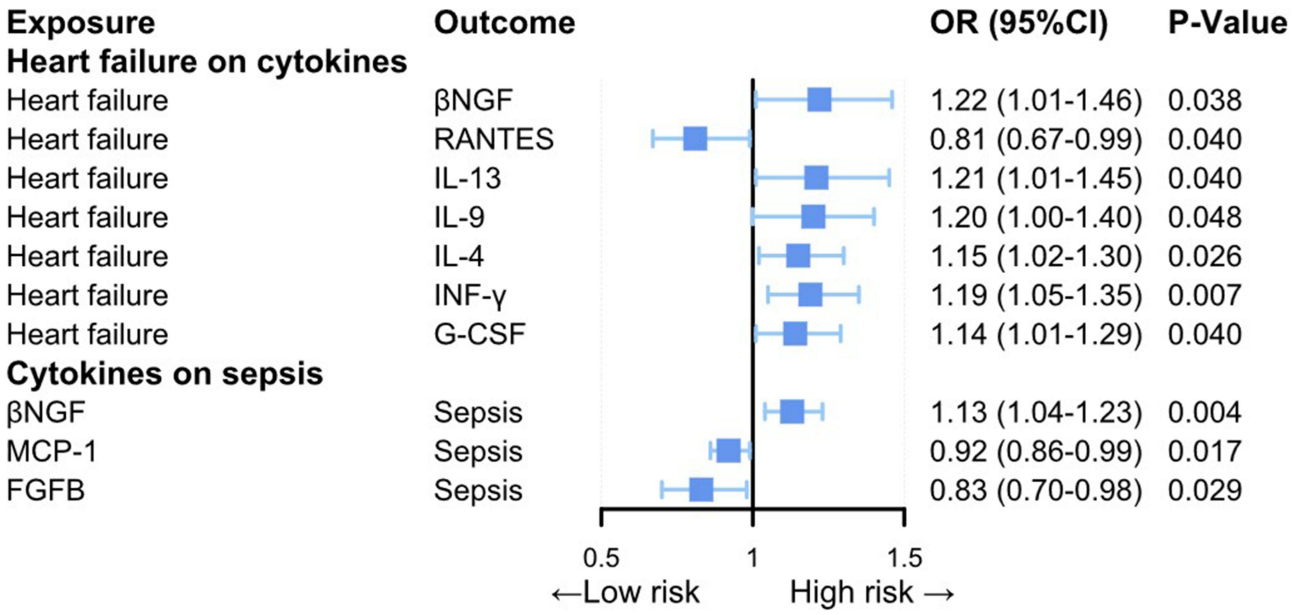

Figure 4 Forest plot illustrating the causal relationship between HF and cytokines, as well as between cytokines and sepsis, using the IVW method. OR, odds ratio; 95% CI, 95% confidence interval.

gamma (INF-γ), and granulocyte-colony stimulating factor (G-CSF) (Figure 4). Additional details can be found in Supplementary Figure S1.Moreover, the MR-Egger intercept test showed no evidence of horizontal pleiotropy (P > 0.05), as demonstrated in the Supplementary Table S4.

Causality of Cytokines and Growth Factors on Sepsis

Univariate MR analysis of 41 factors and sepsis identified causal effects for three factors and sepsis: βNGF (OR = 1.13, 95% CI = 1.04–1.23, P = 0.004), monocyte chemoattractant protein-1 (MCP-1), and fibroblast growth factor basic (FGFB) (Figure 4). Additional details can be found in Supplementary Figure S2.The MR-Egger intercept test did not detect horizontal pleiotropy (P > 0.05) (Supplementary Table S5).

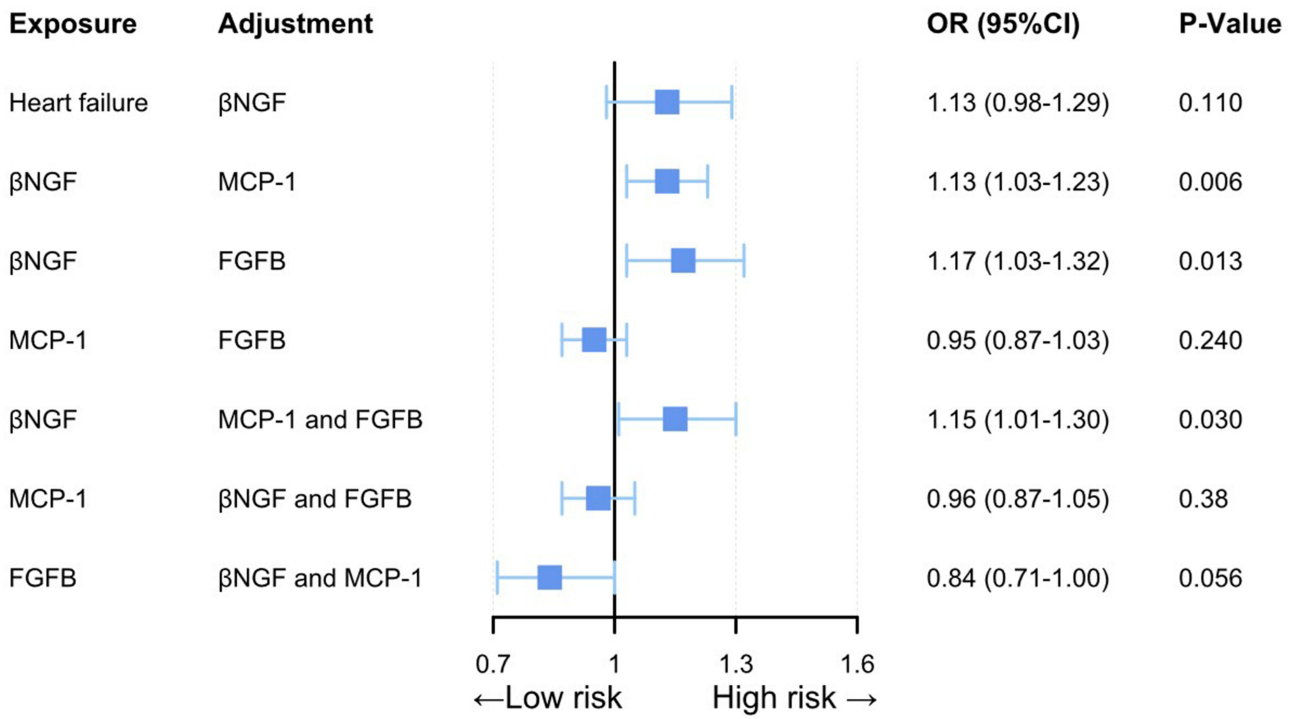

Figure 5 Forest plot illustrating the associations of HF and 3 positive cytokines with sepsis using multivariable MR analyses. OR, odds ratio. 95% CI, 95% confidence interval.

Multivariable MR Analyses Adjusting Potential Confounders

In the analyses of multivariable MR, after adjusting for two potential confounders (MCP-1 and FGFB), the causality of βNGF on sepsis remained. However, after adjusting for βNGF, the causal association between HF and sepsis was no longer statistically significant (OR = 1.13, 95% CI = 0.98–1.29, P = 0.110) (Figure 5).

In the sensitivity analysis of multivariable MR, multivariable MR-Egger regression detected no evidence of horizontal pleiotropy. However, mild to moderate heterogeneity was observed in the analysis of the direct causal relationship between HF and sepsis (Supplementary Table S6).

βNGF Mediates the Causal Effect of HF on Sepsis

Network MR analysis revealed that βNGF mediates the causal effect of HF on sepsis. HF was related to a higher risk of sepsis (IVW: OR = 1.15, 95% CI = 1.02–1.29, P = 0.02) (Figure 3) (Total effect). For direct effects, HF was causally associated with increased βNGF levels (IVW: OR = 1.22, 95% CI = 1.01–1.46, P = 0.038) (direct effect a). Additionally, βNGF was linked to a higher risk of sepsis (OR = 1.13, 95% CI = 1.04–1.23, P = 0.004) (Figure 4) (direct effect b). The causal effect of HF on sepsis, mediated through βNGF, was estimated to be 17.6% (95% CI 2.45%-30.72%) (Table 1). The results showed that no horizontal pleiotropy was detected (P > 0.05) (Supplementary Tables S3-S5).

Table 1 Mediation Effect of βNGF in the Association Between HF and Sepsis

Total effect[a]			Direct effect α[b]			Direct effect β[c]			Mediation effect[d]	
Beta[e]	SE	P	Beta	SE	P	Beta	SE	P	Effect size (95% CI)	Proportion % (95% CI)
0.14	0.06	2.53E-02	0.2	0.09	3.80E-02	0.12	0.04	4.41E-03	0.12 (0.05–0.18)	17.6 (2.45–30.72)

Notes: [a]The causal estimate of HF on sepsis derived from TS-MR analysis. [b]The causal estimate of HF on βNGF derived from TS-MR analysis. [c]The causal estimate of βNGF on sepsis derived from TS-MR analysis. [d]The effect of HF on sepsis mediated by βNGF. [e]The beta coefficient from the random-effects IVW method was utilized in the mediation analysis.

Table 2 Baselines of HF Patients

	Sepsis	Non-sepsis	P-value
Number of patients	1618	4606	
Patient outcomes			
28-day mortality	46.1%	16.3%	<0.001
Patient characteristics			
Age (mean ± SD)	67.09 ± 10.95	67.10 ± 10.37	0.110
Sex (% Female)	40.0%	39.9%	0.955
Race			0.005
Asian	2.8%	2.0%	
Black	12.6%	10.1%	
Hispanic	4.0%	3.2%	
White	65.9%	67.9%	
Other	5.0%	6.0%	
Unknown	9.7%	10.9%	
SOFA at 24 hours (mean ± SD)	6.99 ± 3.35	4.84 ± 3.18	<0.001
Charlson score (mean ± SD)	7.22 ± 2.58	6.42 ± 2.65	<0.001
Heart rate (mean ± SD)	89.69 ± 17.02	84.59 ± 15.56	<0.001
Ramipril use	0.2%	0.3%	0.508
Diabetes	34.6%	25.3%	<0.001
COPD	22.2%	18.6%	0.002
Ischemic etiology	11.1%	8.4%	0.001

Observational Study

Our study cohort included 6224 patients with 48 different types of HF (Supplementary Table S7). Among them, 1618 patients (26.0%) developed sepsis.Table 2 shows the baselines of HF patients with/without sepsis. In general, HF patients with sepsis were likely to have elevated SOFA scores, Charlson scores, and increased risks of diabetes, COPD, ischemic conditions, and mortality. Our analysis included these potential confounders to construct a multivariate logistic regression model, comprehensively exploring the relationship between HF and sepsis and its mortality. The results revealed statistically significant effects on the occurrence of sepsis for the following types of HF: acute on chronic DCHF, chronic combined systolic and diastolic heart failure, chronic diastolic (congestive) heart failure, acute DCHF (OR = 1.78, 95% CI = 1.20–2.65, P = 0.004). Detailed information can be found in Supplementary Figures S3-S8.

We assessed the balance of the matched dataset using PSM. In the histogram of the propensity score distribution, we observed that the matched sepsis and non-sepsis groups had similar propensity score distributions (Supplementary Figure S9). The Love plot shows that the absolute SMD decreases for all covariates. And most of the matched outcomes fall below 0.1 (Supplementary Figure S10), indicating that the matched dataset is balanced. Detailed information can be found in Supplementary Tables S8 and S9.

After PSM, the result of logistic regression indicated that acute on chronic DCHF (OR = 1.59, 95% CI = 1.31–1.93, P < 0.001), acute DCHF (OR = 2.52, 95% CI = 1.61–3.95, P < 0.010), and acute diastolic heart failure (OR = 1.52, 95% CI = 1.06–2.19, P = 0.024) were associated with the occurrence of sepsis. Chronic SCHF was found to increase the 28-day (OR = 1.75, 95% CI = 1.06–2.91, P = 0.030), 1-year (OR = 1.80, 95% CI = 1.08–3.00, P = 0.023), and 2-year (OR = 1.86, 95% CI = 1.12–3.10, P = 0.018) mortality related to sepsis (Figure 6), while no associations were observed between other types of HF and sepsis, as well as its mortality (Supplementary Figure S11-S16).

Discussion

In the real-world cases, The results of PSM and outcome regression showed an association between acute diastolic HF and the occurrence of sepsis, which is consistent with previous studies.[7,44] In particular, chronic SCHF was correlated with increased sepsis-related mortality at 28 days, one year, and two years. In this MR study, we comprehensively investigated the relationship between HF, βNGF and sepsis. The MR analysis revealed a causal relationship between

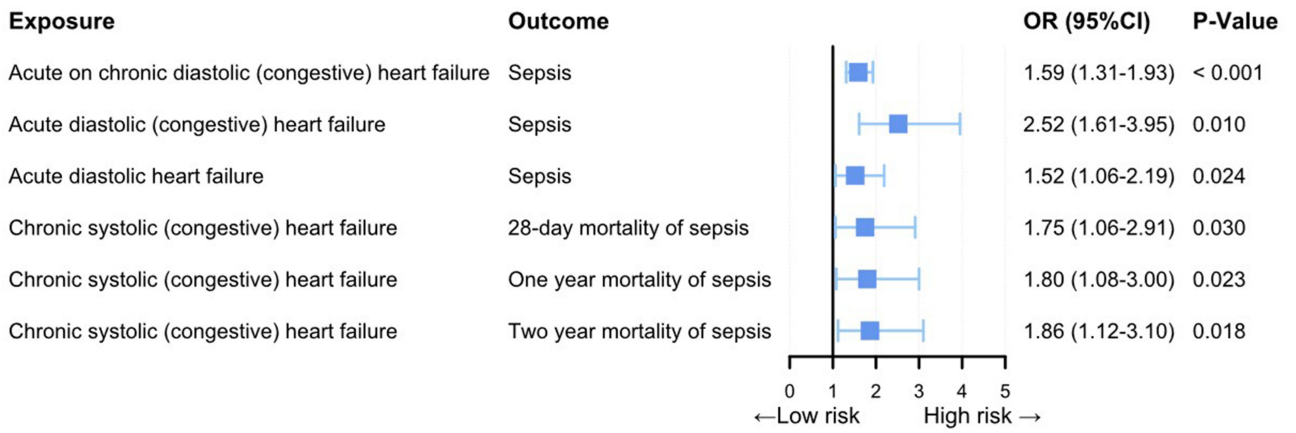

Figure 6 The relationship between different types of heart failure and both sepsis and sepsis-related mortality after propensity score matching (Only positive results. Detailed information can be found in Figures S11-S16).

genetically predicted HF and an increased risk of sepsis. Furthermore, the network MR analysis demonstrated that βNGF mediated 17.6% of the causal relationship between HF and sepsis. Those MR analyses remained stable in the MR-Egger horizontal pleiotropy test and sensitivity analyses. The results of the MR analysis suggest that βNGF may be one of the key mechanisms underlying the development of sepsis in heart failure patients.

In recent years, with the advancement of precision medicine, sepsis research has increasingly focused on achieving personalized treatment by identifying clinical phenotypes, utilizing genomic sequencing, biomarker-based strategies, and multi-platform omics analyses, gradually moving away from the traditional "one-size-fits-all" approach. The host response to pathogens is complex and heterogeneous, and as research progresses, an increasing number of potential therapeutic targets are being discovered across various human systems, such as the immune system, endothelium, and gastrointestinal tract. One such target that has emerged in the context of cardiovascular diseases is βNGF.[45,46] After myocardial injury, βNGF is upregulated, playing a crucial role in nerve regeneration and inflammation.[47,48] Elevated βNGF levels in HF not only promote cardiac nerve regeneration but also exacerbate inflammation by enhancing leukocyte infiltration, mast cell degranulation, and pro-inflammatory cytokine production.[49,50] Additionally, βNGF further contributes to the pathogenesis of sepsis by enhancing neutrophil recruitment, phagocytosis, and bactericidal functions.[51] These findings, supported by Sour MR analysis, suggest that βNGF may be a critical link between HF and the increased risk of sepsis, serving as a mediator in this relationship and providing a potential therapeutic target for personalized treatment in HF patients who are susceptible to sepsis. Nevertheless, further research is needed to clarify its specific role in the pathogenesis of sepsis and its potential link between HF and sepsis.

Our study is the first to systematically investigate the relationship between different types of HF and the incidence of sepsis, as well as its short-, mid-, and long-term mortality. The results indicated that acute diastolic HF is closely associated with the occurrence of sepsis, while chronic systolic congestive heart failure (SCHF) is significantly correlated with sepsis-related mortality at 28 days, one year, and two years. These findings have important implications for developing individualized sepsis prevention strategies for HF patients, particularly for those with acute diastolic HF and chronic SCHF, where infection prevention is crucial to reduce the risk of sepsis and its related mortality.

Several noteworthy aspects are highlighted in this study. The primary advantage of the MR design is its ability to minimize the effect of confounders and reverse causation. Our study suggests that βNGF may be a potential mediator in the progression from HF to sepsis, offering new insights into the early detection and prevention of sepsis. The population was restricted to individuals of European descent, reducing bias due to population stratification. Adequate statistical power (>0.80) for our analysis was achieved with the appropriate sample size. The strength of our observational study lies in its comprehensive scope, including a large cohort of HF patients from the MIMIC-IV database. We adjusted for potential confounders to determine the significance of HF on the occurrence and prognosis of sepsis. Furthermore, we

employed the propensity score method to balance potential confounders between the two groups, enhancing the reliability of our findings.

This work also has some limitations. First, despite adjusting for known confounders, residual confounding may still exist due to the inherent limitations of observational studies, as unmeasured or unknown confounders could affect the results. Second, the reliance on the MIMIC-IV database, sourced from a single institution, may limit the external validity and introduce selection bias, particularly in diverse populations. Third, the relaxation of SNP selection criteria to address the limited number of SNPs at the genome-wide significance threshold of P<5E-8 may increase the risk of false positives. Finally, while no significant horizontal pleiotropy was detected using the MR-Egger intercept test, and MR-PRESSO identified only a few outliers, undetected outliers may still influence the findings.

Conclusion

The primary objective of this study was to explore the causal relationship between HF and sepsis, as well as the potential mediator in this relationship, using both MR and observational study approaches. Our findings provide compelling evidence that acute diastolic HF is associated with the occurrence of sepsis, and chronic SCHF is linked to increased 28-day, 1-year, and 2-year mortality in sepsis patients. Notably, βNGF was identified as a potential mediator, suggesting its critical role in the pathway through which HF contributes to sepsis. This highlights βNGF as a promising therapeutic target in the treatment of sepsis in HF patients. However, further research is warranted to elucidate the specific mechanisms by which βNGF influences the pathogenesis of sepsis and to clarify its intermediary role between HF and sepsis.

Abbreviations

HF, Heart failure; MR, Mendelian randomization; GWAS, Genome-wide association study; βNGF, Beta-nerve growth factor; lVW, Inverse variance weighted; MVMR, Multivariable MR; SOFA, Sequential organ failure assessment; PSM, Propensity score matching; OR, Odds Ratios; CI, Confidence Intervals; COPD, Chronic obstructive pulmonary disease.

Data Sharing Statement

The datasets generated during and/or analysed during the current study are available in the MRC-IEU, https://gwas.mrcieu.ac.uk/datasets/ and MIMIC-IV repository, https://physionet.org/content/mimiciv/2.0/.

Ethics Approval and Informed Consent

This study was approved by the Institutional Review Board (IRB) of the First Affiliated Hospital of Harbin Medical University (IRB Approval Number: IRB-AF/SC-04/02.0). The human data used in this study were obtained from a publicly available database, which had already received ethical approval and patient informed consent.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

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