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## B7-H3在脓毒症诊断与预后中的潜在价值： 一项孟德尔随机化研究

郭名君, 何智辉

(中南大学湘雅三医院重症医学科, 长沙 410013)

**[摘要]** 目的: 脓毒症是全球健康领域的重大挑战, 但目前仍缺乏特异性诊断标志物。本研究通过孟德尔随机化(Mendelian randomization, MR)分析方法探讨B7同源物3(B7 homologue 3, B7-H3)与脓毒症的易感性、严重程度及临床结局之间的因果关联, 以评估其作为潜在生物标志物的价值。方法: 从全基因组关联分析(genome-wide association study, GWAS)数据中提取与脓毒症(脓毒症整体、脓毒症28 d内死亡、重症脓毒症及重症脓毒症28 d内死亡)相关的B7-H3单核苷酸多态性(single nucleotide polymorphisms, SNPs)信息, 筛选出合适的SNPs作为工具变量。采用逆方差加权法(inverse-variance weighted, IVW)作为主要因果效应估计方法, 并使用加权中位数法(weighted median, WME)、MR-Egger回归法作为补充方法, 对B7-H3与脓毒症及其结局的关联进行MR分析, 采用基于约束最大似然和模型平均法(constrained maximum likelihood-model average, cML-MA)进一步增加因果效应估计的可靠性。通过Cochran's Q检验评估异质性, 并采用MR-PRESSO和MR-Egger截距法进行多效性检验。使用留一法进行敏感性分析。以脓毒症为暴露因素, B7-H3为结局, 进行反向MR分析, 以排除反向因果关联。结果: IVW的分析结果显示: B7-H3与脓毒症的易感性、严重程度及临床结局之间均存在显著的正向因果关联。遗传预测的B7-H3水平每增加1个标准差, 发生脓毒症的风险增加10.4%(OR=1.104, 95% CI 1.021~1.194, P=0.013), 脓毒症28 d内死亡的风险增加26.2%(OR=1.262, 95% CI 1.078~1.476, P=0.004), 发生重症脓毒症的风险增加22.3%(OR=1.223, 95% CI 1.023~1.463, P=0.027), 发生重症脓毒症且28 d内死亡的风险增加60.2%(OR=1.602, 95% CI 1.119~2.294, P=0.010)。IVW、WME、MR-Egger和cML-MA这4种分析方法因果效应方向一致, 进一步验证了结果的稳健性和可靠性。Cochran's Q检验未检测到结果的异质性(P>0.05), MR-PRESSO和MR-Egger截距法均提示结果不存在潜在的水平多效性(均P>0.05)。留一法检验结果显示剔除单个SNP后的因果关联估计值与未剔除前的因果关联估计值相近。反向MR分析显示脓毒症和B7-H3之间不存在因果关联。结论: B7-H3可能是脓毒症的重要生物标志物, 与脓毒症的易感性、严重程度及临床结局密切相关。

**[关键词]** B7同源物3; 脓毒症; 重症脓毒症; 孟德尔随机化; 生物标志物; 易感性; 临床结局

## Potential value of B7-H3 in sepsis diagnosis and prognosis: A Mendelian randomization study

GUO Mingjun, HE Zhihui

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第一作者(First author): 郭名君, Email: 228312140@csu.edu.cn, ORCID: 0009-0009-4505-9421

通信作者(Corresponding author): 何智辉, Email: hzh703@csu.edu.cn, ORCID: 0000-0001-5672-9691

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(Department of Critical Care Medicine, Third Xiangya Hospital, Central South University, Changsha 410013, China)

## ABSTRACT

**Objective:** Sepsis remains a major global health challenge, yet specific diagnostic biomarkers are still lacking. This study aims to investigate the causal relationship between B7 homologue 3 (B7-H3) and sepsis susceptibility, severity, and clinical outcomes using Mendelian randomization (MR) analysis, in order to evaluate its potential as a biomarker.

**Methods:** Genetic data related to sepsis (including overall sepsis, sepsis-related mortality with 28 days, severe sepsis, and severe sepsis with 28-day mortality) were extracted from genome-wide association study (GWAS) datasets. Single nucleotide polymorphisms (SNPs) associated with B7-H3 were selected as instrumental variables. The inverse-variance weighted (IVW) was used as the primary approach for causal effect estimation, while weighted median (WME) and MR-Egger regression served as supplementary methods. Additionally, a constrained maximum likelihood-model average (cML-MA) approach was employed to enhance the reliability of causal effect estimation. Cochran's  $Q$  test was conducted to assess heterogeneity, and MR-PRESSO along with the MR-Egger intercept method were used to detect horizontal pleiotropy. Sensitivity analyses were performed using the leave-one-out method. A reverse MR analysis was performed with sepsis as the exposure and B7-H3 as the outcome to exclude potential reverse causation.

**Results:** IVW analysis indicated a significant positive causal association between B7-H3 and sepsis susceptibility, severity, and clinical outcomes. A genetically predicted 1-standard deviation (SD) increase in B7-H3 levels was associated with a 10.4% increased risk of sepsis ( $OR=1.104$ , 95%  $CI$  1.021 to 1.194,  $P=0.013$ ), a 26.2% increased risk of sepsis-related 28-day mortality ( $OR=1.262$ , 95%  $CI$  1.078 to 1.476,  $P=0.004$ ), a 22.3% increased risk of severe sepsis ( $OR=1.223$ , 95%  $CI$  1.023 to 1.463,  $P=0.027$ ), and a 60.2% increased risk of severe sepsis with 28-day mortality ( $OR=1.602$ , 95%  $CI$  1.119 to 2.294,  $P=0.010$ ). The causal effect direction remained consistent across IVW, WME, MR-Egger, and cML-MA analyses, reinforcing the robustness and reliability of the results. Cochran's  $Q$  test showed no heterogeneity ( $P>0.05$ ), while MR-PRESSO and MR-Egger intercept tests indicated no evidence of horizontal pleiotropy (both  $P>0.05$ ). The leave-one-out analysis showed that removing individual SNPs did not significantly alter the causal estimates. Reverse MR analysis showed no causal association between sepsis and B7-H3.

**Conclusion:** B7-H3 may serve as an important biomarker for sepsis, as it is closely associated with sepsis susceptibility, severity, and clinical outcomes.

## KEY WORDS

B7-H3; sepsis; severe sepsis; Mendelian randomization; biomarker; susceptibility; clinical outcomes

脓毒症是指由宿主对感染的反应失调引起的危及生命的器官功能障碍<sup>[1-2]</sup>。脓毒症被认为是造成全球健康损失和疾病负担的一个重要因素。在2017年，全球估计就发生4 890万例脓毒症和1 100万例脓毒症相关死亡，占2017年全球所有死亡人数的20%<sup>[3]</sup>。全球流行病学数据<sup>[4]</sup>显示脓毒症患者重症监护病房和医院的病死率分别为26%和35%。目前，脓毒症

的诊断主要依赖临床表现、实验室检查及微生物学证据，缺乏特异性诊断标志物，脓毒症的治疗主要是对症支持治疗，如稳定血流动力学、抗感染和维持器官功能。早期诊断和识别脓毒症是改善患者预后的关键，因此需要探索稳定、可靠的生物标志物。

B7同源物3(B7 homolog 3, B7-H3)也称CD276，是免疫调节蛋白B7家族的膜蛋白成员，于2001年被

发现,并被鉴定为肿瘤相关抗原<sup>[5]</sup>。作为重要的免疫检查点分子,B7-H3在肿瘤<sup>[6-9]</sup>、自身免疫性疾病<sup>[10-11]</sup>的发病机制中的作用已被广泛研究。脓毒症3.0定义指出机体对感染反应失调与同时发生的失衡的过度炎症和免疫抑制有关<sup>[2]</sup>,调控免疫检查点在脓毒症诱导的过度炎症反应及免疫抑制中发挥重要作用。B7-H3可通过作为先天免疫的共刺激剂来增强炎症反应<sup>[12]</sup>,这可能是脓毒症的关键发病机制之一。研究<sup>[13]</sup>发现:与健康个体相比,脓毒症患者血浆可溶性B7-H3(soluble B7-H3, sB7-H3)水平显著升高,并且该水平与患者的疾病状态和临床结局密切相关。

迄今为止,关于免疫检查点B7-H3与脓毒症风险关联的研究相对较少,B7-H3在脓毒症中的具体作用机制和临床应用前景尚需进一步探讨。此外,由于观察性研究固有的局限性,其研究结果容易受到混杂因素和反向因果偏倚的影响。因此,B7-H3与脓毒症风险之间的因果关系需要更为精确的解释。孟德尔随机化(Mendelian randomization, MR)是一种基于全基因组关联分析(genome-wide association study, GWAS)数据,利用单核苷酸多态性(single nucleotide polymorphisms, SNPs)作为工具变量(instrumental variables, IVs),用于揭示因果关系的新颖流行病学方法,可最大限度地减少反向因果关系和混淆偏倚的机会,效力等同于随机对照试验<sup>[14-16]</sup>。

本研究采用双样本MR分析方法探讨B7-H3与脓毒症的易感性、严重程度及临床结局之间的关联,以期评价B7-H3作为潜在生物标志物的价值,为脓毒症的诊断、风险分层、预后评估、临床管理及治

疗靶点提供全新的理论依据。

## 1 资料与方法

### 1.1 研究设计

本研究根据STROBE-MR指南<sup>[17]</sup>设计。MR研究需要遵循3个假设:1)IVs与暴露(B7-H3)密切相关,与结局(脓毒症)不相关;2)IVs与影响“暴露-结局”的混杂因素无关;3)SNPs只能通过暴露途径来影响结局。此外进行了反向MR分析,以探究脓毒症与B7-H3之间是否存在反向因果关联。

### 1.2 数据来源

B7-H3蛋白质数量性状位点(protein quantitative trait loci, pQTL)的GWAS数据来源于英国生物样本库药物蛋白质组学项目(UK Biobank Pharma Proteomics Project, UKB-PPP),该机构使用基于抗体的Olink蛋白质组学测定法测试了1 610万个序列变异与54 306名英国生物样本库参与者血浆中2 922种蛋白质水平的遗传关联,血浆蛋白B7-H3测定所纳入的有效样本量为33 649<sup>[18]</sup>。

脓毒症GWAS数据包括脓毒症整体、脓毒症28 d内死亡、重症脓毒症及重症脓毒症28 d内死亡4个部分,均来源于IEU Open GWAS数据库。依据国际疾病分类第10版标准<sup>[19]</sup>,使用A02、A39、A40和A41编码筛选脓毒症患者,以确保研究对象的准确性和一致性。

所有参与者均为欧洲血统,确保该研究在同质种群中进行。详细的GWAS数据信息见表1。

表1 GWAS数据信息

Table 1 GWAS data information

| Phenocode                               | Year | Gender          | Total sample size | Number of cases | GWAS ID    | Population |
|-----------------------------------------|------|-----------------|-------------------|-----------------|------------|------------|
| B7 homolog 3                            | 2023 | Male and female | 33 649            |                 |            | European   |
| Sepsis                                  | 2021 | Male and female | 486 484           | 11 643          | IEU-b-4980 | European   |
| Sepsis (28 days death)                  | 2021 | Male and female | 486 484           | 1 896           | IEU-b-5086 | European   |
| Sepsis (critical care)                  | 2021 | Male and female | 431 365           | 1 380           | IEU-b-4982 | European   |
| Sepsis (28 days death in critical care) | 2021 | Male and female | 431 365           | 347             | IEU-b-4981 | European   |

GWAS: Genome-wide association study.

### 1.3 遗传IVs的选择

为有效地评估因果关系,IVs必须满足相关性、独立性和无水平多效性假设。首先以 $P<5\times 10^{-8}$ 为筛选条件,在全基因组水平上选择与暴露因素显著相关而与结局不相关的SNPs作为IVs<sup>[20]</sup>;当B7-H3为

暴露时,可满足上述筛选条件,而当脓毒症为暴露时,上述筛选条件无法满足,故以 $P<5\times 10^{-6}$ 为筛选条件选择脓毒症的IVs<sup>[21]</sup>。然后,通过设置参数( $r^2<0.001$ , clump\_kb=10 000)来排除连锁不平衡;使用效应等位基因频率来协调暴露和结局数据集,以排除

回文结构的 SNPs；使用 PhenoScanner V2 数据库排除可能影响 B7-H3 与脓毒症之间关联的潜在混杂因素(如年龄、性别、基础疾病等)，确保无旁路。最后，为避免弱 IVs 偏移，纳入统计量  $F$  值  $>10$  的 SNPs。计算公式为  $F=\beta^2/SE^2$ ，式中  $\beta$  为 SNP 对暴露的效应量， $SE$  为  $\beta$  的标准误<sup>[22-24]</sup>。

#### 1.4 MR 分析

采用逆方差加权 (inverse-variance weighted, IVW) 作为首选的因果效应估计方法，加权中位数法 (weighted median, WME)、MR-Egger 回归法作为补充方法，验证 B7-H3 与脓毒症的因果关联，结果以比值比 (odds ratio, OR) 和 95% 置信区间 (confidence interval, CI) 呈现。采用基于约束最大似然和模型平均法 (constrained maximum likelihood-model average, cML-MA) 进一步增加因果效应估计的可靠性。cML-MA 法可有效控制相关和不相关的多效性效应，从而提供更加稳健的因果效应估计<sup>[25-27]</sup>。

#### 1.5 敏感性分析

利用 Cochran's  $Q$  检验评估 B7-H3 相关 SNPs 对脓毒症相关特征结果影响的异质性。当  $P<0.05$  时，认为存在异质性，使用随机效应模型；否则，使用固定效应模型。用 MR-PRESSO 和 MR-Egger 截距法进

行多效性检验。用留一法进行敏感性分析，通过依次删除单个 SNP，计算剩余 SNPs 的合并效应值，以此评估每个 SNP 对整体结果的影响。

#### 1.6 反向 MR 分析

以脓毒症为暴露因素，B7-H3 为结局，进行反向 MR 分析，以排除反向因果关联，从而保证结果的稳健性。

#### 1.7 统计学处理

所有分析和数据可视化均使用 R 4.3.2 软件中的 TwoSampleMR 包实现，检验水准  $\alpha=0.05$ ， $P<0.05$  为差异有统计学意义。

## 2 结果

### 2.1 IVs

在排除连锁不平衡、调整等位基因和  $F$  值筛选后，获得 17 个 SNPs，使用 PhenoScanner V2 数据库查找并去除 5 个存在潜在混杂因素的 SNPs (rs55714927、rs4665972、rs3132954、rs11721064、rs4082420)，最后得到 12 个符合条件的 SNPs，MR-PRESSO 检验未检测到离群值，这些 SNP 可作为本次研究的 IVs (表 2)。

表 2 工具变量信息表

Table 2 IVs information table

| SNPs        | Chromosome | Position  | EA | OA | $P$       | $\beta$ | $SE$  | $F$     |
|-------------|------------|-----------|----|----|-----------|---------|-------|---------|
| rs1042704   | 14         | 23312594  | A  | G  | 7.53E-15  | 0.058   | 0.007 | 68.65   |
| rs11072380  | 15         | 72974647  | C  | T  | 1.94E-35  | 0.102   | 0.008 | 162.56  |
| rs112898929 | 16         | 88298795  | A  | T  | 4.54E-10  | -0.072  | 0.012 | 36.00   |
| rs184790191 | 15         | 74357818  | T  | C  | 7.75E-13  | -0.191  | 0.027 | 50.04   |
| rs2239651   | 14         | 94848547  | C  | T  | 8.23E-25  | -0.072  | 0.007 | 105.80  |
| rs2291277   | 15         | 72195229  | C  | T  | 1.62E-12  | -0.166  | 0.024 | 47.84   |
| rs2837988   | 21         | 42619544  | A  | C  | 8.63E-26  | 0.068   | 0.006 | 128.44  |
| rs28597091  | 6          | 81411032  | G  | T  | 1.45E-09  | 0.037   | 0.006 | 38.02   |
| rs62217923  | 21         | 42539293  | G  | C  | 1.50E-25  | 0.074   | 0.007 | 111.76  |
| rs6763543   | 3          | 197766946 | A  | G  | 1.53E-10  | 0.047   | 0.007 | 45.08   |
| rs74023531  | 15         | 74063328  | A  | G  | 1.00E-200 | -0.534  | 0.015 | 1267.36 |
| rs8025183   | 15         | 73715330  | T  | C  | 1.00E-200 | -0.399  | 0.010 | 1592.01 |

IVs: Instrumental variables; SNPs: Single nucleotide polymorphisms; EA: Effect allele; OA: Other allele; SE: Standard error.

### 2.2 MR 分析结果

IVW 的分析结果显示：B7-H3 与脓毒症的易感性、严重程度及临床结局之间均存在显著的正向因果关联。较高的 B7-H3 水平可能与更高的脓毒症发生风险、脓毒症 28 d 内死亡风险、重症脓毒症发生

风险及发生重症脓毒症且 28 d 内的死亡风险显著相关。具体而言，遗传预测的 B7-H3 水平每增加 1 个标准差，发生脓毒症的风险增加 10.4% ( $OR=1.104$ ，95%  $CI$  1.021~1.194， $P=0.013$ )，脓毒症 28 d 内死亡的风险增加 26.2% ( $OR=1.262$ ，95%  $CI$  1.078~1.476，

$P=0.004$ ), 发生重症脓毒症的风险增加 22.3%( $OR=1.223$ , 95%  $CI$  1.023~1.463,  $P=0.027$ ), 发生重症脓毒症且 28 d 内死亡的风险增加 60.2%( $OR=1.602$ , 95%  $CI$  1.119~2.294,  $P=0.010$ ; 图 1)。IVW、WME、MR-Egger 和 cML-MA 这 4 种分析方法因果效应方向一致(图 2), 进一步验证了结果的稳健性和可靠性。

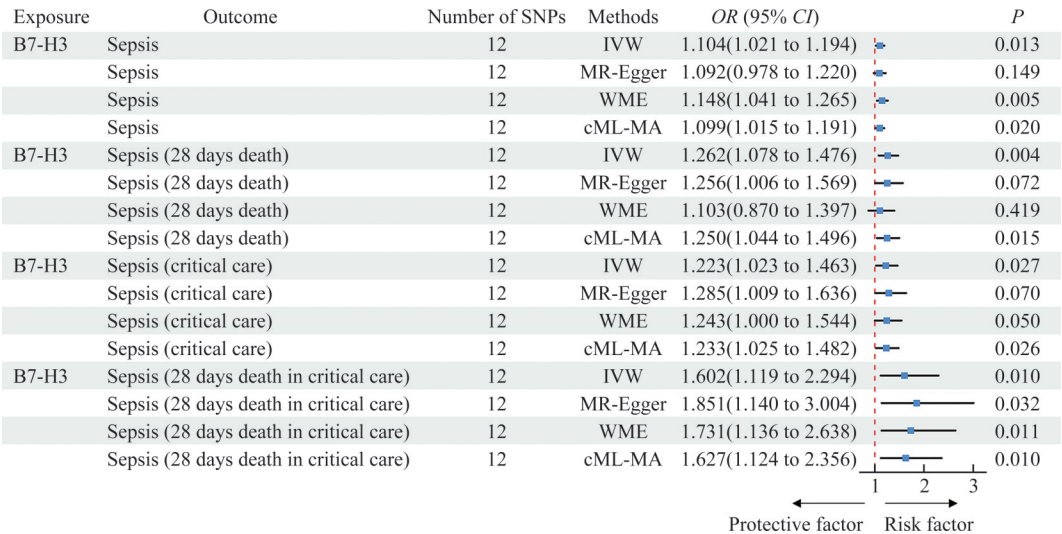


图 1 暴露(B7-H3)与不同严重程度的脓毒症之间关联的 MR 分析结果森林图  
Figure 1 Forest map of MR analysis results on the association between exposure (B7-H3) and sepsis of different severity levels

B7-H3: B7 homolog 3; SNPs: Single nucleotide polymorphisms; IVW: Inverse-variance weighted; MR: Mendelian randomization; WME: Weighted median; cML-MA: Constrained maximum likelihood-model average; OR: Odds ratio; CI: Confidence interval.

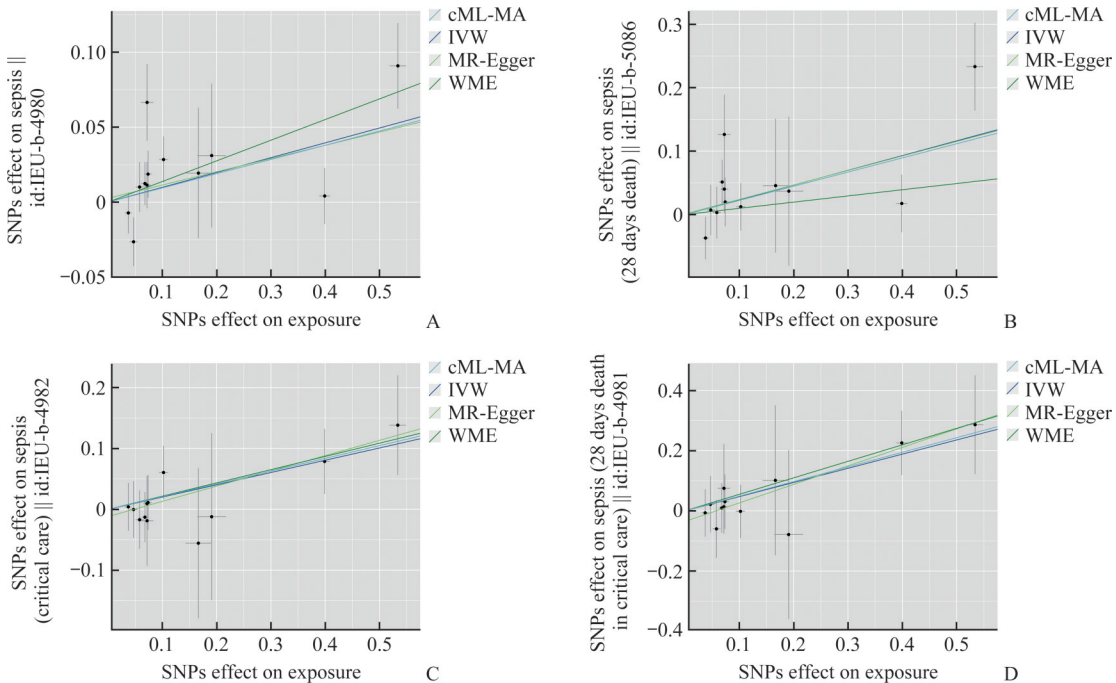


图 2 暴露与不同严重程度的脓毒症之间关联的 MR 分析结果散点图  
Figure 2 Scatter plot of MR analysis results on the association between exposure and sepsis of different severity levels  
A: Effect of B7-H3 on sepsis; B: Effect of B7-H3 on sepsis (28 days death); C: Effect of B7-H3 on sepsis (critical care); D: Effect of B7-H3 on sepsis (28 days death in critical care). B7-H3: B7 homolog 3; MR: Mendelian randomization; SNPs: Single nucleotide polymorphisms; cML-MA: Constrained maximum likelihood-model average; IVW: Inverse-variance weighted; WME: Weighted median.

2.3 敏感性分析结果

Cochran’s *Q* 检验未检测到结果的异质性( $P>0.05$ )，MR-PRESSO 和 MR-Egger 截距法均提示结果不存在潜在的水平多效性(均 $P>0.05$ ，表3)。留一法检验结果显示剔除单个 SNP 后的因果关联估计值与

未剔除前的因果关联估计值相近(图3)。

2.4 反向 MR 分析结果

IVW 的分析结果显示：不同严重程度脓毒症和 B7-H3 之间均不存在因果关联(均 $P>0.05$ ，表4)。

表3 敏感性分析结果

Table 3 Results of sensitivity analysis

| Exposure | Outcomes                                | <i>P</i> * | Intercept <i>P</i> † | <i>P</i> ‡ |
|----------|-----------------------------------------|------------|----------------------|------------|
| B7-H3    | Sepsis                                  | 0.097      | 0.785                | 0.224      |
| B7-H3    | Sepsis (28 days death)                  | 0.383      | 0.958                | 0.362      |
| B7-H3    | Sepsis (critical care)                  | 0.994      | 0.569                | 0.994      |
| B7-H3    | Sepsis (28 days death in critical care) | 0.999      | 0.405                | 0.998      |

\*Cochran’s *Q* test to assess heterogeneity; †MR-Egger to assess horizontal pleiotropy; ‡Global test of MR-PRESSO to assess horizontal pleiotropy. B7-H3: B7 homolog 3; MR: Mendelian randomization.

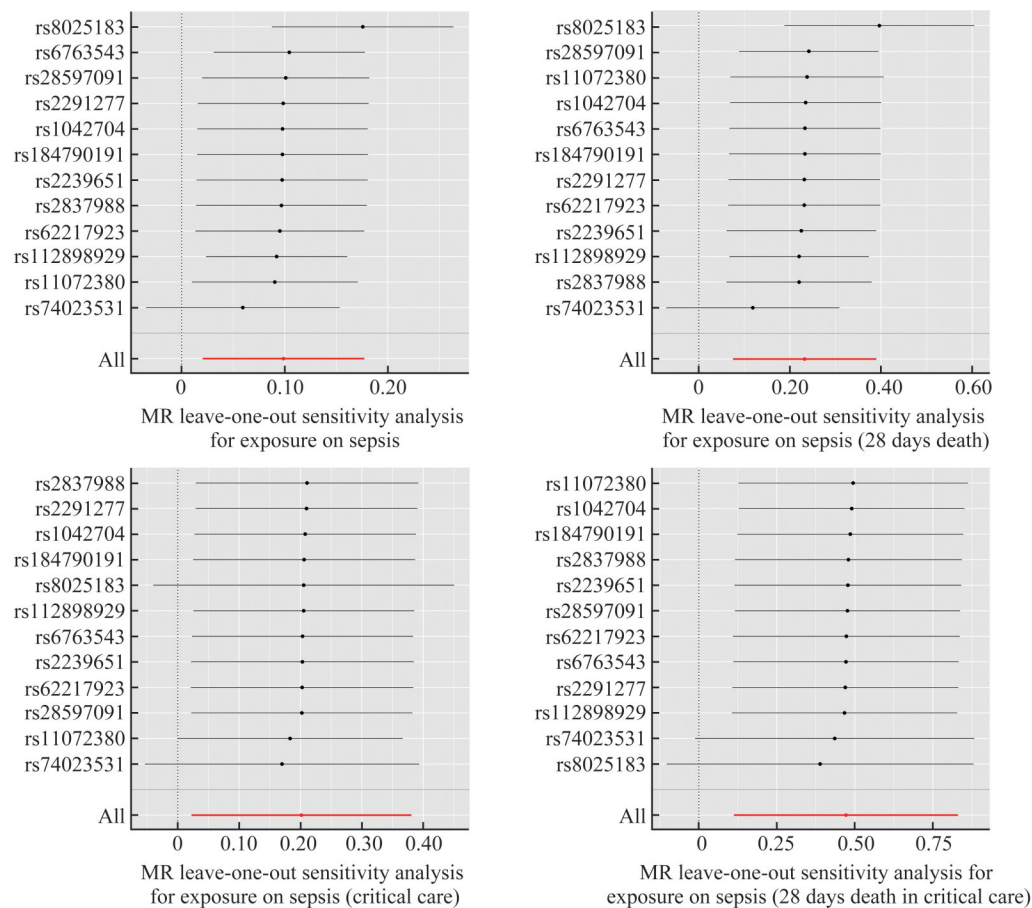


图3 留一法敏感性分析结果

Figure 3 Results of leave-one-out sensitivity analysis

MR: Mendelian randomization; B7-H3: B7 homolog 3.

表4 反向MR分析结果

Table 4 Reverse MR analysis results

| Exposure                                | Outcomes | Method | SNPs | OR    | 95% CI         | P     |
|-----------------------------------------|----------|--------|------|-------|----------------|-------|
| Sepsis                                  | B7-H3    | IVW    | 13   | 0.997 | 0.947 to 1.050 | 0.906 |
| Sepsis (28 days death)                  | B7-H3    | IVW    | 11   | 1.000 | 0.977 to 1.024 | 0.972 |
| Sepsis (critical care)                  | B7-H3    | IVW    | 6    | 1.005 | 0.980 to 1.031 | 0.710 |
| Sepsis (28 days death in critical care) | B7-H3    | IVW    | 7    | 1.005 | 0.994 to 1.017 | 0.377 |

B7-H3: B7 homolog 3; MR: Mendelian randomization; SNPs: Single nucleotide polymorphisms; OR: Odds ratio; CI: Confidence interval.

### 3 讨论

本研究利用公开发表的GWAS数据,通过MR分析方法,深入探讨了B7-H3与脓毒症的易感性、严重程度及临床结局之间的因果关联。研究表明B7-H3可能是脓毒症的重要生物标志物。具体而言,较高的B7-H3水平与更高的脓毒症发生风险、脓毒症28 d内死亡风险、重症脓毒症发生风险及重症脓毒症且28 d内死亡风险显著相关。敏感性分析和cML-MA检验结果进一步验证了这些结果的稳健性和可靠性。既往研究<sup>[28]</sup>结果也显示脓毒症患者血清中B7-H3异常表达与其病情和预后密切相关。

B7-H3除调节T细胞介导的免疫反应外<sup>[29-31]</sup>,还可作为先天免疫的共刺激剂,通过增强单核细胞/巨噬细胞和小胶质细胞中的促炎性细胞因子和趋化因子的产生来发挥作用<sup>[12]</sup>。正常人循环中sB7-H3通常处于较低水平,而脓毒症患者循环中sB7-H3水平显著升高,且脓毒症死亡患者血浆sB7-H3水平明显高于幸存者。用脂多糖(lipopolysaccharide, LPS)、肿瘤坏死因子 $\alpha$ (tumor necrosis factor- $\alpha$ , TNF- $\alpha$ )和干扰素 $\gamma$ 刺激新鲜分离的人单核细胞,与幼稚细胞相比,单核细胞释放大量的sB7-H3<sup>[13]</sup>。进一步研究<sup>[13]</sup>证明,细菌脂蛋白(Toll样受体2激动剂)和LPS(Toll样受体4激动剂)诱导核因子- $\kappa$ B激活, B7-H3可通过增强这一诱导激活作用及增加单核细胞/巨噬细胞中促炎性细胞因子的产生来介导炎症反应。随着脓毒症病情的进展,患者体内的TNF- $\alpha$ 、白介素-6(interleukin-6, IL-6)等细胞因子及炎症因子水平增高<sup>[32]</sup>,这又可导致循环中sB7-H3水平升高,通过瀑布样级联反应放大炎症反应,从而引发持续免疫激活和功能障碍的恶性循环<sup>[33-34]</sup>。脓毒症期间,适量细胞因子对细菌感染的先天免疫反应至关重要,但过度的产生可导致不受控制的全身炎症反应、组织损伤和多器官功能衰竭。脓毒症患者急性期后可发展为慢性危重疾病,称为持续性炎症-免疫抑制-分解代谢综合征<sup>[35]</sup>。

B7-H3通过炎症的共刺激作用放大单核细胞/巨噬细胞介导的炎症反应,在脓毒症的发生和发展中起重要作用,与其严重程度和临床结局密切相关。动物体内实验<sup>[13]</sup>进一步证明了这个观点,先用特异性B7-H3单克隆抗体MIH35中和B7-H3,再用致死剂量的LPS攻击小鼠,小鼠血清TNF- $\alpha$ 和IL-6水平与未用MIH35中和的对照组相比显著降低,同时小鼠存活率显著提高。这也证明血浆sB7-H3与促炎性细胞因子TNF- $\alpha$ 和IL-6之间关系密切<sup>[36]</sup>。重症肺部感染、急性胰腺炎等是脓毒症的常见病因, B7-H3参与许多脓毒症的病理生理过程。一项病例对照研究<sup>[37]</sup>显示:与对照组相比,急性期肺炎支原体肺炎(mycoplasmal pneumonia, MPP)患者的血浆sB7-H3水平显著升高,而与急性期患者相比,恢复期MPP患者的血浆sB7-H3水平显著降低,受试者操作特征曲线显示血浆sB7-H3水平可预测轻度MPP和重度MPP。Yang等<sup>[38]</sup>发现敲低B7-H3表达可减轻小鼠单核吞噬细胞的炎症反应。B7-H3蛋白在L-精氨酸诱导的急性胰腺炎中显著增加,抗B7-H3单克隆抗体可通过减轻炎症反应来改善急性胰腺炎的严重程度<sup>[39]</sup>。

本研究的创新性如下:首先,尽管脓毒症生物标志物的探索已有较多研究,但其中只有少数在大型或重复研究中得到了验证。这些研究中,蛋白质水平与疾病之间的关联往往不足以明确区分原因和结果。为了克服这一局限,本研究采用MR分析方法,可有效避免混杂因素和反向因果的影响,从而提供更具说服力的因果关系证据,使本研究在因果推理方面具备显著优势。其次,本研究利用欧洲人群大样本量的数据验证了先前的小样本量的中国人群研究结果<sup>[28]</sup>。这不仅增强了结果的稳健性,还实现了在不同人群中的外部验证。

当然,本研究也存在一定的局限性。首先,本研究纳入的样本均为欧洲人群,数据库中暂缺乏亚洲和非洲脓毒症的数据信息,因此在将结论推广到其他人群时需谨慎。未来研究需要涵盖更多样化的

人群以进一步验证结果。其次，尽管本研究揭示了B7-H3在脓毒症中的潜在因果作用，但仍需要进一步探究B7-H3在脓毒症病理生理机制中的具体作用。

综上所述，本研究通过MR方法发现了B7-H3与脓毒症风险之间的因果关系，表明B7-H3可能是脓毒症的重要生物标志物，与脓毒症的易感性、严重程度及临床结局密切相关。脓毒症患者血清中sB7-H3的上调可作为诊断、疾病严重程度及预后的生物标志物，靶向这一分子可能为脓毒症治疗提供新的策略。

**作者贡献声明：**郭名君 资料收集，软件操作，数据分析，论文撰写与修改；何智辉 论文设计、指导与修改。所有作者阅读并同意最终的文本。

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