

# Nano-seq 宏基因组测序在关节置换术后 假体周围感染诊断中的应用价值

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**摘要** 目的:探讨 Nano-seq 宏基因组测序在关节置换术后假体周围感染诊断中的应用价值。方法:纳入 38 例人工关节置换术后因疑似假体周围感染再次住院的患者。患者住院后,抽血测定血清 C 反应蛋白(C-reactive protein, CRP)含量、血沉(erythrocyte sedimentation rate, ESR)和血浆纤维蛋白原(fibrinogen, FIB)含量等指标,抽取关节液进行病原微生物培养和 Nano-seq 宏基因组测序。患者出院后,从病历系统中提取患者住院时测定的血清 CRP 含量、ESR、血浆 FIB 含量及病原微生物培养检验报告、Nano-seq 宏基因组测序检验报告及出院诊断结果。分别根据血清 CRP 含量、ESR、血浆 FIB 含量、病原微生物培养检验报告、Nano-seq 宏基因组测序检验报告诊断假体周围感染,并以出院诊断结果为金标准,计算上述指标诊断假体周围感染的敏感度、特异度、准确度、阳性预测值、阴性预测值。采用受试者操作特征(receiver operating characteristic, ROC)曲线评价不同指标诊断假体周围感染的应用价值。结果:血清 CRP 含量诊断假体周围感染的敏感度为 90.48%、特异度为 41.18%、准确度为 68.42%, ESR 诊断假体周围感染的敏感度为 66.67%、特异度为 64.71%、准确度为 65.79%, 血浆 FIB 含量诊断假体周围感染的敏感度为 66.67%、特异度为 70.59%、准确度为 68.42%, 病原微生物培养诊断假体周围感染的敏感度为 61.90%、特异度为 94.12%、准确度为 76.32%, Nano-seq 宏基因组测序诊断假体周围感染的敏感度为 95.24%、特异度为 82.35%、准确度为 89.47%。Nano-seq 宏基因组测序诊断假体周围感染的敏感度高于 ESR、血浆 FIB 含量、病原微生物培养( $P=0.045$ ,  $P=0.045$ ,  $P=0.020$ ), 特异度高于血清 CRP 含量( $P=0.032$ ), 准确度高于血清 CRP 含量、ESR、血浆 FIB 含量( $P=0.047$ ,  $P=0.026$ ,  $P=0.047$ )。血清 CRP 含量、ESR、血浆 FIB 含量、病原微生物培养、Nano-seq 宏基因组测序诊断假体周围感染的 ROC 曲线下面积分别为 0.791( $P=0.002$ )、0.706( $P=0.031$ )、0.734( $P=0.014$ )、0.780( $P=0.000$ )、0.888( $P=0.000$ )。结论:Nano-seq 宏基因组测序在关节置换术后假体周围感染诊断中具有较高的应用价值。

**关键词** 关节成形术, 置换; 假体和植入物; 感染; C-反应蛋白质; 血沉; 纤维蛋白原; 微生物培养检测; Nano-seq 宏基因组测序

## Application value of Nano-seq metagenomic sequencing in diagnosis of periprosthetic infections after arthroplasty

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**ABSTRACT Objective:** To explore the application value of Nano-seq metagenomic sequencing in the diagnosis of periprosthetic infections after arthroplasty. **Methods:** Thirty-eight patients re-hospitalized due to suspected periprosthetic infections after arthroplasty were included in the study. After the hospitalization, the blood and joint fluid samples were drawn from patients. The serum level of C-reactive protein(CRP), erythrocyte sedimentation rate(ESR) and the plasma level of fibrinogen(FIB) were measured, and the pathogenic microorganism detection and Nano-seq metagenomic sequencing were conducted. After hospital discharge, the information including serum level of CRP, ESR, plasma level of FIB, the pathogenic microorganism detection report, the Nano-seq metagenomic sequencing report and the discharge

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diagnosis was extracted from the electronic medical record system. Periprosthetic infections were diagnosed based on the serum level of CRP, ESR, plasma level of FIB, pathogenic microorganism detection report and Nano-seq metagenomic sequencing report respectively. With the hospital discharge diagnosis as the gold standard, the sensitivity, specificity, accuracy, positive predictive value and negative predictive value of the above-mentioned indicators in diagnosing periprosthetic infections were calculated. The application value of different indicators in diagnosing periprosthetic infections was evaluated by using the receiver operating characteristic (ROC) curve. **Results:** The sensitivity, specificity and accuracy of serum CRP level in diagnosing periprosthetic infections were 90.48%, 41.18% and 68.42% respectively. The sensitivity, specificity and accuracy of ESR were 66.67%, 64.71% and 65.79% respectively. The sensitivity, specificity, and accuracy of plasma FIB level were 66.67%, 70.59% and 68.42% respectively. The sensitivity, specificity and accuracy of pathogenic microorganism detection were 61.90%, 94.12% and 76.32% respectively. The sensitivity, specificity and accuracy of Nano-seq metagenomic sequencing were 95.24%, 82.35% and 89.47% respectively. The Nano-seq metagenomic sequencing had higher sensitivity than ESR, plasma FIB level and pathogenic microorganism detection ( $P = 0.045$ ,  $P = 0.045$ ,  $P = 0.020$ ), higher specificity than the serum CRP level ( $P = 0.032$ ), and higher accuracy than the serum CRP level, ESR and plasma FIB level ( $P = 0.047$ ,  $P = 0.026$ ,  $P = 0.047$ ) in diagnosing periprosthetic infections. The areas under the ROC curves of serum CRP level, ESR, plasma FIB level, pathogenic microorganism detection and Nano-seq metagenomic sequencing in diagnosing periprosthetic infections were 0.791 ( $P = 0.002$ ), 0.706 ( $P = 0.031$ ), 0.734 ( $P = 0.014$ ), 0.780 ( $P = 0.000$ ) and 0.888 ( $P = 0.000$ ) respectively. **Conclusion:** Nano-seq metagenomic sequencing demonstrates a high application value in the diagnosis of periprosthetic infections after arthroplasty.

**Keywords** arthroplasty; replacement; prostheses and implants; infection; C-reactive protein; blood sedimentation; fibrinogen; microorganism detection; Nano-seq metagenomic sequencing

人工关节置换是髋、膝关节疾病终末期治疗的有效方法,能够显著提高患者生活质量<sup>[1]</sup>。假体周围感染是人工关节置换的严重并发症之一,发生率为 1%~2%<sup>[2]</sup>。相关研究发现,假体周围感染与人工关节置换手术失败密切相关,而假体周围感染的医疗费用是初次关节置换的 5 倍以上<sup>[3-4]</sup>。此外,部分假体周围感染患者的病原微生物难以通过微生物培养检出,增加了假体周围感染漏诊、误诊的风险<sup>[5]</sup>。Nano-seq 宏基因组测序属于第 3 代测序 (third-generation sequencing, TGS) 技术,具有测序快速、准确等特点,在病原微生物的基因测序中具有独特的优势<sup>[6-9]</sup>。为了探讨 Nano-seq 宏基因组测序在关节置换术后假体周围感染诊断中的应用价值,我们进行了相关研究,现总结报告如下。

## 1 临床资料

**1.1 一般资料** 选取 2020 年 1 月至 2021 年 9 月在郑州市骨科医院采用人工关节置换术治疗后因疑似假体周围感染再次住院的患者为研究对象。试验方案经郑州市骨科医院伦理委员会审查通过,伦理批件号:2019010。

**1.2 纳入标准** ①人工关节置换术后再次住院;②疑似为假体周围感染<sup>[10]</sup>;③神志清醒,智力正常,可配合进行相关检查;④参与本研究,签署知情同意书。

**1.3 排除标准** ①合并其他部位感染者;②入院前 2 周使用抗菌药物者。

**1.4 退出标准** ①抽取关节液不足者;②关节液样品在运输、使用过程中被污染者。

## 2 方法

**2.1 检查方法** 患者住院后,抽血测定血清 C 反应蛋白 (C-reactive protein, CRP) 含量、血沉 (erythrocyte sedimentation rate, ESR) 和血浆纤维蛋白原 (fibrinogen, FIB) 含量等指标;抽取患者 2 份关节液样本,每份 5 mL。将其中 1 份关节液冷冻处理后,送至郑州迪安医学检测所有限公司,并于采集后 4 h 内进行 Nano-seq 宏基因组测序;另 1 份关节液送至检验科进行病原微生物培养。Nano-seq 宏基因组测序后,由郑州迪安医学检测所有限公司进行生物信息学分析,并出具病原微生物检验报告。

**2.2 数据收集与分析方法** 患者出院后,从病历系统中提取患者入院时测定的血清 CRP 含量、ESR、血浆 FIB 含量及病原微生物培养检验报告、Nano-seq 宏基因组测序检验报告及出院诊断结果。分别根据血清 CRP 含量、ESR、血浆 FIB 含量、病原微生物培养检验报告、Nano-seq 宏基因组测序检验报告诊断假体周围感染,并以出院诊断结果为金标准,计算上述指标诊断假体周围感染的敏感度、特异度、准确度、阳性预测值、阴性预测值。血清 CRP 含量、ESR、血浆 FIB 含

量诊断假体周围感染的依据分别为血清 CRP 含量  $> 10 \text{ mg} \cdot \text{L}^{-1}$ <sup>[11]</sup>、ESR  $> 30 \text{ mm} \cdot \text{h}^{-1}$ <sup>[12]</sup>、血浆 FIB 含量  $> 4.01 \text{ g} \cdot \text{L}^{-1}$ <sup>[13]</sup>。Nano-seq 宏基因组测序和病原微生物培养诊断假体周围感染依据检验报告结果。

**2.3 数据统计方法** 采用 SPSS26.0 统计软件对所得数据进行统计学分析。Nano-seq 宏基因组测序诊断假体周围感染的敏感度、特异度、准确度与其他指标的比较均采用 Fisher 确切概率法检验;采用受试者操作特征(receiver operating characteristic, ROC)曲线评价不同指标诊断假体周围感染的应用价值。检验水准  $\alpha = 0.05$ 。

### 3 结果

共纳入 39 例患者,1 例患者关节液使用过程中被污染,最终纳入 38 例患者。血清 CRP 含量诊断假体周围感染的敏感度为 90.48%、特异度为 41.18%、准确度为 68.42%,ESR 诊断假体周围感染的敏感度为 66.67%、特异度为 64.71%、准确度为 65.79%,血浆 FIB 含量诊断假体周围感染的敏感度为 66.67%、特异度为 70.59%、准确度为 68.42%,病原微生物培养诊断假体周围感染的敏感度为 61.90%、特异度为 94.12%、准确度为 76.32%,Nano-seq 宏基因组测序诊断假体周围感染的敏感度为 95.24%、特异度为 82.35%、准确度为 89.47%(表 1 至表 5)。Nano-seq 宏基因组测序诊断假体周围感染的敏感度高于 ESR、血浆 FIB 含量、病原微生物培养( $P = 0.045$ ,  $P = 0.045$ ,  $P = 0.020$ ),与血清 CRP 含量的差异无统计学意义( $P = 1.000$ );Nano-seq 宏基因组测序诊断假体周围感染的特异度高于血清 CRP 含量( $P = 0.032$ ),与 ESR、血浆 FIB 含量、病原微生物培养的差异均无统计学意义( $P = 0.438$ ,  $P = 0.688$ ,  $P = 0.601$ );Nano-seq 宏基因组测序诊断假体周围感染的准确度高于血清 CRP 含量、ESR、血浆 FIB 含量( $P = 0.047$ ,  $P = 0.026$ ,  $P = 0.047$ ),与病原微生物培养的差异无统计学意义( $P = 0.222$ )。血清 CRP 含量、ESR、血浆 FIB 含量、病原微生物培养、Nano-seq 宏基因组测序诊断假体周围感染的 ROC 曲线下面积分别为 0.791( $P = 0.002$ )、0.706( $P = 0.031$ )、0.734( $P = 0.014$ )、0.780( $P = 0.000$ )、0.888( $P = 0.000$ ),见图 1。

### 4 讨论

随着社会老龄化的加剧,人工关节置换的需求不断增加,导致假体周围感染患者人数也随之逐渐增

表 1 血清 C 反应蛋白含量诊断假体周围感染结果

单位:例

血清 C 反应蛋白含量 诊断结果	确诊结果		合计
	阳性	阴性	
阳性	19	10	29
阴性	2	7	9
合计	21	17	38

表 2 血沉诊断假体周围感染结果

单位:例

血沉诊断结果	确诊结果		合计
	阳性	阴性	
阳性	14	6	20
阴性	7	11	18
合计	21	17	38

表 3 血浆纤维蛋白原含量诊断假体周围感染结果

单位:例

血浆纤维蛋白原含量 诊断结果	确诊结果		合计
	阳性	阴性	
阳性	14	5	19
阴性	7	12	19
合计	21	17	38

表 4 病原微生物培养诊断假体周围感染结果

单位:例

病原微生物培养 诊断结果	确诊结果		合计
	阳性	阴性	
阳性	13	1	14
阴性	8	16	24
合计	21	17	38

表 5 Nano-seq 宏基因组测序诊断假体周围感染结果

单位:例

Nano-seq 宏基因组测序 诊断结果	确诊结果		合计
	阳性	阴性	
阳性	20	3	23
阴性	1	14	15
合计	21	17	38

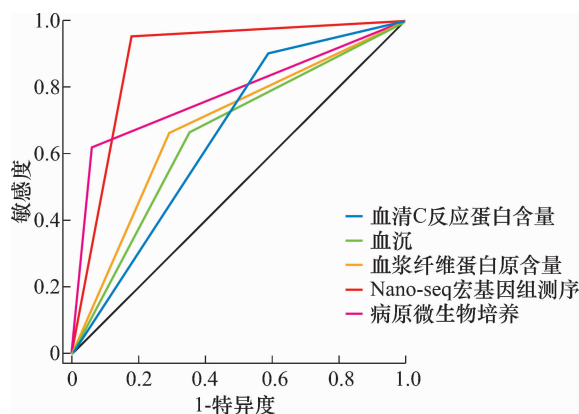


图 1 不同指标诊断假体周围感染的受试者操作特征曲线

加<sup>[14]</sup>。早期诊断假体周围感染并明确病原微生物种属对于假体周围感染的治疗具有重要意义。血清 CRP 含量和 ESR 在辅助诊断假体周围感染中具有一定的应用价值<sup>[15]</sup>。然而,部分假体周围感染患者的临床症状不典型,血清 CRP 含量、ESR 等指标无异常,导致假体周围感染漏诊的风险增大,进而降低关节置换的成功率、增加假体翻修的风险<sup>[16]</sup>。Akgun 等<sup>[17]</sup>回顾性分析了 215 例假体周围感染患者的病例资料,其中 77 例术前血清 CRP 含量正常,进一步分析这些患者的致病菌种属发现,血清 CRP 含量对丙酸杆菌、凝固酶阴性葡萄球菌和肠球菌等低毒力致病菌感染导致的假体周围感染的诊断敏感度较低。Watanabe 等<sup>[18]</sup>的研究结果也表明,部分假体周围感染患者的血清 CRP 含量和 ESR 在正常范围内。因此,依据血清 CRP 含量和 ESR 诊断假体周围感染可能会导致误诊,从而延长假体周围感染患者的诊疗周期。血浆 FIB 含量升高能够提示机体炎症反应的发生<sup>[19]</sup>。黄金承等<sup>[11]</sup>研究发现,血浆 FIB 含量可用于辅助诊断假体周围感染。目前关于血清 CRP 含量、ESR、血浆 FIB 含量诊断假体周围感染的标准以及应用价值均存在争议<sup>[20-21]</sup>。本研究结果显示,这些指标在诊断假体周围感染中具有一定的应用价值,血清 CRP 含量诊断假体周围感染的敏感度较高,但特异度较低,而 ESR 和血浆 FIB 含量诊断假体周围感染的敏感度和特异度均不高,且这 3 项指标的准确度均不高。

Nano-seq 宏基因组测序采用 Nanopore 测序平台进行,能够实现单分子实时测序。该技术通过捕捉 DNA 或 RNA 通过纳米孔道时形成的特征性电信号变化,并将电信号转换为碱基序列,完成核酸序列的测定;Nano-seq 宏基因组测序具有更长的读取长度、更低的碱基错配率,且能够检测的病原微生物种属范围更广<sup>[9]</sup>。在完成测序后,通过生物信息学分析,可以获得病原微生物的相关信息,进而为医生制定治疗方案提供帮助<sup>[22-23]</sup>。Luo 等<sup>[24]</sup>收集了 70 例上呼吸道感染患者的支气管肺泡灌洗液样本,分别采用微生物培养和 TGS 进行病原微生物检测,结果显示微生物培养的阳性率为 25.71%,TGS 的阳性率为 84.29%。Wang 等<sup>[25]</sup>研究发现,基于 Nanopore 测序平台的 TGS 技术在鉴别假体周围感染患者的病原微生物种属方面具有显著优势。Yu 等<sup>[26]</sup>收集肝癌合并腹水感染

患者的腹水样本进行 TGS,结果显示 TGS 在检测多种细菌合并感染方面具有显著优势。Huang 等<sup>[27]</sup>的研究结果表明,基于 Nanopore 测序平台的 TGS 技术检测病原微生物的敏感性较高。相关研究发现,近年来真菌、分枝杆菌、布鲁氏杆菌等需要特定检测方法检测的病原微生物导致的假体周围感染患者人数呈上升趋势,而依据传统微生物培养检查结果为阴性的假体周围感染患者占假体周围感染患者 40% 以上<sup>[28-29]</sup>。Nano-seq 宏基因组测序在真菌、病毒等病原微生物的检测方面具有显著优势<sup>[25]</sup>。此外,传统的微生物培养检测存在结果滞后问题,而 Nano-seq 宏基因组测序可在 24 h 内得到检测结果,并可提供更加准确、全面的病原微生物信息,进而为假体周围感染的早期诊断和治疗提供可靠依据<sup>[30]</sup>。

本研究结果表明,Nano-seq 宏基因组测序在关节置换术后假体周围感染诊断中具有较高的应用价值。Nano-seq 宏基因组测序专业性较强、成本较高,目前在临床中的应用较少。但随着科技的发展和技术的进步,Nano-seq 宏基因组测序将会在假体周围感染的诊断中发挥更加重要的作用。

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