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ORIGINAL RESEARCH

Evaluation of High-Throughput Gene Chip Array for Enhanced Diagnosis of Bone and Joint Infections: A Comparative Analysis with mNGS and Conventional Culture Methods

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Background: While conventional culture-based diagnosis of bone and joint infections (BJI) requires prolonged incubation periods and metagenomic next-generation sequencing (mNGS) remains cost-prohibitive for routine clinical use, there is an urgent need for diagnostic strategies that balance timeliness with economic feasibility. This study investigates the clinical utility of a high-throughput (HT) gene chip array as a novel solution, offering significantly shorter turnaround time while maintaining cost-effectiveness than mNGS expenses.

Methods: Thirty-six patients of the BJI group (28 positives and 8 negatives diagnosed by clinician) and 20 patients of respiratory tract infection (RTI) group (14 positives and 6 negatives diagnosed by clinician) were included in this study. Synovial fluid and ultrasound fluid samples of BJI group and alveolar lavage fluid samples of RTI group were collected and subjected to microbiological analysis performed by HT gene chip array, metagenomic next-generation sequencing (mNGS) and conventional culture. Sensitivity, specificity, accuracy, positive predictive value (PPV) and negative predictive value (NPV) were calculated. Positive and negative percent agreement and Cohen`s kappa coefficient were calculated.

Results: The sensitivity and accuracy of HT gene chip assay for BJI detection was 71.43% and 77.78%, respectively (p value <0.05). HT gene chip assay exhibited the 100% of specificity and PPV, which is significantly higher than those of mNGS (62.5%, 89.29%) and conventional culture (78.57% and 88.89%). Our results position HT gene chip assay as a clinically actionable solution for accurate and timely bone and joint infection management.

Conclusion: HT gene chip assay demonstrates superior diagnostic specificity and cost-effectiveness with rapid turnaround, significantly reducing unnecessary invasive procedures while maintaining high concordance with mNGS, and exhibited higher clinical value of BJI diagnosis compared with mNGS and conventional culture.

Keywords: bone and joint infection, metagenomic next generation sequencing, mNGS, conventional culture, high-throughput gene chip array, HT

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Introduction

Bone and joint infections (BJI) can be life-threatening and commonly associated with long-term disability.[1–3] The spectrum of the disease includes periprosthetic joint infection, prosthetic joint infection and haematogenous osteomyelitis, etc.[4] In clinic, bacteria colonize bone via direct inoculation from trauma or surgery, the contiguous infection spreads to other organs such as lung. Diagnosis requires clinical symptoms, appropriate radiological imaging and microbiological sampling. BJI is usually diagnosed through arthrocentesis. It is usually diagnosed by synovial fluid extraction, traditional blood tests such as C-reactive protein (CRP), neutrophilic granulocyte (NE), serum amyloid A (SAA), procalcitonin (PCT) and white blood cell count (WBC), or by intraoperative tissue cultures.[5] Conventional culture has been shown to have a long cultivation time and a high false-negative rate due to inconsistency of sample collecting. It is in critical need to adopt faster and more accurate approach to identify the bacteria species for precise BJI treatment.

Metagenomic next-generation sequencing (mNGS) is a rapidly evolving and widely used in pathogen detection and identification in clinic by high-throughput sequencing the whole genome of pathogens in the patients' samples. The detection spectrum of mNGS covers all known or unknown pathogens, including fungi, bacteria, mycoplasma and parasites, etc.[6–9] mNGS is often considered unbiased pathogen identification test thanks to its comprehensive pathogenic species and their abundance analysis. The clinical mNGS diagnoses are usually time-consuming and costly which could delay treatment and increase economic burden for patients. Several studies have shown that mNGS exerts higher sensitivity and specificity for BJI detection than conventional culture.[10–15]

Given the high cost of mNGS sequencing of pathogen genomes in a large number of samples, DNA arrays have been demonstrated the comparable capability of detection, surveillance, and screening of pathogens.[16,17] The whole genome tiling arrays with high density oligonucleotide features that cover each base of the genome of interest leads to accuracy improvement and production cost reduction.[18–20] Here we describe a previously unreported application of high-throughput (HT) gene chip array technology for diagnosing BJI. This cost-effective platform, covering 40 pathogens (including 23 bacteria, 8 fungi and 7 viruses) (Supplemental Table S1), was successfully implemented for bacterial species detection in both BJI and respiratory tract infection (RTI) clinical samples, demonstrating significant cost advantages compared to mNGS.[21–23] Our results indicate that our HT gene chip array achieves comparable sensitivity and accuracy as well as higher specificity and positive predictive value (PPV) compared with mNGS and conventional culture, ultimately positioning it as a clinically superior alternative to both mNGS and conventional culture for precise bone and joint infection management.

Methods

Study Population Selection

The selection of patients for this study was approved by the Medical Ethics Committee of the Shanghai Sixth People's Hospital [2024-KY-055(K)] and conducted in accordance with the Declaration of Helsinki. All patients provided informed consent by signing an informed consent form. Clinical trial number: not applicable. Patients with suspected BJI and patients with respiratory tract infection (RTI) who underwent surgery at our hospital were enrolled. In this cohort, 29 cases (51.8%) were classified as chronic infections, while 27 cases (48.2%) presented as acute infections. Among the patients, 22 cases (39.3%) had recurrent infection and 34 cases (60.7%) were first-time infection. Thirty-seven cases (66%) were BJI, and 19 cases (34%) were RTI.

The diagnosis of BJI was based on the American Musculoskeletal Infection Society (MSIS) diagnostic criteria, which were confirmed by one major criterion or four of six minor criteria.[24] The diagnosis of RTI was based on the ICM respiratory infection diagnostic criteria. Patients were divided into the BJI group and the RTI group (Figure 1).

The inclusion criteria for patients in the BJI group were as follows:

1. Patients diagnosed with BJI according to MSIS diagnostic criteria and treated in our hospital;
2. Sinus tract communicating with the joint prosthesis (fistula); Two or more positive cultures of periprosthetic tissue or fluid yielding the same organism. Meeting either of these suffices for a definitive BJI diagnosis;
3. Patients with complete medical records.

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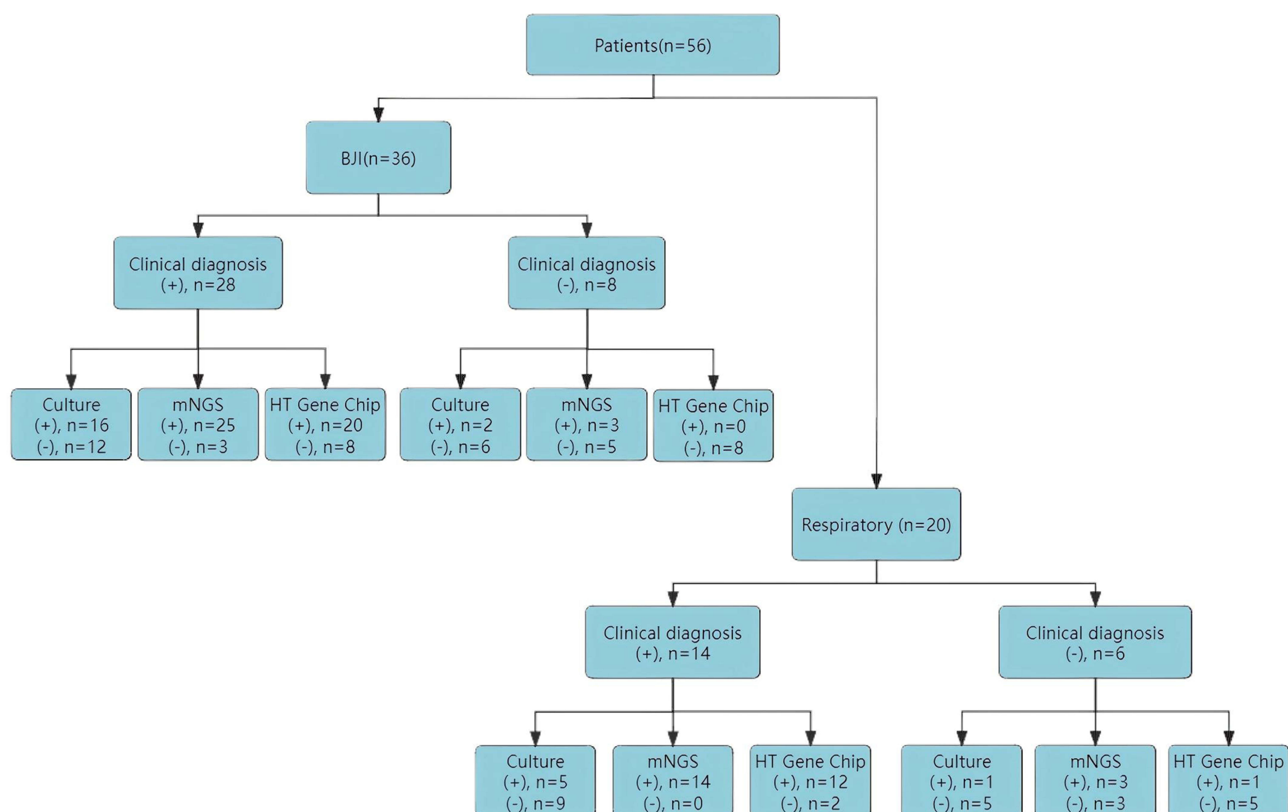

Figure 1 Flow Chart. Patient selection flowchart. BJI, Respiratory, + Positive, − Negative.

Exclusion criteria are as follows:

Patients presenting with other inflammatory lesions or malignant tumors that may affect prognosis.

The inclusion criteria for patients in the RTI group were as follows:

1. Patients diagnosed with BJI according to the ICM diagnostic criteria and receiving treatment in our hospital;
2. Patients with complete medical records.

The exclusion criteria were as follows:

Patients presenting with other inflammatory lesions or malignancies that may affect prognosis.

Specimen Collection and Bacterial Culture

Surgeons collected synovial fluid and ultrasound fluid samples from patients with suspected BJI intraoperatively through arthrocentesis under ultrasound guidance, and intraoperatively through ultrasonic cutting. Prostheses and inflammatory apparent tissues were excised, and tissues, synovial fluid and ultrasound fluid samples were retained. The samples were immediately collected and transferred to the microbiology laboratory for microbiological culturing. Respiratory infection samples were collected from patients' alveolar lavage fluid as guided by the standard clinical processing protocol.

Conventional Culture

A total of 0.1 mL aliquots of joint fluid and ultrasound-treated fluid were incubated on blood agar at 35–37°C, 5–7% CO_2, for 7 days and 14 days under aerobic and anaerobic conditions, respectively. The positive results were determined by the criteria of the Clinical and Laboratory Standards Institute (CLSI). If the result is positive, it is passed on the blood AGAR Tissues were homogenized in broth and inoculated according to the above protocol, and each sample was plated in triplicate. All bacterial identifications were performed using the Vitek 2 strain (BioMerieux Vitek, Inc., Cambridge, MA, USA).

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mNGS Testing

mNGS materials were prepared as described previously. Sample preprocessing was first performed: 1 mL of ultrasonicated lavage fluid, synovial fluid, and bronchoalveolar lavage fluid were collected and centrifuged at 10,000 × g for 5 minutes. The supernatant was discarded, and 1 mL of Hypotonic Disruption Solution (HDS) was added to the pellet to lyse host cells. The mixture was vortexed and incubated at room temperature for 15 min, followed by centrifugation at 10,000 × g for 5 minutes. The supernatant was removed. Subsequently, 25 µL of Proteinase K was added to the pellet, incubated at 55°C for 10 min, and then cooled at 4°C for 5 min. Finally, DNA was extracted from samples using the TIANamp Maxi DNA Kit (DP710, Tiangen Biotech, Beijing, China) following the manufacturer's standard protocols. The extracted DNA was fragmented to 200–300 bp in size by ultrasound. DNA library construction was performed using the UltraClean Universal Plus DNA Library Prep Kit for Illumina V3 (UND637, Vazyme Biotech, Nanjing, China) according to the manufacturer's standard protocols, including steps of Fragmentation, End Preparation & dA-tailing, Adapter Ligation, and Library Amplification. Quality control of the libraries was assessed using the Agilent 2100 system (Agilent Technologies, Santa Clara, USA).

The qualified libraries were sequenced on an Illumina NextSeq platform (Genoxor Medical Technology, Shanghai, China). The sequencing data were generated after filtering out low-quality, low-complexity, and shorter reads by bcl2fastq2. The human sequences were excluded by mapping to the human reference genome using an alignment tool Bowtie2. The remaining data were aligned to the Microbial Genome Databases (downloaded from NCBI), including 13434 whole-genome sequences of viral taxa, 7982 bacterial genomes or scaffolds, 917 fungi related to human infection, 4411 viruses related to human infection, and 124 parasites associated with human diseases.

High-Throughput Gene Chip Array

We used a high throughput gene chip (Summit™ gene chip) from Centrillion Biotechnologies with capability of detecting 40 common pathogens. Briefly, sample DNA was extracted using TIANamp Maxi DNA Kit (DP710, Tiangen Biotech, Beijing, China). 0.05 µL of purified DNA product was amplified with 0.4 M of pre-designed primer sets by target multiplex PCR amplification using VAHTSTM AmpSeq Multi-PCR Module V3 (Vazyme: NA215). To prepare samples for hybridization to the chips, the PCR products were fragmented using DNase I (D4263, Sigma). Samples were incubated for 30 minutes at 37°C, and the reactions were stopped by adding EDTA to a final concentration of 12.5 mM and incubating for 20 minutes at 75°C. 45 µL of the fragmented sample was hybridized overnight at 45°C to the chip in a 60 µL final volume containing 5 mM EDTA, 6.25 m MHEPES pH 8.0, 312.5 mM NaCl, 1.25% Ficoll 400. Following hybridization, chips were washed for 10 minutes at room temperature in Wash A (2x SSC, 0.1% TWEEN-20) and then for 10 minutes at 39°C in Wash B (0.5xSSC, 0.1% TWEEN-20). Chips were stained for 15 minutes at room temperature using 0.02 mg/mL Cy3-Streptavidin (Thermo) in 4x SSC and washed for 5 minutes at room temperature using 4xSSC. Chips were scanned using a custom built confocal scanner for 0.5, 1, 4, and 8 seconds in the green (Cy3) channel in 4x SSC. The hybridization signals were scanned by a gene chip scanner, and the final test results were automatically interpreted by the Summit™ gene chip array platform.

Statistical Analysis

Differences between BJI and respiratory infection were analyzed using the chi-square test or Fisher's exact test, and non-normally distributed parameters were analyzed using the Mann–Whitney *U*-test. Sensitivity, specificity, positive predictive rate (PPV), negative predictive rate (NPV) and accuracy were calculated for each diagnostic method. The McNemar cardinality adoption test (two-sided) was used to compare the sensitivity and specificity of diagnostic tests. All analyses were performed using *SPSS* software v26.0 with p value <0.05 considered statistically significant.

Results

The BJI group (13 samples of ultrasonic shock fluid, 9 samples of joint fluid and 14 samples of tissue) included 28 clinically diagnosed positive cases and 8 clinically diagnosed negative cases. The RTI group (alveolar lavage fluid samples) included 14 clinically diagnosed positive cases and 6 clinically diagnosed negative cases were included in the study (Figure 1). There was no significant difference in age, gender, and body mass index between the two groups

(Table 1). The serological markers CRP, PCT, WBC, SAA and NE showed no significant differences between the clinically diagnosed positive group and the clinically diagnosed negative group. The area under the curve (AUC) of CRP and PCT were 0.523 and 0.477, respectively. The AUC of WBC, SAA and NE were 0.44, 0.62, and 0.613, respectively (Table 2, Supplemental Figure S1).

In the BJI group, the sensitivity and specificity of HT gene chip array were 71.43% (20 out of 28) and 100% (8 out of 8) compared with 89.29% (25 out of 28) and 62.50% (5 out of 8) of mNGS respectively, suggesting higher negative case detection accuracy and comparable positive case detection level between HT gene chip array and mNGS ($p<0.005$) (Table 3, Supplemental Figure S2A, Figure 2A). HT gene chip array also showed superior sensitivity and specificity than conventional culture method (59.52% and 78.57%) (p value <0.05). The ACC, PPV and NPV for HT gene chip array were 77.78% (28 out of 36), 100% (20 out of 20) and 53.33% (8 out of 15) indicating higher PPV rate over mNGS (89.29%) and conventional culture (88.89%) (p value <0.05) (Table 3, Figure 2A).

Using RTI as a comparison group, the sensitivity and specificity of HT gene chip array were 85.71% (12 out of 14) and 83.33% (5 out of 6) compared with 100.00% (14 out of 14) and 50.00% (3 out of 6) of mNGS, respectively, suggesting a comparable detection effectiveness between HT gene chip array and mNGS (Table 3, Supplemental Figure S2B, Figure 2B). HT gene chip array exhibited superior sensitivity and specificity than conventional culture method (35.71% and 35.71%) (p value <0.05) (Table 3, Supplemental Figure S2B, Figure 2B). The ACC, PPV and NPV for HT gene chip array were 85.00% (17 out of 20), 92.31% (12 out of 13) and 71.43% (5 out of 7) indicating higher PPV rate over mNGS (82.35%) and conventional culture (35.71%) (p value <0.05) (Table 3, Figure 2B).

When combining BJI with RTI group, HT gene chip array exhibited the sensitivity and specificity of 76.19% (32 out of 42) and 92.86% (13 out of 14) in consistent with 92.86% (39 out of 42) and 57.14% (8 out of 14) of mNGS (Table 3,

Table 1 Demographic Characteristics of Tested Patients

Characteristics	BJI (n=36)	RTI (n=20)	*p* value
Age, years, median(range)	62.19±12.61	65.79±9.72	0.854
Women	14(38.89)	6(30.00)	0.792
Men	22(61.11)	14(70.00)	0.758
BMI	27.1±2.6	26.9±2.3	0.561

Abbreviation: BMI, Body Mass Index.

Table 2 mNGS, Conventional Culture, HT Gene Chip and Serum Biomarker Test Results

	Infection Group	Non-Infection Group	*p* value
CRP (mg/dL)	43.07 (3.29–132.71)	46.08 (0.5–183)	0.86
SAA (mg/L)	72.35 (2.5–202.7)	164.44 (2.5–550)	0.06
PCT (ng/mL)	0.0903 (0.02–0.33)	0.265 (0.02–5.07)	0.25
WBC (10^9/L)	8.06 (4.6–19.1)	7.48 (2–19.7)	0.64
NE (%)	0.636 (0.46–0.809)	0.683 (0.405–0.909)	0.20
mNGS			<0.05
+	39(92.9)	6(42.9)	
−	3(7.1)	8(57.1)	
Conventional culture			<0.05
+	21(50)	3(21.4)	
−	21(50)	11(78.5)	
HT Gene Chip			<0.05
+	32(76.1)	1(7.1)	
−	10(23.8)	13(92.8)	

Note: + positive, - negative.

Table 3 The Diagnostic Capabilities of mNGS, Conventional Culture, HT Gene Chip in Three Group

	BJI Group			RTI Group			BJI+RTI Combined Group		
	mNGS	**Conventional Culture**	**HT Gene Chip**	**mNGS**	**Conventional Culture**	**HT Gene Chip**	**mNGS**	**Conventional Culture**	**HT Gene Chip**
FP	3	2	0	3	1	1	6	3	1
TP	25	16	20	14	5	12	39	21	32
TN	5	6	8	3	5	5	8	11	13
FN	3	12	8	0	9	2	3	21	10
P	<0.005	<0.005	<0.005	<0.005	<0.005	<0.005	<0.005	<0.005	<0.005
ACC	83.33	61.11	77.78	85.00	50.00	85.00	83.93	42.86	80.36
Sen	89.29	59.52	71.43	100.00	35.71	85.71	92.86	50.00	76.19
Spe	62.50	78.57	100.00	50.00	35.71	83.33	57.14	78.57	92.86
P	<0.005	<0.005	<0.005	<0.005	<0.005	<0.005	<0.005	<0.005	<0.005
PPV	89.29	88.89	100.00	82.35	83.33	92.31	86.67	87.50	96.97
NPV	62.50	33.33	53.33	100.00	35.71	71.43	72.73	34.38	56.52

Abbreviations: FP, False positive; TP, True positive; TN, True negative; FN, False negative; ACC, Accuracy; Sen, Sensitivity; Spe, Specificity; PPV, Positive predictive value; NPV, Negative predictive value.

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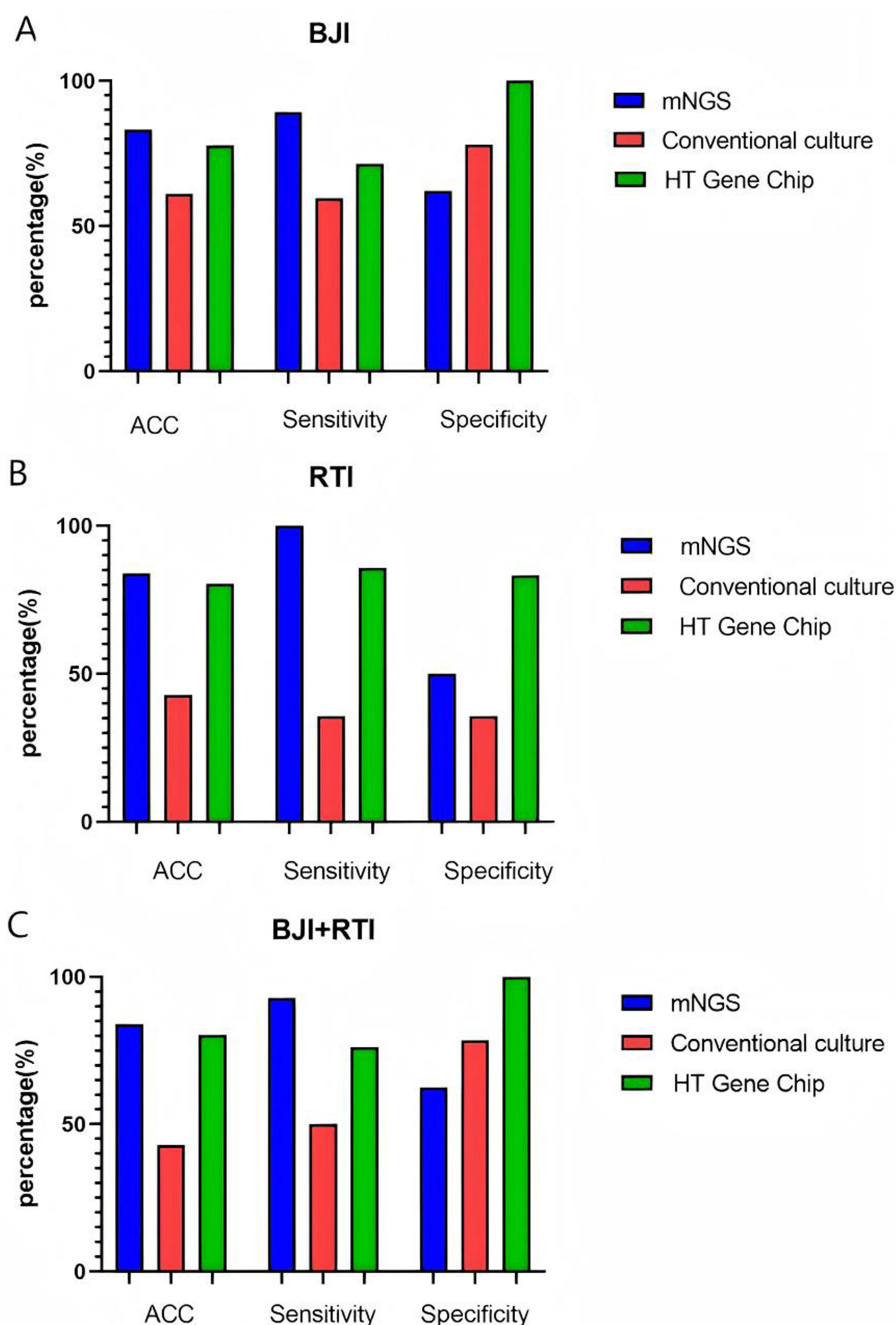

Figure 2 Compare the ACC, Sensitivity and Specificity in BJI, RTI, BJI and RTI. (**A**–**C**), Bar graphs showed the comparison among mNGS, conventional culture, and HT gene chip results under the diagnosis of BJI (**A**), RTI (**B**), and BJI+RTI (**C**).

Figure 2C). In this group, the ACC, PPV and NPV for HT gene chip array were 80.36% (45 out of 56), 96.97% (32 out of 33) and 56.52% (13 out of 23) indicating higher PPV rate over mNGS (86.67%) and conventional culture (87.50%) (p value <0.05) (Table 3, Figure 2C).

mNGS detected 22 pathogen species including Staphylococcus aureus (9 samples), Pseudomonas aeruginosa (4 samples), Staphylococcus epidermidis (4 samples), and so on. The conventional culture tested 13 kinds of pathogens including Staphylococcus aureus (10 samples) Candida albicans (6 samples), and Staphylococcus epidermidis (3 samples) and so on.

Table 4 Comparing Consistency Between Different Approaches

Group Comparison	Kappa Coefficients	*p* value
HT Gene Chip vs Conventional Culture	0.393	0.015
mNGS vs Conventional Culture	0.344	0.014
HT Gene Chip vs mNGS	1	<0.005

The HT gene chip examined 14 types of pathogens which included Staphylococcus aureus (11 samples), Candida albicans (8 samples), Pseudomonas aeruginosa (5 samples), and so forth (Supplemental Table S2).

Through consistency comparison, conventional culture with Kappa coefficient of 0.393 and 0.344 showed low consistency with HT gene chip array and with mNGS, respectively. Kappa coefficient of 1 between HT gene chip array vs mNGS exhibited significantly high consistency (p value <0.05) (Table 4).

Discussion

The rapid and precise diagnosis of bone and joint infections takes into account clinical, radiological and microbiological criteria.[25] At present, there is still lack of reference diagnostic standard. We herein explored the clinical value of HT gene chip array in comparison with mNGS and conventional culture for diagnosis of BJI.

Our results showed the optimal specificity (100%) and PPV (100%) of HT gene chip array for BJI diagnosis which exhibits superior detection efficiency of false positives than mNGS and conventional culture. The accuracy of HT gene chip array and mNGS for BJI diagnosis both achieved greater than 80% suggesting a comparable positive detection efficiency between the two methods despite the lower sensitivity of gene chip array than that of mNGS. The Kappa coefficient between the two methods reached 1 (p value <0.05) indicating a significantly high effectiveness consistency of BJI diagnosis. In clinic, mNGS based diagnostic measures are often costly and dramatically increase economic burden for patients and medical institutions.[26,27] In this study, we used the HT gene chip array at a cost of less than one tenth of mNGS and showed that HT gene chip array exhibits the similar or better diagnostic efficacy compared with mNGS. This HT gene chip technology could be applied to clinical diagnostic tools for BJI and other bacterial infections.[13,14,28] However, long-term efficacy and recurrence rates based upon HT gene chip array should be assessed in the future study.

HT gene chip array turnaround time usually takes only about 4.5 hrs or less which is much shorter than 28 hrs of mNGS. This advantage of HT gene chip array provides a rapid access to bacterial infection information for clinicians to treat patients in a timely fashion.

Conventional culture of synovial fluid or tissue samples is the present diagnostic gold standard for the definitive diagnosis of BJI. Our results showed that HT gene chip array exhibits significantly higher effectiveness than conventional culture in terms of sensitivity, specificity, accuracy, PPV and NPV, suggesting that HT gene chip array could be considered as an alternative detection option for BJI and other infections. The conventional culture has a limited sensitivity and specificity of distinguishing contamination and requires a long operative time of up to 14 days. HT gene chip array can overcome these limitations to produce higher efficacy and shorter process time in clinic. Compared with other emerging diagnostic technologies (such as CRISPR-Cas-based detection platforms), HT gene chip array demonstrated comparable diagnostic performance.[29]

CRP, PCT, WBC, SAA and NE have not proved as secure preoperative infection markers although they are suggested to improve diagnostic performance. Our results suggested that there is no significant difference in the expression level of these markers between the infected group and non-infected group. Varying specimen, such as synovial fluid, biopsies from bone or periprosthetic tissues or the sonication fluid from the removed prosthesis itself show different performances in different diagnostic procedures and complicate the comparison between existing studies.

There are some limitations to this study. The relatively small sample size was used for this study analysis. The samples used for the assay were not from consecutive cases, which may have resulted in selection bias. Future prospective studies need to be designed to improve the reliability of the results. More samples or multicenter studies should be conducted to further validate the effectiveness of HT gene chip array.

In summary, given its optimal diagnostic effectiveness, low cost and rapid turnaround time, HT gene chip array could be considered as an advanced diagnostic tool for BJI in clinic. And in the future, we propose expanding HT gene chip

validation through multicenter cohorts, incorporating antibiotic resistance gene panels and AI-guided automated detection systems, while establishing long-term outcome correlations and multimodal diagnostic frameworks integrating biomarkers for optimized BJI management.

Data Sharing Statement

All the data used to support the findings of this study are available from the corresponding author upon request.

Ethics Approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Shanghai Sixth People's Hospital (No. 2024-KY-055(K)). Clinical trial number: not applicable.

Consent to Participate

Informed consent was obtained from all individual participants included in the study.

Acknowledgments

Yunjiao Zhang and Qingxin Guo are co-first authors for this study.

Author Contributions

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work. The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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