The PJI-TNM classification for periprosthetic joint infections

Clinical application and implementation of an app-based classification tool

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Aims

This study aimed to evaluate the clinical application of the PJI-TNM classification for periprosthetic joint infection (PJI) by determining intraobserver and interobserver reliability. To facilitate its use in clinical practice, an educational app was subsequently developed and evaluated.

Methods

A total of ten orthopaedic surgeons classified 20 cases of PJI based on the PJI-TNM classification. Subsequently, the classification was re-evaluated using the PJI-TNM app. Classification accuracy was calculated separately for each subcategory (reinfection, tissue and implant condition, non-human cells, and morbidity of the patient). Fleiss' kappa and Cohen's kappa were calculated for interobserver and intraobserver reliability, respectively.

Results

Overall, interobserver and intraobserver agreements were substantial across the 20 classified cases. Analyses for the variable 'reinfection' revealed an almost perfect interobserver and intraobserver agreement with a classification accuracy of 94.8%. The category 'tissue and implant conditions' showed moderate interobserver and substantial intraobserver reliability, while the classification accuracy was 70.8%. For 'non-human cells,' accuracy was 81.0% and interobserver agreement was moderate with an almost perfect intraobserver reliability. The classification accuracy of the variable 'morbidity of the patient' reached 73.5% with a moderate interobserver agreement, whereas the intraobserver agreement was substantial. The application of the app yielded comparable results across all subgroups.

Conclusion

The PJI-TNM classification system captures the heterogeneity of PJI and can be applied with substantial inter- and intraobserver reliability. The PJI-TNM educational app aims to facilitate application in clinical practice. A major limitation was the correct assessment of the implant situation. To eliminate this, a re-evaluation according to intraoperative findings is strongly recommended.

Article focus

- The PJI-TNM classification is a new system to capture the complex disease of periprosthetic joint infection in one code.
- This study focuses on the validation of reproducibility and classification accuracy to identify strengths and weaknesses for potential future refinement and optimization.

Key messages

- The PJI-TNM classification demonstrated substantial reproducibility and can be adequately applied by clinicians.
- The PJI-TNM educational app was developed to improve access and availability of the classification in clinical practice to support its use.

Strengths and limitations

- Classification was performed in two rounds by ten international orthopaedic surgeons from different hospitals.
- A third round of classification was performed by eight orthopaedic surgeons using the specially developed PJI-TNM app.
- Cases were retrospectively assessed by observers and distributed according to their clinical frequency rather than homogeneously within the classification.

Introduction

Periprosthetic joint infections (PJIs) represent a feared complication after arthroplasty, with high socioeconomic costs and an enormous burden on the individual patient, characterized by prolonged hospitalization, long-term antimicrobial treatment protocols with their side effects, and reduced quality of life.[1-4] As society ages, an increase in primary implantations of hip and knee joint endoprostheses could be recorded worldwide and is predicted for the coming decades.[5] Consequently, this development is expected to be accompanied by an absolute increase in PJI cases, which poses an immense challenge to the treating physicians, the affected patients, and their social environment.[3,5,6] Besides its impairments in quality of life and mobility, PJI is associated with substantially higher mortality. In PJI of the hip, one-year mortality is indicated with a rate of up to 13.6%, which rises to 25.6% within five years. Both reduced quality of life and mortality are similar or even worse when compared to several tumour diseases.[7,8] For PJI, there is still no universally accepted classification system, so existing studies remain highly heterogenous, making it difficult to compare patient cohorts and outcomes across studies. The most popular classification system was proposed by McPherson et al,[9,10] and a more recently developed system is the BACH classification by Hotchen et al.[11,12] In oncology, a success story was written with the introduction of the TNM classification system by Pierre Denoix in the 1940s and 1950s, which is now used worldwide for almost all solid tumour diseases and enables therapeutic and prognostic predictions.[13] On the basis of the oncological TNM classification, the PJI-TNM classification for PJI was developed.[14,15] This classification system includes several dimensions relevant to treatment decisions and aims to provide a detailed description of the complexity of PJI. Analogous to the oncological classification, the three main subcategories are abbreviated T, N, and M, but in this context represent factors relevant to PJI. 'T' represents 'tissue and implant', describing the stability of the implant, the soft-tissue status, and the type of endoprosthesis (standard vs revision implant). 'N' considers the pathogens and the degree of maturity of the biofilm (previously acute or chronic). 'M' considers the patient's coexisting diseases, while a preceding 'r' is used for a recurrent prosthetic infection. To limit confusion with the oncological system, the PJI-TNM classification code is preceded by the affected joint (e.g. Hip-PJI-T1aN2bM2).[14,15] Thus, a detailed code can be generated for each patient, taking into account individual risk factors, which could provide the basis for the development of individualized treatment algorithms in the future. After the introduction of this classification,[15] an app-based educational tool was developed in order to facilitate the application of the PJI-TNM classification system in clinical practice and to potentially support new users. To establish a reliable classification system, the objectives of the present study were: 1) to test the PJI-TNM classification system for interobserver and intraobserver reliability and classification accuracy while identifying strengths and weaknesses; and 2) to evaluate the clinical application of the PJI-TNM educational app.

Methods

Patients

In total, 20 cases of PJI were defined to cover a broad spectrum of this disease entity. All patients were diagnosed with PJI according to the European Bone and Joint Infection Society (EBJIS) criteria.[16,17] Anonymized information on patients' histories and patient-related data were retrospectively extracted from the medical records. Information presented to the observer consisted of: PJI-related history (site of infection, primary implantation, duration of symptoms, revision surgeries); patient's age, sex, and pre-existing conditions; the appearance of the covering soft-tissue; microbiological results including susceptibility testing; and radiographs (anteroposterior (AP) and lateral view) of the affected joint. An existing soft-tissue defect was defined and described in written form if plastic surgery was required for soft-tissue coverage. For the microbiological samples, original clinical reports were provided in anonymous form containing susceptibility testing according to EUCAST guidelines,[18] including rifampicin or ciprofloxacin susceptibility testing for Gram-positive and Gram-negative bacteria, respectively. Overall, sensitivity to four to 14 different antimicrobial agents was indicated for each germ.

Primary inter- and intraobserver analysis

Ten clinicians were invited to classify the presented cases according to the PJI-TNM classification system (Figure 1).[14,15] Observers were required to have at least completed their specialist training in trauma and orthopaedic surgery and to practice in this field. In addition to the case presentation, a user manual was provided containing the classification of an exemplary case to correctly apply the classification system without any support (Supplementary Material). Six weeks thereafter, the observers were asked to classify the cases once more to obtain intraobserver reliability. For both assessments, observers were allowed to take as much time as required. Statistical analysis was carried out for each of the following categories: 'reinfection', 'Tissue and implant conditions',

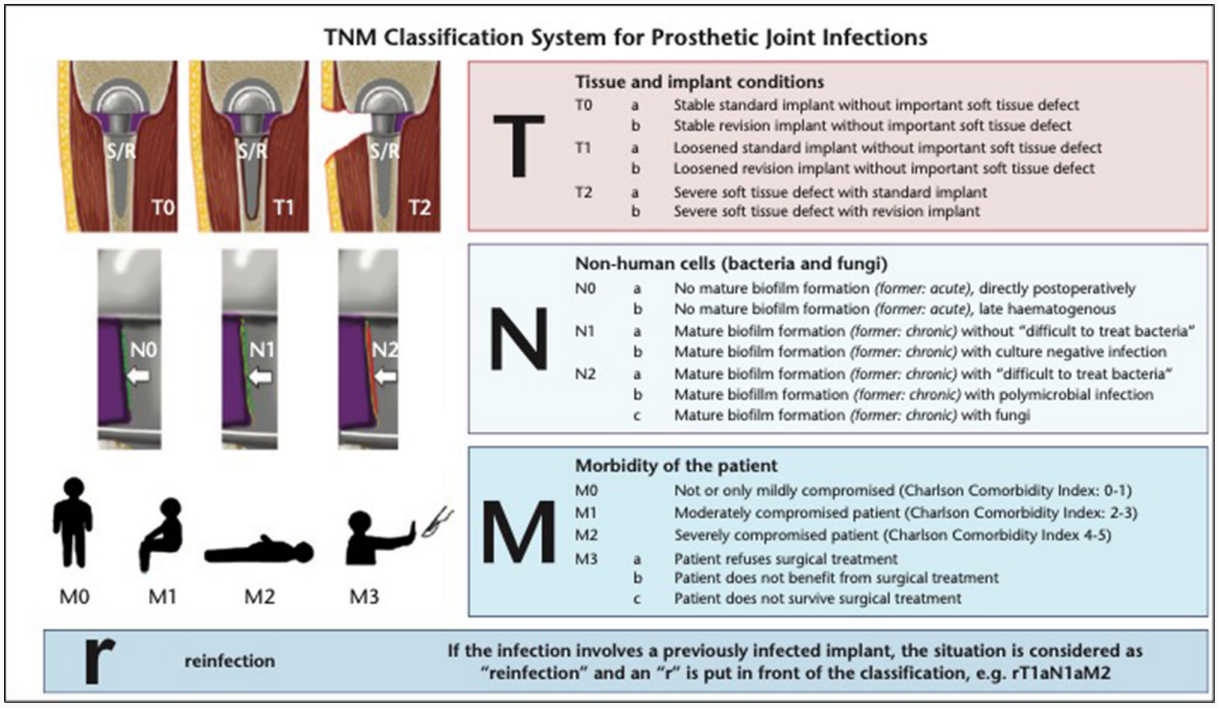

Fig. 1
The PJI-TNM classification system by Alt et al.[15]

'Non-human cells (bacteria and fungi)', and 'Morbidity of the patient'. The latter was assessed using the Charlson Comorbidity Index (CCI).[19] Missing answers were considered incorrect answers.

Assessment of the PJI-TNM educational app

After setting up a beta version of the PJI-TNM education app, observers were again asked to classify the clinical cases using the app provided. The app guides step-by-step through the classification system, asking for relevant information to be considered in the r, T, N, and M subcategories. Representative screenshots are shown in Figure 2. The resulting PJI-TNM codes were again assessed for classification accuracy by comparing the given answer with the reference answer. For interobserver and intraobserver reliability, responses were compared with the results of the second round of classification to account for any learning effect that might occur during repeated classification rounds.

Statistical analysis

Classification accuracy was determined separately for each subcategory by comparing the observers' responses to the reference response defined by the authors. Classification accuracy was calculated by determining the percentage of observers who provided the correct response divided by the total number of observers who participated in the assessment. Specifically, there were ten observers in the first and second rounds of assessment, and eight observers in the third round using the PJI-TNM educational app. Interobserver reliability was assessed using Fleiss' kappa (F_k), while for intraobserver reliability Cohen's kappa (C_k) was calculated. Fleiss' and Cohen's kappa coefficients are measurements for intra- and interobserver agreement for categorical data, taking into account the agreement occurring by chance. Intra- and interobserver agreements were calculated for each subcategory r, T, N, and M and reported as means with 95% confidence intervals. By calculating the mean of the kappa values of all categories, an overall Fleiss' and Cohen's kappa was determined. According to Landis and Koch,[20] kappa values below 0.00 are interpreted as 'poor agreement', values between 0.01 and 0.20 as 'slight agreement', values between 0.21 and 0.40 as 'fair agreement', values between 0.41 and 0.60 as 'moderate agreement', values between 0.61 and 0.80 as 'substantial agreement', and values > 0.81 as 'almost perfect agreement' (Table I). To assess the interobserver reliability and percentage agreement, the mean values of both sessions were used. SPSS version 24.0 (IBM, USA) was used for the statistical analysis.

Results

Patients

The evaluated 20 cases consisted of 13 infected hip arthroplasties, six PJIs of the knee, and one anatomical shoulder PJI. The overall patient ages ranged from 40 to 88 years, with a mean age of 72.5 years (standard deviation (SD) 13.4), while the sex ratio was 1:1. Evaluating implant and soft-tissue conditions, the cohort consisted of ten stable (T0a) and four loosened (T1a) standard implants, five stable revision implants (T0b), whereas one patient with a standard implant presented with a severe soft-tissue defect (T2a). The mean duration of symptoms was 8.8 weeks with a minimum of one day to a maximum of six years. In seven cases, the duration of symptoms was less than three weeks, thus no mature biofilm was assumed. Of these, two acute infections occurred postoperatively (N0a), whereas haematogenous infection was present in five cases (N0b). Among 13 chronic infections exhibiting symptoms lasting longer than three weeks and in which a mature biofilm was suspected, ten non-difficult-to-treat pathogens

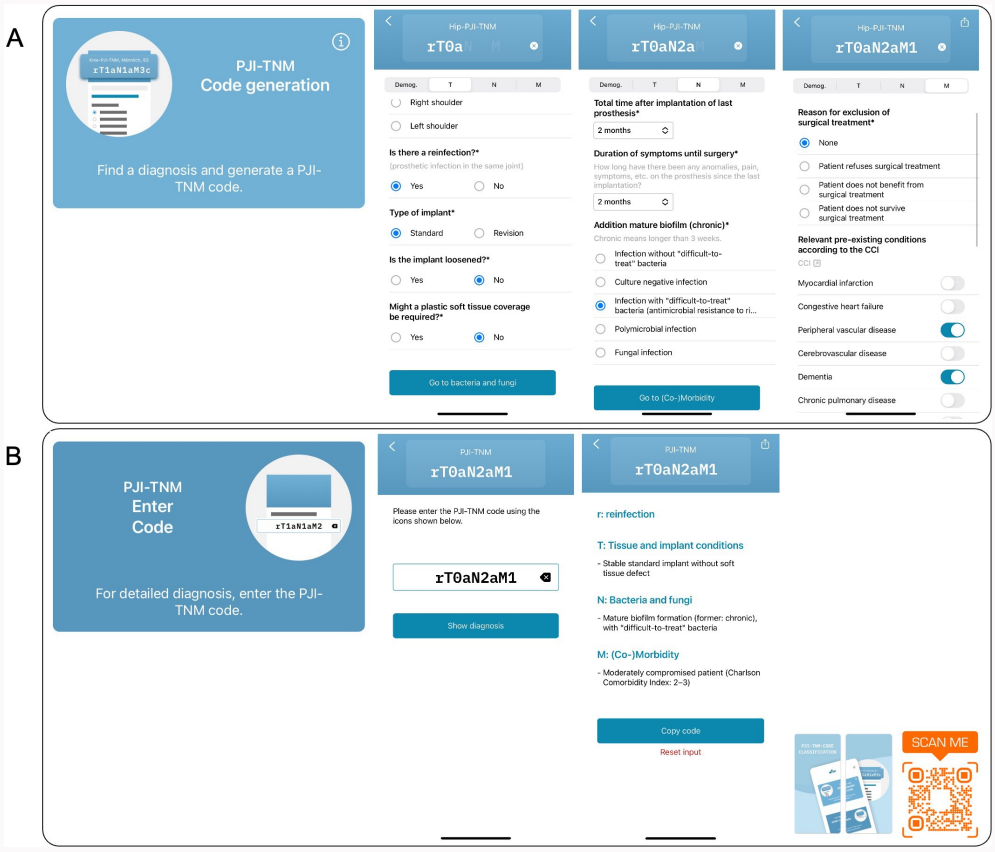

Fig. 2
Representative screenshots of: a) generating a PJI-TNM code and b) entering an existing PJI-TNM code via the PJI-TNM educational app. An example patient classified here suffers from a periprosthetic joint infection (PJI) of the hip and presented with a stable standard indwelling implant without soft-tissue defect. Infection was caused by a difficult-to-treat pathogen and the patient experienced symptoms for longer than three weeks, so biofilm was deemed mature. Pre-existing diseases were dementia and peripheral vascular disease, resulting in an M1 patient.

(N1a), two difficult-to-treat germs resistant to either rifampicin and/or ciprofloxacin (N2a), and one polymicrobial infection (N2b) were detected. The cohort included nine so-called M0 patients with no or only minor comorbidities, seven moderately compromised M1 patients, and three severely compromised patients (M2). One patient refused surgical treatment (M3a).

r – reinfection

Analysis of the interobserver reliability revealed an almost perfect agreement with a F_k of 0.90 (95% confidence interval (CI) 0.87 to 0.93). The classification accuracy of the variable 'reinfection' was 94.8% (95% CI 89.6 to 99.9). With a mean of 96% (95% CI 93.2 to 98.8), the observers' answers corresponded to their answers given in the first session, resulting in an almost perfect intraobserver agreement with a C_k of 0.92 (95% CI 0.86 to 0.98).

T – tissue and implant conditions

The interobserver assessment of the 'tissue and implant conditions' variable demonstrated an accuracy of 70.8% (95% CI 71.5 to 82.5) among users. In 69.0% (138/200) of T0a, 78.0% (78/100) of T0b, 60.0% (48/80) of T1a, and 95.0% (19/20) of T2a cases, the returned response correlated with the reference response. Within the category of a stable standard implant without soft-tissue defect (T0a), the implant was considered to be loosened in 22.5% (45/200) of cases and therefore the T1a option was selected, whereas loosened standard endoprostheses (T1a) were considered stable (T0a) in 38.8% (31/80) of the cases. Likewise, stable revision implants (T0b) were classified as loosened in 18.0% (18/100) of the cases on the provided radiographs. A detailed comparison of the given answers versus the reference answers is presented in Figure 3a. A moderate agreement was revealed for interobserver reliability with an F_k of 0.48 (95% CI 0.46 to 0.50). Intraobserver agreement exposed a substantial agreement with a C_k of 0.68 (95% CI 0.53 to 0.82) and a percentage agreement of 76.5% (95% CI 65.4 to 87.6).

N - non-human cells (bacteria and fungi)

The overall classification accuracy in the category 'non-human cells' reached a mean of 80.0% (95% CI 71.0 to 89.0). The lowest accuracy (40.0%) was observed for acute postoperatively PJI cases (N0a). In 30% (12/40) of these responses, acute polymicrobial infections, as well as acute fungal PJIs misled observers to the chronic categories 'N2b' and 'N2c', respectively. In comparison, accuracy in N0b cases (late haematogenous infection without mature biofilm) and N1a cases (chronic infection without 'difficult-to-treat bacteria') increased to 77.0% and 87.0%, respectively. Furthermore, both in N2a cases (mature biofilm and 'difficult to treat bacteria') and in N2b cases (mature biofilm with polymicrobial infection), 95.0% (38/40) of the given answers correlated with the reference answer (Figure 3b). Assessment of interobserver

Table I. Criteria for the interpretation of Kappa values by Landis and Koch.[20]

Kappa statistics	Strength of the agreement
< 0.00	Poor
0.01 to 0.20	Slight
0.21 to 0.40	Fair
0.41 to 0.60	Moderate
0.61 to 0.80	Substantial
> 0.81	Almost perfect

reliability exhibited a Fκ of 0.60 (95% CI 0.59 to 0.62) and therefore a moderate agreement among users. The intraobserver assessment demonstrated a mean agreement of 87.0% (95% CI 80.9 to 93.1) comparing the two classification results of each user. Moreover, a C_k of 0.81 (95% CI 0.72 to 0.89) indicated an almost perfect agreement for intraobserver reliability.

M – morbidity of the patient

The classification accuracy within the category 'morbidity of the patient' reached 73.5% (95% CI 67.7 to 79.3). In 73.9% (133/180) of M0 cases (not or only mildly compromised patients), 63.6% (89/140) of M1 cases (moderately compromised patients), 88.3% (53/60) of M2 cases (severely compromised patients), and 95% (19/20) within the M3a cases (patient refuses surgical treatment), the observers' responses correlated with the reference answer (Figure 3c). Patients in the M0 and M1 subgroups tended to be assessed as having higher comorbidity (20.6% in M0 cases and 24.3% in M1 cases). Detailed case analysis of the M0 cases revealed that all of these patients who were misclassified had pre-existing conditions, however not all of them were included in the CCI. Similarly, the M1 patients had multiple pre-existing diseases, not all of which are scored according to CCI. For the M2 subgroup, morbidity was underestimated in11.7% (7/60) of the cases. With a Fκ of 0.45 (95% CI 0.43 to 0.47), the interobserver assessment of patients' morbidity resulted in a moderate agreement among the observers. Intraobserver reliability analysis yielded a Cκ of 0.72 (95% CI 0.55 to 0.89), representing substantial agreement. In an overall mean of 81.5% of cases, the answers given by each user in the first and second assessments coincided.

Assessment of the PJI-TNM educational app

Eight out of ten observers were available for a third round of classification by using the PJI-TNM educational app. The classification accuracy resulted in 100.0% for 'Reinfection', 70.6% for 'Tissue and implant conditions', 75.0% for 'Non-human cells', and 70.0% within the subcategory 'Morbidity of the patient', which was comparable to the conventional classification method. Overall, there was substantial agreement across all subcategories, corresponding to a $F_κ$ value of 0.61 with and without the use of the app. In detail, interobserver agreement in the r, T, N, and M subcategories ranged from moderate to almost perfect, as indicated by $F_κ$ values of 1, 0.50, 0.52, and 0.42, respectively (Figure 4a). For intraobserver reliability, the overall $C_κ$ of 0.76 indicated a substantial agreement similar to the values revealed in the conventional classification. Thus, $C_κ$ values of 0.94, 0.63, 0.74, and 0.73 were obtained in the subcategories for r, T, N, and M, respectively (Figure 4b).

Discussion

In summary, substantial intraobserver and interobserver agreements were revealed across all subcategories. Furthermore, values for classification accuracy ranging between 70.8% and 94.8% indicate that the classification can be correctly applied by physicians. Our reassessment using the PJI-TNM educational app yielded comparable results. The PJI-TNM classification system allows for individual classification, taking into account multiple complicating factors in each subcategory, reflecting the complex and heterogenous picture of PJI. However, due to the very detailed evaluation within the subcategories T, N, and M, this is also accompanied by several limitations.

One of the main difficulties in correctly classifying the preoperative implant situation within the category 'tissue and implant conditions' is the discrimination between a loosened and a stable indwelling implant on radiographs. Although conventional radiographs remain the standard tool in the evaluation of arthroplasty, a definitive assessment preoperatively remains difficult.[21,22] A meta-analysis by Temmerman et al[22] examining the implant situation in hip arthroplasty revealed a mean sensitivity and specificity of 82% and 81%, respectively, using conventional radiographs. Parallel to the final histological classification in the oncological system postoperatively, a reassessment and reclassification of the implant situation according to the intraoperative findings postoperatively is likewise possible and mandatory. Furthermore, the providence of other imaging techniques such as bone scintigraphy, dual-energy CT, subtraction arthrography, or nuclear arthrography might have resulted in higher classification accuracy and improved intra- and interobserver agreement.

Within the variable 'non-human cells', a very sufficient overall classification accuracy (80.0%), as well as substantial intraobserver and interobserver agreements, were achieved. However, especially in the case of acute postoperative infections, misclassification was common. In nearly 30% of these responses, acute polymicrobial infections and acute fungal PJIs misled observers to the chronic categories 'N2b' and 'N2c', respectively. This was also present when observers were supported by the PJI-TNM educational app. The reasons for this misleading may lie in the controversial discussion about the cut-off timepoint at which a distinction is made between acute and chronic infections or whether time should have any influence at all on treatment decisions.[23,24] Similarly, there is still no consensus on the timepoint at which a biofilm can be regarded as mature.[25,26] Finally, there is currently no diagnostic method to distinguish between these two entities, and thus the categorization still depends on the medical history reported by the patient.[24] Since the timing and maturity of biofilm are still considered important by most treating physicians, the authors believe that this distinction remains relevant, particularly in the context

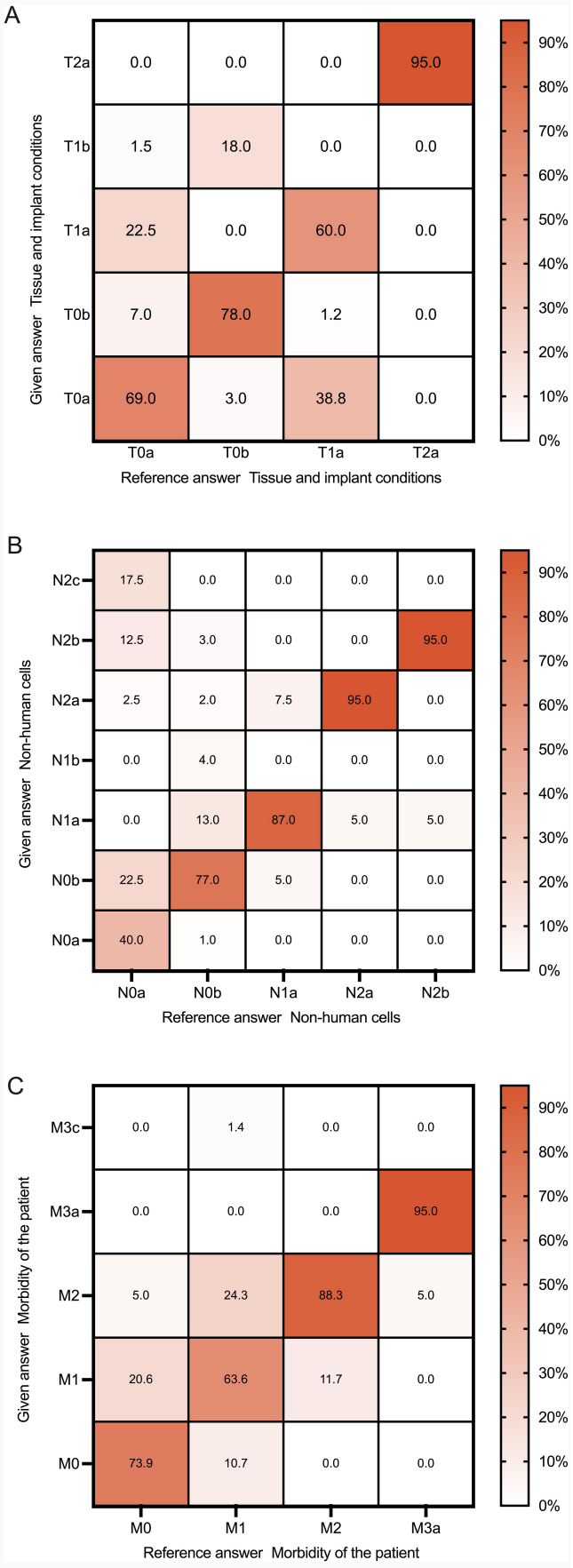

Fig. 3
Heat maps demonstrating the returned answers versus the reference answer for: a) 'tissue and implant conditions'; b) 'non-human cells'; and c) 'morbidity of the patient'.

of future evaluation treatment strategies and clinical outcomes based on the PJI-TNM classification system.

The category 'patient morbidity' is classified using the CCI.[14,19] The observers tended to rate patients in the M0 and M1 subgroups as more comorbid than they would have been according to the CCI. Several patient-related risk factors associated with PJI have been described in the literature.[27,28] Among them, obesity, smoking, or age are the most frequently identified, none of which are considered in CCI. Since patients who were not or only mildly impaired (M0 or M1) had additional comorbidities reported in the case presentation that were not reflected in the CCI, this may have led to a higher assessment of comorbidity by the observers. More generally, the CCI is a quite outdated and non-specific score that is still widely used for various risk assessments due to the lack of more modern and evidence-based alternatives.[29] In the future, a specific risk score for PJI would be beneficial and could allow detailed risk assessment and informed decision-making in clinical practice.

Two other classification systems, namely the McPherson classification and the Joint-Specific BACH classification, have been published for PJI.[10,11] However, the McPherson classification has not yet been validated for inter- and intraobserver reliability, making it inappropriate for direct comparison with the present results.[9] On the other hand, the Joint-Specific BACH classification, adapted from the BACH classification of long bone osteomyelitis by Hotchen et al,[11,12] has been validated. It categorizes cases into 'uncomplicated', 'complex', and 'limited options' based on four subcategories: joint-specific bone involvement, antimicrobial options, coverage of soft-tissues, and host status. In their work, four observers evaluated the presence of loosening, bone loss, periprosthetic fracture, and the nature of the implant in situ, which corresponds to the 'tissue and implant conditions' subcategory, and the host status, which corresponds to the variable 'morbidity'. Their evaluations resulted in higher values of interobserver agreement.[11,12] The simplicity of the Joint-Specific BACH classification's categorization process, assigning cases to three categories ('uncomplicated', 'complex', and 'limited options'), may contribute to its higher agreement compared to the PJI-TNM classification. Simplifying the PJI-TNM classification, such as reducing it to T0, T1, and T2 categories, may lead to improved interobserver agreement. Future refinement of the PJI-TNM classification could consider simplification while balancing the need for detailed classification to enhance interobserver agreement.[30]

In the present study, the use of the PJI-TNM educational app was comparable to the conventional classification method. Although an increase in interobserver reliability was expected due to increased support provided by the classification tool, the lack of improvement could be due to the persistent difficulties of the classification system, for example, in the preoperative assessment of implant stability or the assessment of morbidity, as mentioned above. Another reason could be that the observers were already familiar with the classification so the effect might be underestimated in the present study. Whether the use of the app could facilitate the classification in terms of time and simplify access to the PJI-TNM classification should be investigated in the future.

There are several noteworthy limitations to this study. First, not all combinations of the categories T, N, and M

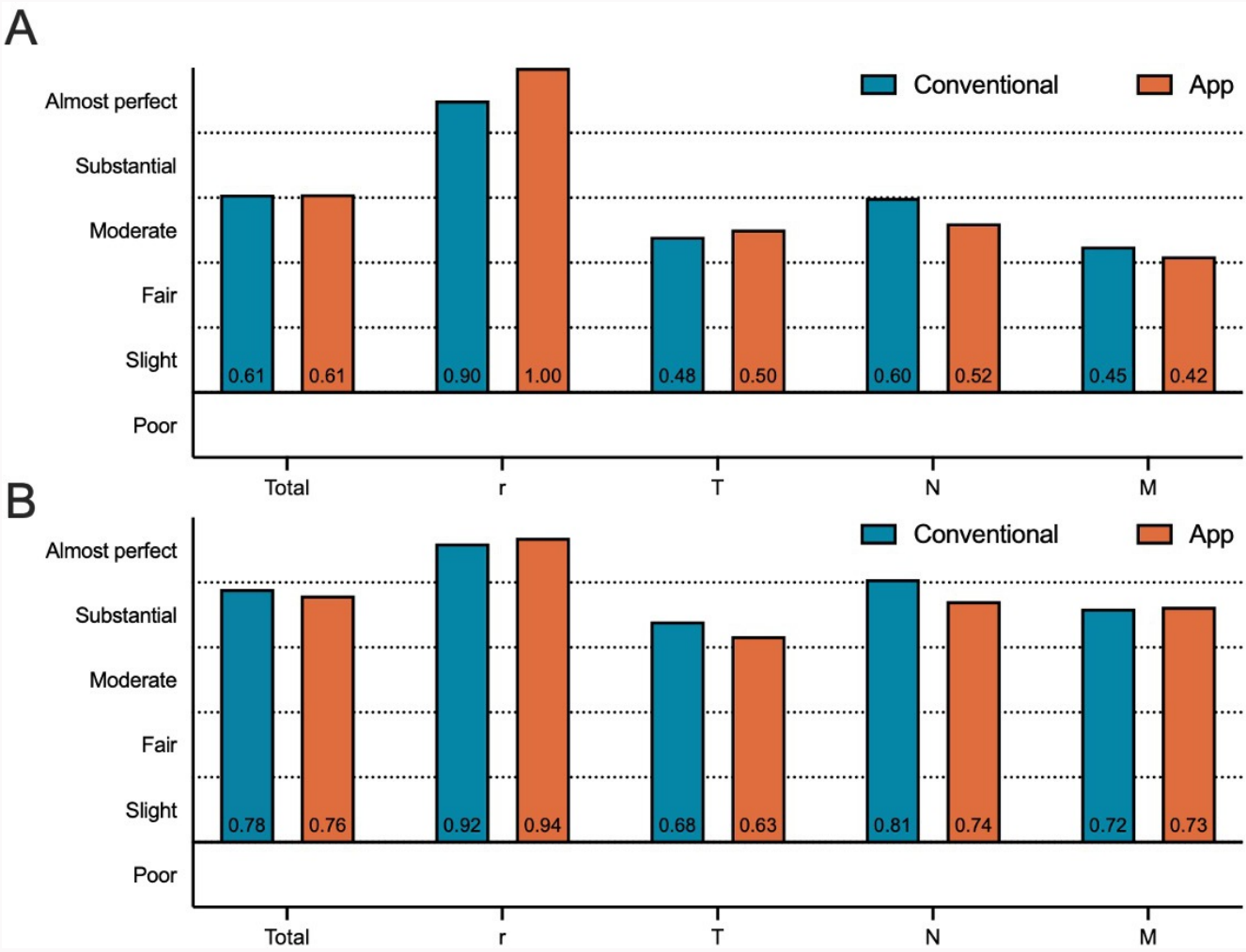

Fig. 4

a) Interobserver and b) intraobserver agreement for the conventional classification method (blue bars) and classification using the PJI-TNM learning app (orange bars). The values overall and for each subcategory (r, T, N, and M) are: a) Fleiss' kappa values for interobserver agreement; and b) Cohen's kappa values for intraobserver reliability.

were included in the case presentation. Notably, patients who would not benefit from or survive surgical treatment (M3b and M3c cases) were excluded from the reference responses, leading to a case mix that is not entirely reflective of the patient population encountered by clinicians. The main reason for excluding these cases was that these decisions are generally influenced by subjective assessments of the treating clinicians, as well as disease- and patient-specific circumstances that are difficult to assess without detailed patient knowledge. However, inclusion of these cases as a reference answer could have resulted in higher response variability, leading to lower values in terms of interobserver reliability and classification accuracy. Nevertheless, in each of the presented cases, observers had the opportunity to select these options based on the provided information, which was also done by one observer (DFA). In addition, due to the numerous subcategories and resulting combinations reflecting the heterogeneity of PJI, not all subcategories (e.g. N1b or N2c) could be adequately represented in the selected clinical cases and are therefore not entirely representative of the broad clinical spectrum of PJI in daily routine. However, the inclusion of more than 20 clinical cases would have resulted in a lower response rate as clinicians would have been overburdened by the time commitment required. Second, whether observers thoroughly read the user manual in its entirety as provided was not monitored, which may have led to misclassification in some instances. For practical reasons, the users were not asked to evaluate example cases, which might have led to an even more accurate assessment, especially in terms of classification accuracy. Third, the classification of clinical cases was performed retrospectively based on a case presentation. Therefore, observers were not able to obtain additional information regarding medical history, microbiological findings, or patient-related risk factors. However, a prospective evaluation approach was not pursued in order to include clinicians from different hospitals. Fourth, two out of ten observers were not available for the third round of evaluation using the PJI-TNM educational app. Since the results were compared with the preceding responses, recruiting additional observers a posteriori was not reasonable. Finally, the present study does not allow conclusions to be drawn about whether the classification is useful for treatment decisions or predicting treatment success. Although Lunz et al[30] already described a predictive value regarding surgery

(duration of surgery, blood loss, and bone loss during surgery), to determine the likelihood of reimplantation, and patient mortality during the first 12 months after diagnosis based on the PJI-TNM classification and its modified version, further studies are needed to support these results.

In conclusion, the complexity of the PJI-TNM classification corresponds to the heterogenous appearance of PJI with all its facets, such as the local soft-tissue conditions, the stability and type of implant, the causative pathogens, the duration of ongoing infection, the morbidity of the patient, and the presence of reinfection. In addition, the specially developed PJI-TNM educational app may be a novel and helpful tool to classify patients correctly and quickly according to the PJI-TNM classification in everyday clinical practice. Future studies may address treatment outcomes based on the PJI-TNM classification and therapy. Similarly to oncology, it is hoped that the PJI-TNM classification will help to derive an appropriate and individual therapy recommendation for each patient suffering from PJI in the foreseeable future. Thus, retrospective and prospective evaluations are planned to assess the prognosis and management of PJI, with further refinement of the classification in the future.

Supplementary material

User manual for the application of the PJI-TNM classification.

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Data sharing

The data that support the findings for this study are available to other researchers from the corresponding author upon reasonable request.

Ethical review statement

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