Research Square

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Synovial Fluid Alpha-Defensin Levels and Serum Fibrinogen Levels for Optimization of the Differential Diagnosis of Complications of Joint Arthroplasties

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Abstract

Background

Differential diagnosis of periprosthetic joint infection (PJI) remains a major clinical challenge despite advances in diagnostic criteria and laboratory methods. Although modern definitions such as the EBJIS criteria have improved diagnostic accuracy, uncertainty persists in selected cases, particularly when microbiological findings are negative or inconclusive.

Methods

At our institution, we focused on two complementary biomarkers for the differential diagnosis of complications of joint arthroplasties: synovial fluid alpha-defensin (HNP 1–3) concentrations measured by high-performance liquid chromatography (HPLC) and serum fibrinogen levels. A total of 141 patients with painful joint arthroplasties underwent diagnostic aspiration between 2021 and 2024. Synovial fluid samples were analyzed microbiologically (culture with prolonged incubation and PCR testing) and by HPLC for precise HNP 1–3 concentrations. C-reactive protein (CRP), leukocyte count, D-dimers, and fibrinogen were measured in venous blood samples.

Results

Statistical analysis demonstrated that comparison of synovial HNP 1–3 concentrations with serum fibrinogen levels improves differentiation between infectious and aseptic complications. Simultaneous elevation of both HNP 1–3 and fibrinogen was strongly associated with infectious etiology, reflecting a systemic inflammatory response. In contrast, isolated elevation of HNP 1–3 with normal fibrinogen levels was predominantly associated with aseptic loosening, especially in case of metal wear, suggesting localized inflammation without systemic activation, or in patients with rheumatologic conditions.

Conclusions

These findings indicate that the combined assessment of HNP 1–3 and serum fibrinogen represents a clinically meaningful and readily available non-microbiological diagnostic approach for optimizing the differential diagnosis of joint arthroplasty complications.

1 Introduction

Periprosthetic joint infection (PJI) represents a serious complication. Its successful management requires early and accurate differential diagnosis. Despite all efforts, this complication may lead to

extensive and irreversible changes in a patient's life and impose a significant burden on healthcare systems [1–3].

Differential diagnosis of complications of joint arthroplasties is not always straightforward. It is crucial to determine whether the condition represents PJI or implant loosening, for example due to wear granuloma, in order to plan optimal surgical management for the patient. Orthopedic societies devote considerable attention to the differential diagnosis of PJI [4, 5]. However, despite advances in diagnostic methods, particularly in cases of low-grade or mitigated infections, there are still situations in which diagnostic certainty is not achieved.

Joint aspiration is central to this assessment. However, limited synovial fluid volume, test availability, turnaround time, and cost may prevent comprehensive testing. A practical diagnostic approach therefore requires a small number of complementary, accessible markers [6].

With the development of additional diagnostic methods, an updated evidence-based definition was introduced in 2018 [7]. Subsequently, in 2021, the EBJIS criteria were established, categorizing findings into three risk groups: (1) infection unlikely, (2) infection likely, and (3) infection confirmed [4, 8–10].

At our institution, joint aspiration with microbiological examination of synovial fluid, including culture with prolonged incubation and PCR testing, is considered a fundamental diagnostic procedure. In addition, we determine precise concentrations of HNP 1–3 in synovial fluid using high-performance liquid chromatography (HPLC). This method and the AFDFkit® were developed at our clinic in collaboration with the Department of Medical Chemistry and Clinical Biochemistry, Second Faculty of Medicine, Charles University and Motol University Hospital, Prague. We consider this examination highly beneficial in the differential diagnosis of joint arthroplasty complications and various types of arthritis, and we have established cut-off concentrations and gray-zone ranges for HNP 1–3 [11].

Alpha-defensins are antimicrobial peptides produced in the musculoskeletal system exclusively by activated leukocytes in response to ongoing inflammation [12, 13]. The highest concentrations are observed in purulent arthritis, while elevated levels may also occur in Borrelia-associated arthritis, rheumatologic diseases, crystal arthropathies, and reactive arthritis. In PJI, HNP 1–3 levels may not reach those observed in purulent arthritis; the cut-off concentrations are 38 mg/L for PJI and 98 mg/L for purulent arthritis [11].

Elevated alpha-defensin levels may also arise from causes other than infection, including certain forms of wear granuloma, potentially involving immune activation by cells of the monocyte–macrophage and mesenchymal lineages [14]. Therefore, when HNP 1–3 levels are elevated but cultures and PCR are negative, it remains unclear whether PJI is present. Negative cultures occur in 5–40% of PJI cases, while PCR has an estimated sensitivity of approximately 86% and specificity of 91% [15, 16] .

In such situations, additional diagnostic markers are required. At our institution, serum fibrinogen has proven to be an important complementary marker for the differential diagnosis of joint arthroplasty

complications.

To verify the benefit of these diagnostic approaches and to develop a practical diagnostic algorithm, we conducted a retrospective study including patients with implanted hip and knee arthroplasties who presented with complications of various etiologies.

2 Methods

2.1 Patients

We evaluated a cohort of 141 patients with implanted hip (n = 109) or knee (n = 32) arthroplasties who underwent differential diagnostic evaluation of joint arthroplasty complications according to the standard procedures established at our institution between 2021 and 2024.

Patients were divided into three diagnostic groups according to the final diagnosis:

(1) non-infectious complications without aseptic loosening (22 patients with total knee arthroplasty and 65 patients with total hip arthroplasty),(2) periprosthetic joint infection (6 patients with knee PJI and 26 patients with hip PJI),

(3) aseptic loosening with wear granuloma (4 patients with total knee arthroplasty and 18 patients with total hip arthroplasty).

The mean age of the entire cohort was 73.7 years (range 46–88 years). The mean age was 72.6 years (range 46–87 years) in the non-infectious group, 73.3 years (range 48–87 years) in the infection group, and 75.2 years (range 61–88 years) in the aseptic loosening group.

In all patients, medical history was obtained, and clinical examination as well as radiographic evaluation of the joint arthroplasty were performed.

All patients underwent aspiration of the hip or knee joint with arthroplasty in an outpatient operating theatre under sterile conditions and imaging guidance (ultrasound or fluoroscopy). The obtained synovial fluid was sent for microbiological examination, including culture with prolonged incubation and PCR testing, and for determination of precise HNP 1–3 concentrations using high-performance liquid chromatography (HPLC). The HPLC method for determination of HNP 1–3 concentrations is implemented at our institution as a standard diagnostic procedure. For alpha-defensin measurement, we use the AFDFkit® assay set.

Venous blood samples were collected from all patients to determine CRP levels, complete blood count, D-dimers, and fibrinogen.

In the majority of patients, the final diagnosis was established based on intraoperative findings and on the results of tissue and periprosthetic fluid samples obtained during surgery. The diagnosis was

determined according to the EBJIS criteria. All patients provided informed consent for the diagnostic procedures, including joint aspiration of the arthroplasty.

Written informed consent was obtained from all patients prior to inclusion and before retrospective data evaluation.

2.2 Methods

Concentrations of serum CRP and the sum HNP 1–3 in synovial fluid were measured at the Department of Medical Chemistry and Clinical Biochemistry. Samples were collected at the time of diagnosis.

CRP was determined by an immunoturbidimetric assay using the Atellica CH 930 analyzer (Siemens, USA). Levels of HNP 1–3 in synovial fluid were determined by high-performance liquid chromatography (HPLC) on an Agilent 1260 Infinity system (Agilent Technologies, USA) [11].

Synovial fluid (1 mL) obtained from knee or hip joints by aspiration was diluted with a stabilizing solution (1:1). This strongly acidic aqueous–organic solvent ensures optimal solubility and stability of cationic alpha-defensin peptides. An aliquot of this solution was further diluted with acetonitrile (1:1), and the sample was subsequently analyzed by reversed-phase high-performance liquid chromatography (RP-HPLC) to quantify the concentration of HNP 1–3.

Samples were bacteriologically examined at the Department of Clinical Microbiology.

Fibrinogen and D-dimers were determined at the Department of Clinical Haematology using a point-of-care testing (POCT) analyzer. Quantitative determination of D-dimers was performed using a latex-enhanced immunoturbidimetric method.

Fibrinogen was measured using the Clauss coagulation method. In diluted platelet-poor plasma, fibrinogen is converted to fibrin by a high concentration of thrombin.

2.3 Statistical Analysis

Biomarker values were dichotomized using predefined cut-off values (HNP ≥ 38 mg/L; fibrinogen ≥ 4.5 g/L), yielding four HNP/fibrinogen combinations. The primary analysis was restricted to patients with periprosthetic joint infection or aseptic loosening. Binary logistic regression was used to estimate the odds of infection, with aseptic loosening as the reference outcome and HNP ↑ / fibrinogen ↓ as the reference biomarker combination. Results are reported as odds ratios (OR) with 95% confidence intervals. Patients with neither infection nor aseptic loosening were analyzed descriptively only. Statistical significance was set at $\alpha = 0.05$. Analyses were performed using R version 4.3.1.

3 Results

A total of n = 141 patients were included in the analysis; complete measurements of both HNP1-3 and fibrinogen were available in n = 99 patients for the analysis of biomarker combinations (Table 1, Fig. 1

and Fig. 2). The distribution of patients according to biomarker combinations and type of complication is presented in Table 1 and graphically illustrated in Fig. 3. The table demonstrates that individual combinations of alpha-defensin and fibrinogen levels exhibit markedly different distributions of diagnoses.

Table 1

Distribution of patients according to biomarker combinations of alpha-defensin (HNP) and fibrinogen and according to type of complication. Values are presented as number of patients and percentage within each biomarker combination. *Note: Positivity thresholds were 38 mg/L for HNP and 4.5 g/L for fibrinogen.*

Biomarker combination	Infection (PJI)	Aseptic loosening	No infectious or aseptic loosening	Total
HNP ↑ / Fibrinogen ↓	3 (33.3%)	5 (55.6%)	1 (11.1%)	9 (100%)
HNP ↑ / Fibrinogen ↑	13 (92.9%)	1 (7.1%)	0 (0.0%)	14 (100%)
HNP ↓ / Fibrinogen ↓	0 (0.0%)	11 (16.4%)	56 (83.6%)	67 (100%)
HNP ↓ / Fibrinogen ↑	3 (33.3%)	0 (0.0%)	6 (66.7%)	9 (100%)

Binary logistic regression restricted to patients with periprosthetic joint infection or aseptic loosening showed that, compared with HNP ↑ / fibrinogen ↓, the HNP ↑ / fibrinogen ↑ combination was associated with higher odds of infection (OR = 22; 95% CI 2.4–512.0; p = 0.015). The wide confidence interval reflects the small numbers in some biomarker combinations. Effect estimates for the two HNP-low combinations were not reliably estimable because of sparse cells and separation.

These findings suggest that simultaneous elevation of alpha-defensins and fibrinogen in patients with postoperative joint arthroplasty complications is strongly associated with infectious etiology compared with aseptic loosening.

Additional laboratory markers

CRP levels were higher in patients with infection than in patients with neither infection nor aseptic loosening (29.7 vs. 7.4 mg/L; p = 0.001) and those with aseptic loosening (29.7 vs. 8.9 mg/L; p = 0.005), with no difference between the latter two groups (p = 0.72). D-dimer levels were higher in patients with infection than in those with aseptic loosening (2.03 vs. 0.86 mg/L; p = 0.048), whereas the other comparisons were not statistically significant (p ≥ 0.12). WBC counts did not differ significantly between groups (all p > 0.49).

4 Discussion

Periprosthetic joint infection (PJI) is a serious complication for patients and a substantial societal burden. Because management is not straightforward, PJI must be considered whenever complications occur after joint arthroplasty. The EBJIS criteria classify cases as infection unlikely, infection likely, or infection confirmed. Diagnosis integrates clinical findings, serum CRP, synovial leukocyte and polymorphonuclear cell counts, synovial alpha-defensin, cultures of synovial fluid or periprosthetic tissue, implant sonication, histology, and scintigraphic imaging [4].

When the clinical presentation is not unequivocal, such as a communicating sinus tract or the so-called mirror sign, additional investigations are required. Serum CRP may be only mildly elevated or normal in low-grade infection [17–19].

For accurate and timely diagnosis of PJI, joint aspiration prior to potential surgery is essential. This procedure should be performed under sterile conditions, ideally in an outpatient operating room, and under ultrasound or radiographic guidance. Examination of synovial fluid or intraoperative tissue samples includes microbiological, cytological, histological, and biochemical methods.

Under the EBJIS criteria, PJI is confirmed when at least two periprosthetic tissue or fluid cultures yield the same pathogen. Culture nevertheless remains an imperfect gold standard: negative results have been reported in up to 40% of PJI cases, particularly after antibiotic treatment or with difficult-to-culture organisms[15, 17, 20].

Accordingly, PJI may be diagnosed without positive cultures when a communicating sinus tract is present, synovial leukocytes exceed 3000/µL or polymorphonuclear cells exceed 80%, or histology shows at least five neutrophils in five high-power fields or visible bacteria [4].

Non-microbiological criteria must be interpreted cautiously. Metallosis, active gout, and inflammatory rheumatologic arthritis may increase synovial leukocyte counts [21–24], and the leukocyte threshold is less reliable within six weeks after arthroplasty [25]. These alternative causes should be excluded before PJI is established, although infection must remain in the differential diagnosis. In addition, aspiration may yield too little synovial fluid to perform every recommended examination, making prioritization of diagnostically useful tests necessary.

To optimize this process, our institution developed and implemented HPLC quantification of synovial HNP 1–3 [11]. We established cut-off concentrations of HNP 1–3 for both PJI and infectious arthritis. For PJI, the cut-off concentration of alpha-defensins is 38 mg/L, while for infectious arthritis it is 98 mg/L.

Since elevated HNP 1–3 levels may also be observed in non-purulent inflammatory arthritis, we additionally defined a so-called “gray zone” ranging from 68 to 108 mg/L. Values within this range may prompt further diagnostic evaluation to exclude, for example, Lyme arthritis or rheumatoid arthritis.

Measurement of precise HNP 1–3 concentrations in synovial fluid using HPLC represents a diagnostic method with substantial clinical value. It provides insight into whether inflammation is present within the

joint and, based on the measured alpha-defensin concentration, allows estimation of the intensity of leukocyte activation.

Another advantage of this method is that the presence of blood in the sample does not affect the result, and only a relatively small volume of synovial fluid (0.1–0.5 mL) is required. The collected synovial fluid sample is subsequently transferred using an insulin syringe to ensure accurate volume measurement and placed into a tube containing a stabilizing solution (AFDFkit®). This allows measurement of HNP 1–3 concentrations by HPLC even after a time delay without compromising the accuracy of the results.

Quantification of HNP 1–3 concentrations in synovial fluid using HPLC is a published method that can be implemented in biochemical laboratories equipped with HPLC instrumentation. Moreover, the examination is not financially demanding.

Since alpha-defensin concentrations directly reflect leukocyte activity in response to intra-articular inflammation, cytological or histological examinations may not provide substantially greater additional benefit in certain situations. Measurement of precise HNP 1–3 concentrations by HPLC can therefore be considered sufficiently accurate for assessing the presence and intensity of ongoing joint inflammation.

However, inflammation in a joint with an endoprosthesis is not necessarily caused by infection alone. It may also result from other conditions such as metallosis, rheumatologic disease, or trauma. Therefore, additional diagnostic methods are required to aid in the differential diagnosis of joint arthroplasty complications. Among additional inflammatory markers, D-dimers and serum fibrinogen have been described [26–29]. Both are related to the coagulation cascade and may also increase in malignancy, thromboembolic disease, and other inflammatory conditions; fibrinogen additionally functions as an acute-phase protein [26].

Of these markers, serum fibrinogen appeared more informative for differential diagnosis in our cohort. PJI-associated inflammation around the implant can induce a systemic response with increased hepatic fibrinogen production. By contrast, when elevated synovial HNP 1–3 reflects non-infectious inflammation, fibrinogen is typically not elevated, consistent with a localized reaction without substantial systemic activation. Thus, the two markers provide complementary information rather than functioning as interchangeable indicators of inflammation.

Accordingly, simultaneous elevation of synovial HNP 1–3 and serum fibrinogen was predominantly associated with PJI, whereas elevated HNP 1–3 with normal fibrinogen was more characteristic of wear-particle granuloma or active rheumatologic disease. This pattern was confirmed in our patient cohort by binary logistic regression and supports combining a marker of local leukocyte activation with a systemic acute-phase marker when distinguishing infectious from aseptic arthroplasty complications.

5 Conclusion

Based on our results, we verified that measurement of precise alpha-defensin concentrations in synovial fluid by HPLC is sufficiently accurate for determining whether inflammation is present in the joint and estimating its intensity (the higher the HNP 1–3 level, the greater the probability of infection). In combination with serum fibrinogen measurement, this approach allows improved differentiation between infectious etiology (systemic inflammatory response) and non-infectious causes such as wear-particle granuloma or rheumatologic disease (without fibrinogen elevation). These two markers, as non-microbiological positive criteria, are therefore essential for the differential diagnosis of joint arthroplasty complications.

The accuracy, accessibility, relatively small required sample volume (approximately 0.1–0.5 mL of synovial fluid), and cost-effectiveness of these examinations significantly contribute to optimization of the differential diagnostic process in PJI.

A limitation of this study is the relatively small patient cohort, which may restrict the generalizability of the findings. Further research in a larger and statistically more robust patient population is therefore necessary to confirm our conclusions.

The statistical analysis was intentionally focused on differentiation between infectious and aseptic (wear-related) complications of joint arthroplasty, which represents the key clinical decision-making challenge in daily practice. Patients without infection and without aseptic loosening were intentionally excluded from regression modeling, as joint pain in these individuals may be caused by a wide range of mechanisms beyond the scope of this study, and their inclusion would have led to results that are difficult to interpret.

The chosen analytical approach therefore reflects the real-world clinical scenario in which the goal is to distinguish between infectious and aseptic etiology in a patient with an already confirmed joint arthroplasty complication.

Declarations

Data availability: The data that support the findings of this study are not publicly available due to privacy and ethical restrictions but are available from the corresponding author upon reasonable request.

Author contributions: All authors have read and agreed to the published version of the manuscript.

PM, DJ, TJ and VB: Diagnosed patients and collected the samples for the measurements. **PM:** Writing original draft preparation, oversight and leadership responsibility for the research activity planning and execution, including mentorship external to the core team. **EK**: Determined biochemical markers concentrations in serum by different analytical techniques, final revision. **RK:** Contributed to drafting and revising the paper., data evaluation. **MM:** Preparation, creation, and/or presentation of the published work by those from the original research group, specifically critical review, commentary or revision. **VS:** Statistical analysis, **PF**: Final revision.

Ethical Statement: This study was conducted in accordance with the principles of the 1964 Declaration of Helsinki and its later amendments. The study was approved by the Ethics Committee for Multi-Centric Clinical Trials of Motol University Hospital (Reference No.: EK-132/15; approval date: 4 February 2015). Written informed consent was obtained from all patients prior to inclusion and before retrospective data evaluation.

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Competing interests: The contact author has declared that none of the authors has any competing interests.

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Figures

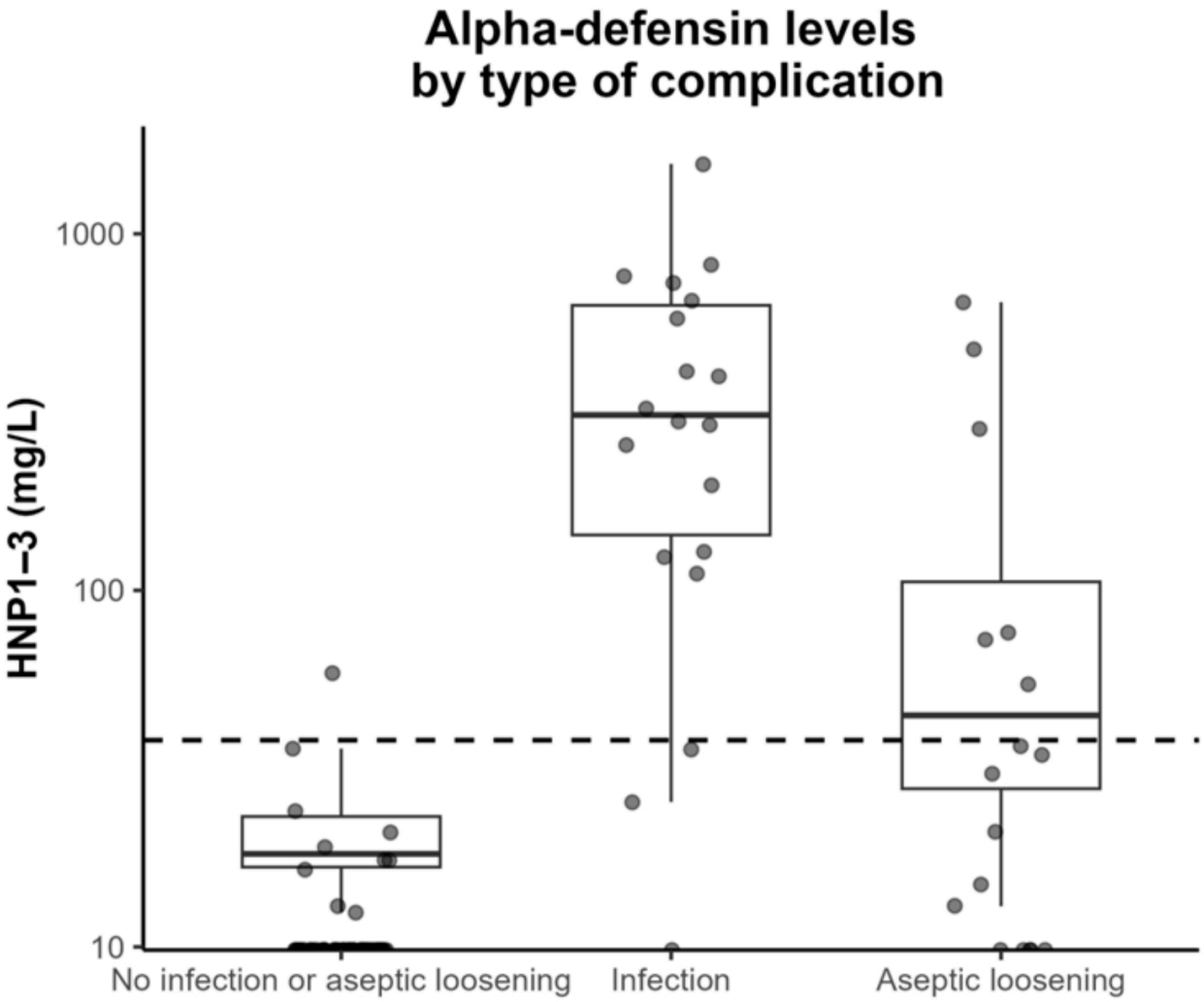


Figure 1

Concentrations of alpha-defensins (HNP 1–3, mg/L) in synovial fluid measured by HPLC in patients with periprosthetic joint infection, aseptic loosening, and without infection or aseptic loosening. The horizontal line represents the median, the box indicates the interquartile range (IQR), and the whiskers extend to 1.5 × IQR. Individual points represent outliers. The dashed line indicates the cut-off value of 38 mg/L for periprosthetic joint infection. Values on the y-axis are displayed on a logarithmic scale (log10) due to the pronounced right-skewed distribution of concentrations.

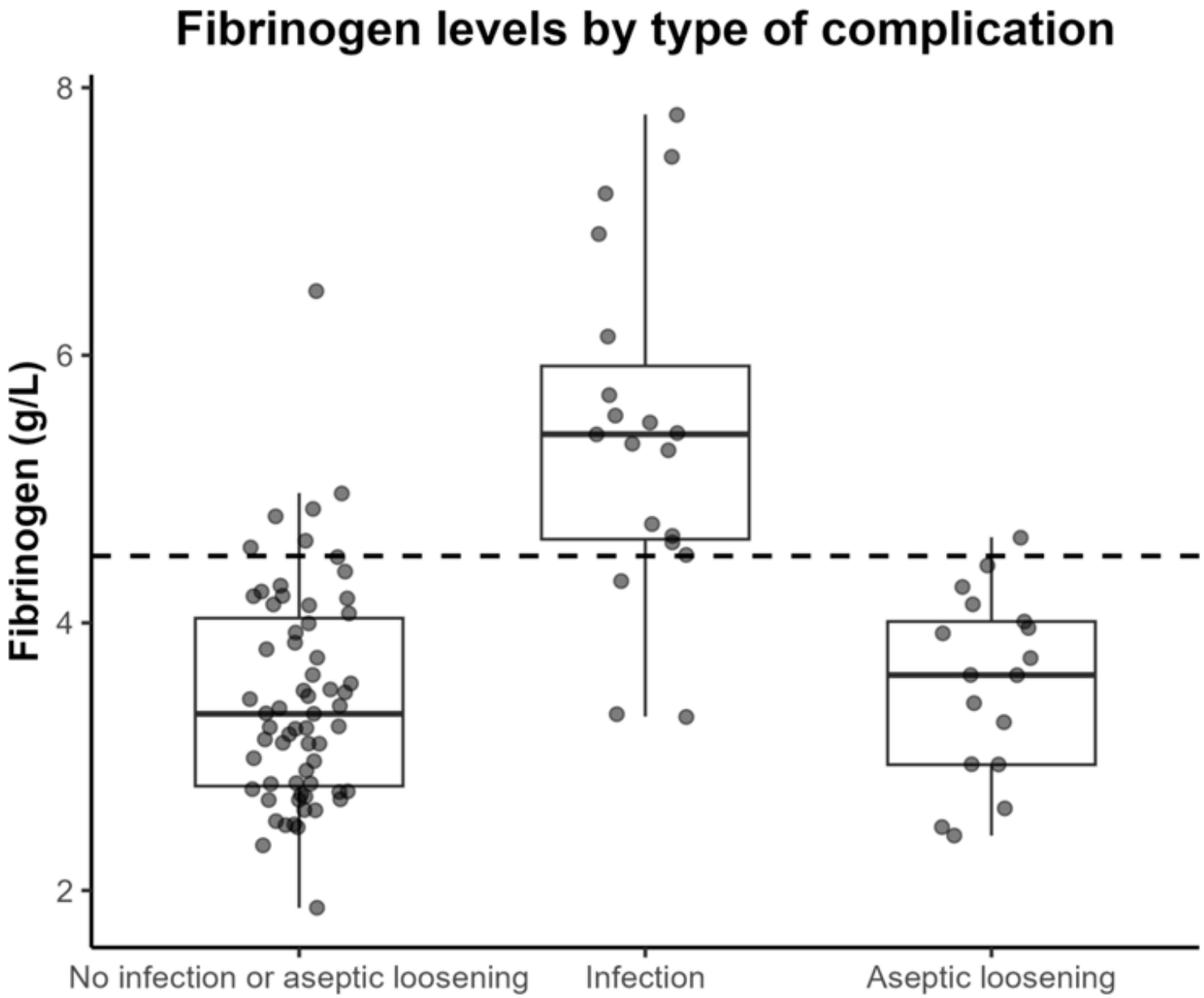


Figure 2

Serum fibrinogen levels (g/L) in patients with periprosthetic joint infection, aseptic loosening, and without infection or aseptic loosening. Elevated fibrinogen levels were observed predominantly in patients with infectious etiology. The dashed line indicates the cut-off value of 4.5 g/L.

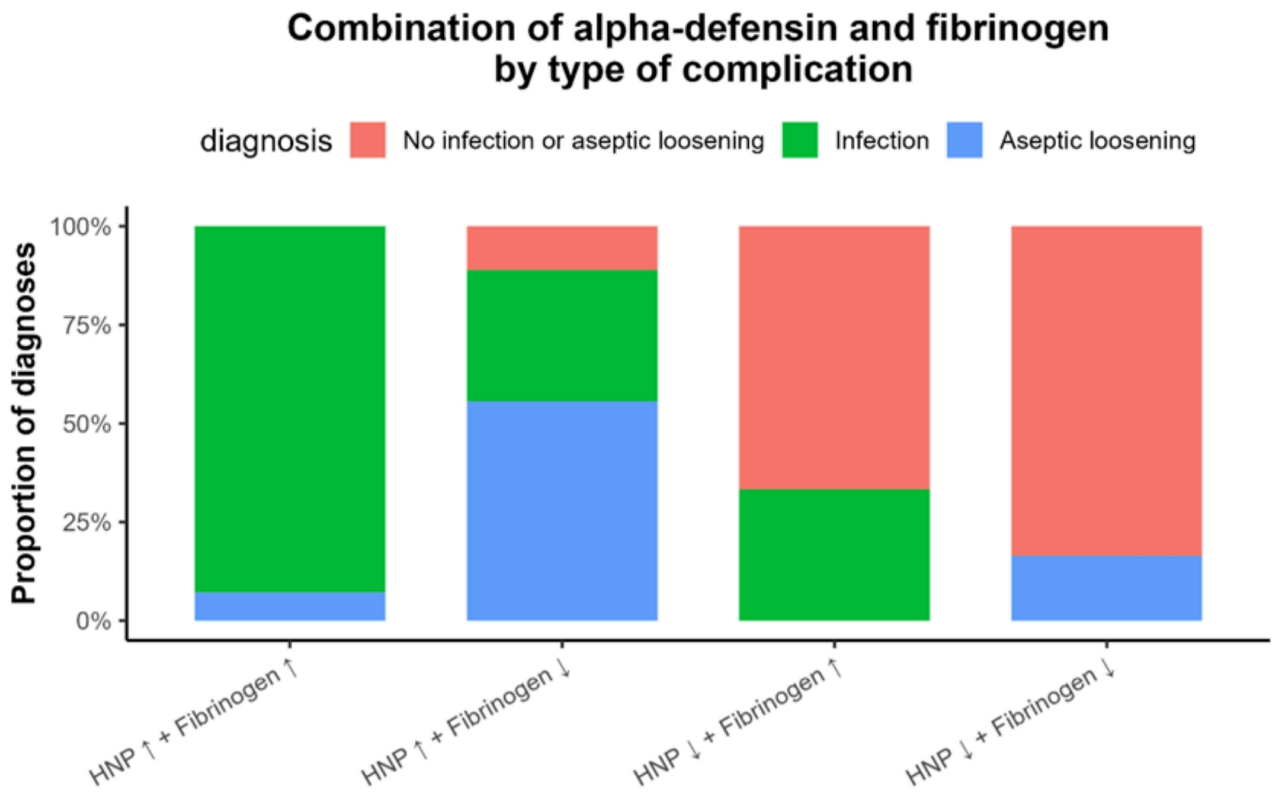


Figure 3

Association between combinations of synovial fluid alpha-defensin (HNP 1–3) levels and serum fibrinogen levels and the type of postoperative complication of joint arthroplasty. Simultaneous elevation of both markers was predominantly associated with infectious etiology, whereas isolated elevation of alpha-defensins without fibrinogen elevation was characteristic of aseptic complications.