

Evaluation of Leukocyte Threshold Values in Semen to Detect Inflammation Involving Seminal Interleukin-6 and Interleukin-8

Artin Aghazarian, Igor Stancik, Wolfgang Huf, and Heinz Pflüger

OBJECTIVE	To evaluate leukocyte threshold values in semen to detect inflammation involving seminal interleukin (IL)-6 and IL-8.
MATERIALS AND METHODS	The levels of leukocytes, IL-6, and IL-8 in semen were determined. The 75th and 90th percentiles of seminal IL-6 and IL-8 were considered as “high” and “very high” concentrations, respectively. Inflammatory semen was defined based on high levels of IL-6 (≥ 86.75 pg/mL) or IL-8 (≥ 4460 pg/mL). Very high levels of IL-6 (≥ 228 pg/mL) or IL-8 ($\geq 12,480$ pg/mL) were used to define acute seminal inflammation. On the basis of high and very high levels of IL-6 or IL-8, receiver operating characteristic curves were generated to evaluate leukocyte threshold values.
RESULTS	Leukocytes at a cutoff level of 1×10^6 /mL had 51% sensitivity and 95% specificity to detect high levels of IL-6, whereas on the basis of very high levels of IL-6, the same cutoff level revealed 82% sensitivity and 90% specificity. Similarly, leukocytospermia demonstrated low sensitivity (56%) to detect high levels of IL-8 but acceptable sensitivity (94%) and specificity (92%) to predict very high levels of IL-8. The cutoff level of 0.315×10^6 leukocytes/mL had optimal sensitivity and specificity for predicting high levels of inflammatory cytokines.
CONCLUSION	Leukocytospermia demonstrated poor sensitivity to detect seminal inflammation, as defined by high levels of inflammatory cytokines. The optimal threshold value to detect inflammation was found to be 0.315×10^6 leukocytes/mL. On the basis of very high levels of IL-6 or IL-8, leukocytospermia is a sensitive and specific marker to predict acute seminal inflammation. UROLOGY 86: 52–56, 2015. © 2015 Elsevier Inc.

According to the recommendations of the World Health Organization, leukocytospermia is defined as the presence of $\geq 1 \times 10^6$ leukocytes per mL in ejaculate.¹ This threshold value has been investigated from different perspectives with controversial outcomes in previous studies.

Sharma et al² demonstrated the presence of oxidative stress in patients with leukocytes between 0 and 1×10^6 /mL, and therefore, they were unable to define a low limit for leukocytes. Henkel et al³ demonstrated a significant decrease in motility and DNA integrity in patients with leukocyte levels $< 1 \times 10^6$ /mL, thereby suggesting the necessity for a reevaluation of the leukocyte threshold value. Consistent with these findings, the use of an

unconventional cutoff value of ≥ 1 polymorphonuclear leukocytes per 100 sperms revealed a significant deterioration in semen quality and DNA fragmentation index.⁴ In addition, previous studies evaluating seminal leukocyte cutoff points with regard to microbiological findings demonstrated very low sensitivity for leukocytospermia.^{5,6} Cutoff levels of $\geq 0.275 \times 10^6$ and $\geq 0.5 \times 10^6$ leukocytes/mL had the highest sensitivity and specificity for predicting bacteriospermia by Gdoura et al⁵ and Lackner et al,⁶ respectively.

In contrast, some authors have found leukocytospermia in infertile patients to be beneficial for the improvement of both sperm fertilization ability and clinical pregnancy rate.⁷ Moreover, in fertile donors, the normal pregnancy rate was associated with leukocytospermia.⁸ In addition, because the elevated number of leukocytes in semen and the effect of these cells on basic semen parameters can be scavenged by an efficient seminal antioxidant system,⁹ the use of higher threshold values, that is, $> 2 \times 10^6$ leukocytes/mL, was suggested by Ochsendorf.¹⁰

The involvement of proinflammatory cytokines, including interleukin (IL)-6 and IL-8, as key elements in

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From the Department of Urology, Krankenhaus Hietzing mit Neurologischem Zentrum Rosenhügel, Vienna, Austria; and the Center for Medical Physics and Biomedical Engineering, Medical University of Vienna, Vienna, Austria

Address correspondence to: Artin Aghazarian, M.Sc., Department of Urology, Krankenhaus Hietzing mit Neurologischem Zentrum Rosenhügel, Wolkersbergenstr.1, A-1130 Vienna, Austria. E-mail: artin_ghazarian@yahoo.com

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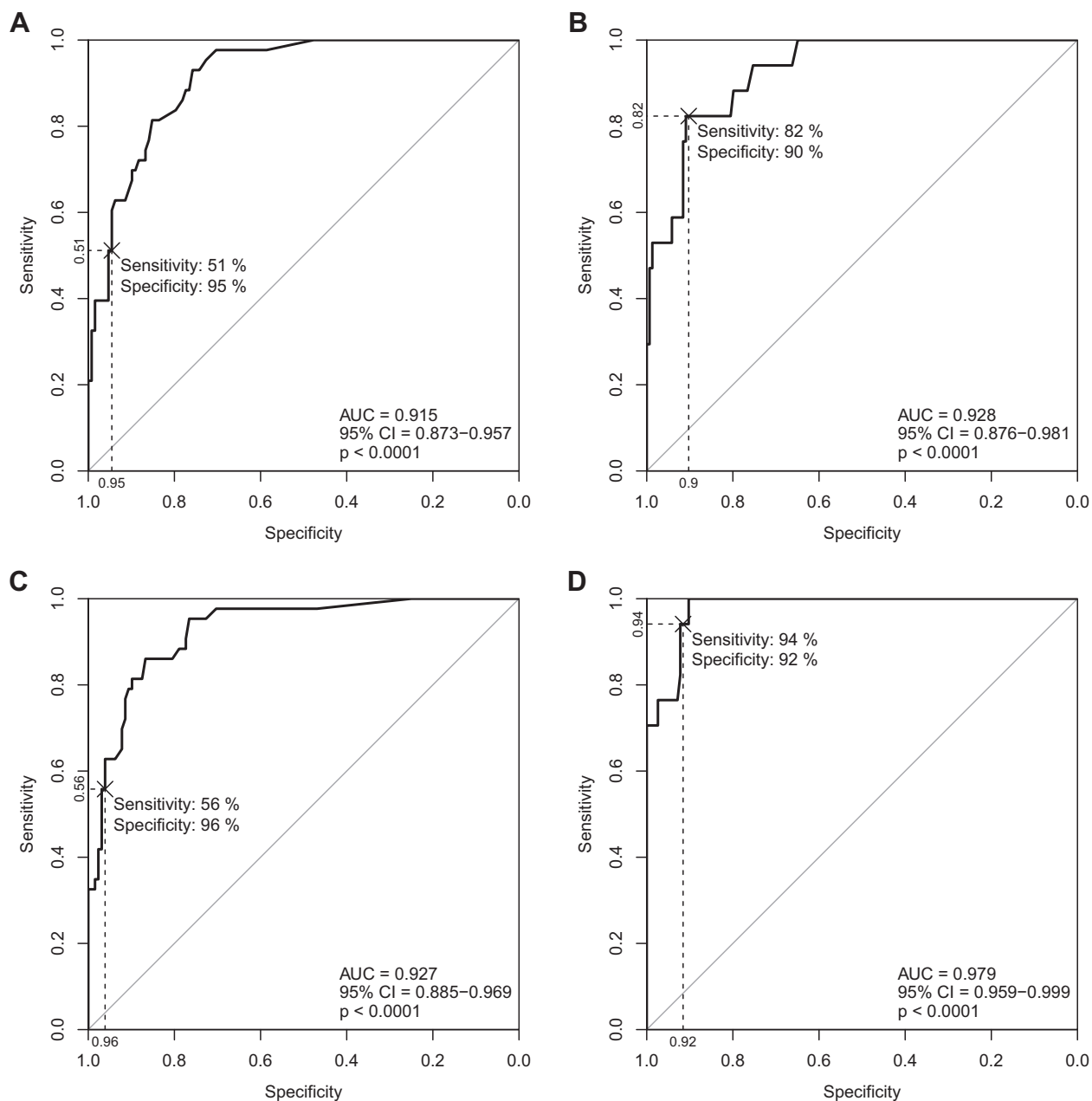


Figure 1. (A, C) Receiver operating characteristics curves of leukocytospermia to detect seminal inflammation based on “high” levels of IL-6 (A) and IL-8 (C). (B, D) Receiver operating characteristic curves of leukocytospermia to detect acute seminal inflammation based on “very high” levels of IL-6 (B) and IL-8 (D). AUC, area under the curve; 95% CI, 95% confidence interval; P, statistical significance.

the inflammatory condition of semen has been reported.^{11,12} Thus, studies have been performed to evaluate the cutoff points of these cytokines to differentiate between inflammatory and noninflammatory semen. Zalata et al¹³ performed receiver operating characteristic (ROC) curve analysis of IL-6 and determined a cutoff value of 45.3 pg/mL. Depuydt et al¹⁴ found IL-6 at a cutoff value of 14.8 pg/mL to be the most specific marker to distinguish between cases with or without inflammation in seminal plasma. Furthermore, the use of IL-8 as a surrogate marker in the diagnosis of chronic prostatitis/chronic pelvic pain syndrome has been previously

described by Penna et al.¹⁵ These authors demonstrated that IL-8 can distinguish between chronic prostatitis/chronic pelvic pain syndrome and controls at a cutoff value of 2480 pg/mL. In addition, the 75th percentile of IL-6 and IL-8 was used to define “high” levels of these cytokines in semen. On this basis, Eggert-Kruse et al¹⁶ defined concentrations of ≥ 2000 pg/mL as high IL-8 and concentrations of ≥ 30 pg/mL as high IL-6, whereas IL-8 and IL-6 levels at a threshold of ≥ 1049.04 and ≥ 42.07 pg/mL, respectively, were defined as high in normospermatic males by Ulcova-Galova et al.¹⁷

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