Research Square

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Pharmacokinetic Evaluation of Unbound Serum Concentrations and Related Tissue Concentrations of Cefazolin in Urological Surgery

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Research Article

Keywords: cefazolin, unbound serum concentration, tissue concentration, perioperative antimicrobial prophylaxis, robot-assisted partial nephrectomy, robot-assisted radical prostatectomy

Posted Date: November 26th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11591183/v1

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Additional Declarations: No competing interests reported.

Abstract

Purpose

The efficacy of cefazolin (CEZ) prophylaxis is usually inferred from total serum (TS) concentrations, although unbound serum (US) concentrations better reflect pharmacological activity. The aim of this study was to measure TS, US, and tissue CEZ concentrations during robot-assisted partial nephrectomy (RAPN) and radical prostatectomy (RARP) to evaluate the adequacy of the current regimen.

Methods

Patients who received a single 1-g CEZ dose 1 hour before surgery between December 2021 and February 2025 were included (RAPN, n = 26; RARP, n = 67). TS, US, renal tissue (RT), and peri-organ adipose tissue concentrations were measured by high-performance liquid chromatography at specimen removal and compared with the minimum inhibitory concentrations for 90% of isolates (MIC_{90}) of the three most frequently isolated skin bacteria.

Results

In RAPN, median (interquartile ranges) TS, US, and RT concentrations were 55 (39–62) mg/L, 5.0 (4.3–6.3) mg/L, and 82 (56–226) μg/g, respectively; in RARP, TS and US concentrations were 62 (51–74) and 5.7 (4.7–7.5) mg/L, respectively. The median US/TS ratios were 0.105 and 0.094, with individual values of 0.05–0.35. MIC_{90} values were 0.5 mg/L for coagulase-negative staphylococci and 2 mg/L for methicillin-susceptible *Staphylococcus epidermidis* and *Corynebacterium* spp.; all TS, US, and RT concentrations exceeded them. No surgical site infections occurred.

Conclusion

A single 1-g CEZ dose yielded serum and RT concentrations above the MIC_{90} of the main skin flora. This is the first report of CEZ concentrations in renal parenchyma during RAPN. Direct measurement is preferable for assessing unbound concentrations.

Introduction

Cefazolin (CEZ) is recommended by guidelines in Japan and internationally as a first-line agent for perioperative antimicrobial prophylaxis in many surgical procedures, including clean surgery, because of its low cost and narrow spectrum of activity [1]. Surgical site infections (SSIs) are important complications to prevent because they prolong hospital stays and increase healthcare costs [2, 3]. For antimicrobial prophylaxis to be effective, CEZ concentrations in the target tissues must remain above the

minimum inhibitory concentrations (MIC) of the causative pathogens from incision to wound closure [1, 4].

The efficacy of cefazolin (CEZ) has traditionally been inferred from total serum (TS) concentrations. However, it is the unbound fraction, which is not bound to plasma proteins, that determines tissue penetration and pharmacological activity [5]. The reported protein binding of CEZ is approximately 80–86%, corresponding to an unbound fraction of 14–20% [6–8]. Its protein binding is saturable and concentration dependent and is influenced by serum albumin levels [9, 10]. Consequently, assessments based solely on total concentrations may misinterpret antibacterial activity, particularly in patients with conditions that alter protein binding, such as hypoalbuminemia.

High penetration of CEZ into prostatic tissue has been reported [11]. However, its penetration into adipose tissue may vary by anatomical site and patient characteristics [12, 13]. To our knowledge, no previous study has directly measured or evaluated CEZ concentrations in renal parenchyma or the surrounding adipose tissue.

Therefore, the aim of this study was to (1) evaluate patients undergoing robot-assisted partial nephrectomy (RAPN) and robot-assisted radical prostatectomy (RARP), measuring TS, US, and total concentrations in the relevant tissues at the time of tissue excision and (2) compare these concentrations with the MIC_{90} values for the three most frequently isolated bacterial species in skin cultures obtained before incision to evaluate the adequacy of the current prophylactic regimen.

Patients and methods

Patients

This study included patients aged 18 years or older who underwent RARP or RAPN at the Department of Urology, Kitasato University Hospital, between December 2021 and February 2025 and received a single 1-g dose of CEZ for perioperative antimicrobial prophylaxis. Pregnant or breastfeeding patients were excluded. Wound infection was identified using the United States Centers for Disease Control and Prevention criteria guidelines [14].

Sample collection

A single 1-g dose of CEZ was administered intravenously 1 hour before surgery. Blood samples for serum analysis were collected around the time of surgical specimen removal. Renal tissue (RT) and perirenal adipose tissue (PRAT) were collected during RAPN, and periprostatic adipose tissue (PPAT) was collected during RARP, each at surgical specimen removal.

Skin cultures and susceptibility testing

Before the surgery and skin antisepsis, specimens were collected from the skin surrounding the planned incision site and cultured to isolate bacteria. Bacterial species were identified using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI Biotyper Sirius system; Bruker). Antimicrobial susceptibility testing was performed using the broth microdilution method recommended by the Clinical and Laboratory Standards Institute [15, 16], and the MIC of CEZ was determined. The MIC_{90} was calculated for each of the three most frequently isolated bacterial groups.

Assay of CEZ concentrations

TS, US, and tissue CEZ concentrations were measured by high-performance liquid chromatography with ultraviolet detection at 254 nm, according to previously reported methods [5, 9]. Unbound concentrations were determined in the filtrate of serum centrifuged through an ultrafiltration device at 10,000 × g for 15 minutes. Tissue samples were pulverized in liquid nitrogen and homogenized in buffer, and the supernatant was mixed with methanol to precipitate proteins before analysis. The calibration curve was linear over the clinically relevant concentration range, and the intra-day and inter-day coefficients of variation were < 5%. Tissue concentrations were calculated per gram of wet tissue (μg/g), assuming a tissue density of 1.0 kg/L.

Data analysis

Analyses were performed in R (version 4.6.1; R Core Team, R Foundation for Statistical Computing, Vienna, Austria) with the dplyr, tidyr, gtsummary, flextable, and ggplot2 packages. Continuous variables were summarized as medians (interquartile ranges [IQRs]) and categorical variables as counts (percentages), separately for the RAPN and RARP groups. Individual concentrations were plotted with lines connecting the measurement categories and the MIC_{90} values as horizontal lines, and the ratios of US and tissue concentrations to TS concentration were plotted against TS concentration. No hypothesis testing was performed; the analysis was descriptive.

Ethics statements

This study was approved by the Ethics Committee of Kitasato University Hospital (B21-148) and performed in accordance with the principles of the Helsinki Declaration. Written informed consent for the publication of this report was obtained from all patients.

Results

Clinical features of the study sample

This study included 26 patients who underwent RAPN and 67 who underwent RARP (Table). Females were present only in the RAPN group (n = 5, 19%). The RAPN group had higher serum creatinine levels and lower creatinine clearance.

Isolated bacteria, MIC_{90} values, and SSIs

The three most frequently identified bacterial groups were methicillin-susceptible coagulase-negative staphylococci (MSCNS; 61 isolates), *Corynebacterium* spp. (35 isolates), and methicillin-susceptible *Staphylococcus epidermidis* (MSSE; 28 isolates). Their MIC_{90} values for CEZ were 0.5, 2, and 2 mg/L, respectively. No SSIs were observed.

CEZ concentration

The median time from the start of surgery to serum sampling was 2.4 hours in the RAPN group and 1.5 hours in the RARP group, and the median interval between serum and RT sampling was 0 hours. RT concentrations were substantially higher than TS concentrations but varied widely among patients (3 to 1,196 μg/g). PRAT concentrations also varied, ranging from 1 to 120 μg/g. (Table 1)

Table 1
Patient characteristics, cefazolin concentrations, concentration ratios, and sampling times in the RAPN and RARP groups

Patient characteristics[a]	**RAPN (n = 26)**	**RARP (n = 67)**
Age (years)	69.5 (55.5, 73.8)	70 (64.5, 73)
Body weight (kg)	64.8 (59.5, 70.7)	64.9 (59.3, 69.5)
Sex, n (%)		
Female	5 (19%)	0 (0%)
Male	21 (81%)	67 (100%)
Serum creatinine (mg/dL)	1.18 (0.98, 1.47)	0.91 (0.82, 1.04)
AST (U/L)	26.5 (22, 32.3)	22 (18, 28.5)
ALT (U/L)	19.5 (14.5, 27.8)	15 (11, 19.5)
Total bilirubin (mg/dL)	0.9 (0.6, 1.1)	1.0 (0.8, 1.4)
Albumin (g/dL)	3.1 (2.9, 3.4)	3.2 (3.0, 3.4)
Ccr (mL/min)	56 (42.5, 69.3)	69 (60.5, 85)
Concentration, **median (IQR) [range]**[b]		
Total serum (mg/L)	55 (39, 62) [15, 124]	62 (51, 74) [11, 125]
Unbound serum (mg/L)	5.0 (4.3, 6.3) [2.2, 14.5]	5.7 (4.7, 7.5) [2.2, 16.1]
Renal tissue (μg/g)	82 (56, 226) [3, 1,196]	–
Perirenal adipose tissue (μg/g)	7.4 (3.7, 9.5) [1.0, 119.9]	–
Periprostatic adipose tissue (μg/g)	–	3.6 (2.3, 5.9) [0.6, 17.7]

[a]Median (interquartile range) for continuous variables; number (percentage) for categorical variables

[b]Median (interquartile range) [range]

[c]Perirenal adipose tissue in RAPN and periprostatic adipose tissue in RARP

[d]2 mg/L is the MIC_{90} of methicillin-susceptible *Staphylococcus epidermidis* and *Corynebacterium* spp.

RAPN, robot-assisted partial nephrectomy; RARP, robot-assisted radical prostatectomy; AST, aspartate aminotransferase; ALT, alanine aminotransferase; Ccr, creatinine clearance; IQR, interquartile range; MIC_{90}, minimum inhibitory concentration for 90% of isolates

Patient characteristics[a]	RAPN (n = 26)	RARP (n = 67)
Concentration ratio, median (IQR) [range][b]		
Unbound serum / total serum	0.105 (0.087, 0.118) [0.054, 0.207]	0.094 (0.083, 0.108) [0.051, 0.353]
Renal tissue / total serum	1.73 (1.08, 4.97) [0.10, 21.1]	–
Adipose tissue / total serum[c]	0.125 (0.073, 0.180) [0.019, 2.50]	0.056 (0.040, 0.095) [0.006, 0.325]
Adipose tissue / unbound serum[c]	0.92 (0.66, 1.59) [0.17, 33.1]	0.58 (0.39, 0.98) [0.07, 4.32]
Time from the start of surgery to sampling, median (IQR) (h)		
Serum	2.4 (1.9, 2.7)	1.5 (1.2, 1.7)
Renal tissue	2.6 (2.3, 3.1)	–
Adipose tissue[c]	2.5 (1.9, 2.9)	1.5 (1.2, 1.6)
Patients with a concentration < 2 mg/L, n (%)[d]		
Unbound serum	0 (0%)	0 (0%)
Renal tissue	0 (0%)	–
Adipose tissue[c]	6 (23%)	10 (15%)

[a]Median (interquartile range) for continuous variables; number (percentage) for categorical variables

[b]Median (interquartile range) [range]

[c]Perirenal adipose tissue in RAPN and periprostatic adipose tissue in RARP

[d]2 mg/L is the MIC_{90} of methicillin-susceptible *Staphylococcus epidermidis* and *Corynebacterium* spp.

RAPN, robot-assisted partial nephrectomy; RARP, robot-assisted radical prostatectomy; AST, aspartate aminotransferase; ALT, alanine aminotransferase; Ccr, creatinine clearance; IQR, interquartile range; MIC_{90}, minimum inhibitory concentration for 90% of isolates

Individual concentration profiles are shown in Fig. 1a for RAPN and Fig. 1b for RARP. TS, US, and RT concentrations exceeded the MIC_{90} values for all three of the most frequently isolated bacterial groups in every patient. All measured adipose tissue concentrations exceeded the MIC_{90} for MSCNS (0.5 mg/L). Concentrations below the MIC_{90} for *Corynebacterium* spp. and MSSE (2 mg/L) were observed for PRAT in 6 of 26 patients (23%) and PPAT in 10 of 67 patients (15%) (Table).

Relationship between serum and tissue concentration of CEZ

In the RAPN group, the median (IQR) US/TS and RT/TS ratios were 0.105 (0.087–0.118) and 1.73 (1.08–4.97), respectively. The RT/TS ratio exceeded 1 in 20 of 26 patients (77%) and was substantially higher than the US/TS and PRAT/TS ratios, even on a logarithmic scale. PRAT concentrations exceeded US concentrations in 12 of 26 patients (46%). In the RARP group, the median (IQR) US/TS ratio and PPAT/TS ratio were 0.094 (0.083–0.108) and 0.056 (0.040–0.095), lower than the US/TS ratio. PPAT concentrations exceeded US concentrations in 17 of 67 patients (25%) (Fig. 2a, Fig. 2b, and the Table).

Discussion

To our knowledge, this is the first study to measure CEZ concentrations in renal parenchyma and perirenal adipose tissue during RAPN. Patients who underwent RARP or RAPN who received a single 1-g dose of CEZ had TS and US concentrations in both groups, and RT concentrations in the RAPN group, that exceeded the MIC_{90} values of the three most frequently isolated bacterial groups from skin cultures in every patient at the time of surgical specimen removal. These findings support the adequacy of the current regimen of 1-g of CEZ administered 1 hour before surgery for both procedures.

Although contamination of the tissue homogenates with urine and blood components partly contributed to the high CEZ penetration into RT and cannot be excluded, CEZ is primarily eliminated by the kidneys [6], and its concentration within the renal tubules may partly explain why RT concentrations exceeded serum concentrations. Because RT concentrations varied widely (3 to 1196 μg/g), possibly reflecting differences in renal function or intraoperative procedures, median RT concentration alone cannot be used to assess exposure in individual patients.

Median PPAT concentration (3.6 μg/g) was broadly consistent with the previously reported mean of 4.54 μg/g [5]. In patients who underwent transurethral resection of the prostate who received 2-g of CEZ, concentrations in prostatic parenchyma were approximately 60% of serum concentrations [11]. The PPAT concentrations in the present study appeared substantially lower, suggesting that CEZ penetration may differ considerably between prostatic parenchyma and the surrounding adipose tissue. The median PPAT-to-TS concentration ratio was low (0.056), broadly consistent with a report that CEZ concentrations in the joint capsule during total hip arthroplasty were approximately 10% of serum concentrations [17]. This finding is also consistent with CEZ being a hydrophilic drug with high protein binding.

In both groups, the US/TS ratio was generally between 0.05 and 0.2 across a broad range of TS concentrations (11–125 mg/L), with no clear association with TS concentration. The median ratios (0.105 and 0.094) were slightly lower than the previously reported unbound fraction of 14–20% [6–8] and close to the approximately 12% reported in a population pharmacokinetic analysis of 152 patients [9]. Because CEZ protein binding is saturable and albumin dependent [9, 10], and unbound fractions of 23–40% have been reported, including in hypoalbuminemia [18, 19], a single fixed fraction is unreliable: individual US/TS ratios ranged from 0.05 to 0.35 even though median albumin concentrations were 3.1–3.2 g/dL, and similar difficulty has been noted in critically ill patients [20]. Our findings therefore do not support a fixed conversion factor, and direct measurement is preferable when unbound concentrations need to be assessed [21].

The CEZ MIC_{90} values for MSCNS and MSSE in our study were broadly comparable to published values, including 0.5 mg/L for 15 *S. lugdunensis* isolates [22] and 4 mg/L in a Canadian series of 42 isolates [23]. Direct comparison of the *Corynebacterium* results is difficult because the species differed, but our MIC_{90} (2 mg/L) was lower than the reported values of 64 mg/L for five *C. resistens* isolates [24] and ≥ 32 mg/L for cephalosporins in *C. striatum* [25].

Reported SSIs rates after urological procedures are generally low, including 0.53% after RAPN [26] and six cases among 1,084 patients (0.6%) after RARP [27]. Potential reasons include low frequency of incision-related complications [26, 27], small size of incisions, and limited exposure of internal tissues and organs to the external environment [28]. Although our study had no control group and cannot establish a causal relationship, CEZ penetration into the relevant tissues may also contribute. Notably, no SSIs occurred even among the six RAPN patients (23%) and ten RARP patients (15%) whose adipose tissue concentrations fell below the MIC_{90} of 2 mg/L for *Corynebacterium* spp. and MSSE. A study of lower gastrointestinal surgery showed no association between cefmetazole concentrations in subcutaneous or mesenteric adipose tissue and SSI [29]. This raises the possibility that antibiotic concentrations in peri-organ adipose tissue alone may have a limited direct impact on SSI risk in clean or clean-contaminated minimally invasive surgery.

This study has several limitations. First, tissue concentrations at each site were measured only once at the time of specimen removal, so serial changes over time and whether adequate concentrations were maintained until wound closure could not be directly evaluated. Second, tissue concentrations were measured in tissue homogenates, which represent average concentrations across intracellular, interstitial, and vascular compartments rather than the unbound concentration within the interstitial fluid where bacteria proliferate. Third, patients weighing ≥ 80 kg who received 2 g of CEZ were excluded, so the adequacy of weight-based dosing in heavier patients could not be assessed. Further studies with serial sampling through wound closure are warranted.

Conclusion

A single 1-g dose of CEZ administered 1 hour before surgery achieved unbound serum and renal tissue concentrations that consistently exceeded the MIC_{90} values of the main skin flora during RAPN and RARP, with exceptionally high penetration into the renal parenchyma. The findings also suggest that US concentrations may provide the most informative measure of pharmacologically active CEZ exposure.

Declarations

Competing interest

The authors have no competing interests to declare.

Ethics approval

This study was approved by the Ethics Committee of Kitasato University Hospital (B21-148) and performed in accordance with the principles of the Helsinki Declaration.

Informed consent

Written informed consent for the publication of this report was obtained from all patients.

Author contributions

Conceptualization: T.Y. and T.K. Data collection and analysis: T.Y., T.K., A.Y., N.S., I.M., T.H., and I.D. Writing–original draft preparation: T.Y., and T.K. Supervision: O.H., M.K., and I.M. All authors critically reviewed and revised the draft and approved the final version of the manuscript.

Funding/Support

This study was supported by the Charitable Trust Laboratory Medicine Research Foundation of Japan and by JSPS KAKENHI Grant Number 23K09632.

Author Contribution

Author contributionsConceptualization: T.Y. and K.T. Data collection and analysis: T.Y., K.T., A.Y., N.S., I.M., T.H., and I.D. Writing–original draft preparation: T.Y., and K.T. Supervision: O.H., I.M., and M.K. All authors critically reviewed and revised the draft and approved the final version of the manuscript.

Acknowledgments

We would like to thank all staff members of the urology and anesthesiology departments, the operating room nurses, and clerks. This study was supported by the Charitable Trust Laboratory Medicine Research Foundation of Japan and by JSPS KAKENHI Grant Number 23K09632.

Data availability

No datasets were generated or analyzed during the current study.

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Figures

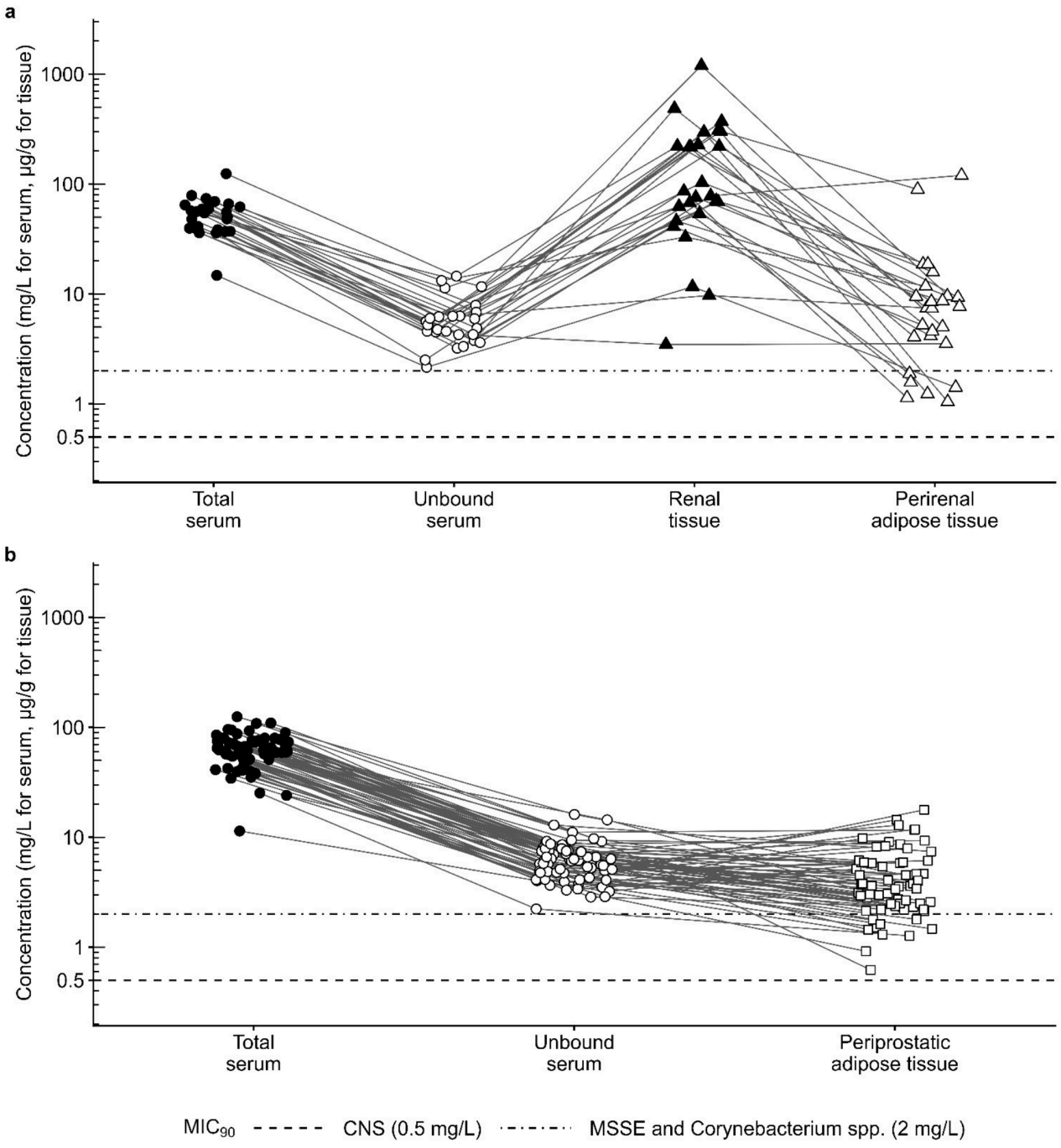


Figure 1

Individual concentration profiles of cefazolin in patients who underwent robot-assisted partial nephrectomy (RAPN) (a) and robot-assisted radical prostatectomy (RARP) (b). Lines connect the values of each patient: total serum (filled circles), unbound serum (open circles), renal tissue (filled triangles), perirenal adipose tissue (open triangles), and periprostatic adipose tissue (open squares). Horizontal lines indicate the minimum inhibitory concentration for 90% of isolates (MIC_{90}) of coagulase-negative

staphylococci (dashed line, 0.5 mg/L) and of methicillin-susceptible *Staphylococcus epidermidis* and *Corynebacterium* spp. (dash-dotted line, 2 mg/L). The y-axis is logarithmic.

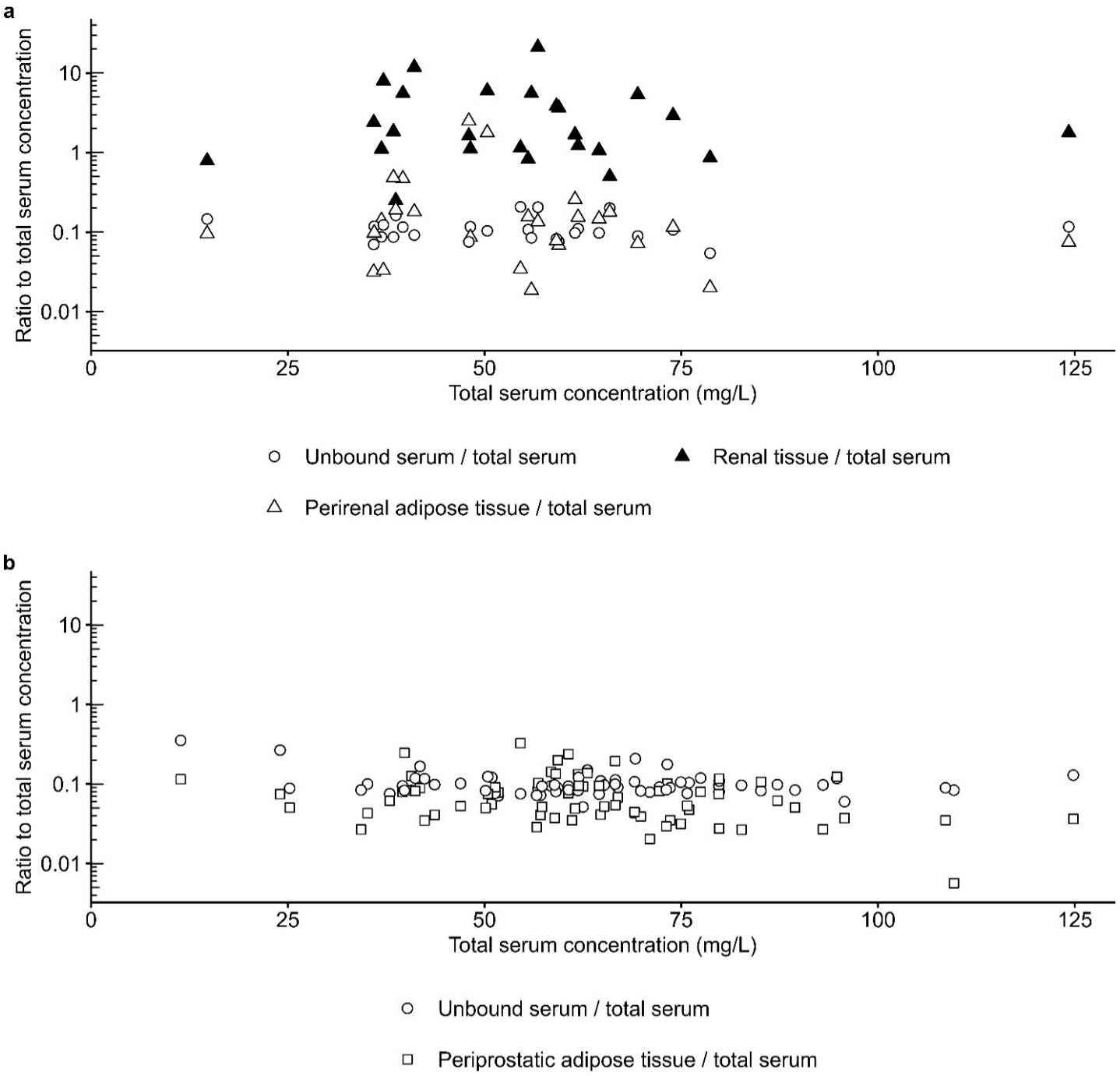


Figure 2

Ratios of unbound serum and tissue concentrations of cefazolin to total serum concentration plotted against total serum concentration in patients undergoing RAPN (a) and RARP (b). Open circles, unbound serum/total serum; filled triangles, renal tissue/total serum; open triangles, perirenal adipose tissue/total serum; open squares, periprostatic adipose tissue/total serum. The y-axis is logarithmic.