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High tartrate-resistant acid phosphatase (TRACP 5b) level in cystic fluid is a significant prognostic marker for postoperative recurrence in solitary bone cysts

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Abstract

Purpose: The pathogenesis of cystic fluid storage in solitary bone cysts remains unclear. We aimed to compare the results of the biochemical analysis of cystic fluid with clinical findings. We identified a significant marker of postoperative recurrence.

Methods: Twenty-seven male and eight female patients were studied; the median age at diagnosis was 11 (5–23) years. The mean follow-up period was 60 months (range: 14–146 months). Clinical information including sex, age, affected site, radiological findings of phase (active or latent), surgical procedure, outcome, and biochemical analysis of serum and cystic fluid was obtained.

Results: The 5-year healing rate was 64.0%. Biochemical analysis revealed that total protein and albumin values in the cystic fluid were significantly lower, compared to those in the serum. Levels of bone turnover markers, such as alkaline phosphatase, bone-specific alkaline phosphatase, and tartrate-resistant acid phosphatase 5b were remarkably elevated in the cystic fluid than in the serum. *R* values were 0.127, 0.076, and 0.095 for alkaline phosphatase, bone-specific alkaline phosphatase, and tartrate-resistant acid phosphatase 5b, respectively. Areas under the receiver operating characteristic curves, calculated to assess the association of alkaline phosphatase, bone-specific alkaline phosphatase, and tartrate-resistant acid phosphatase 5b levels in the cystic fluid with postoperative recurrence, were 0.57, 0.51, and 0.70, respectively.

Conclusions: No clear correlation of bone turnover marker levels between the serum and cystic fluid was observed. The high tartrate-resistant acid phosphatase 5b level in the cystic fluid was associated with postoperative recurrence. The bone resorption caused by osteoclasts is considered to affect postoperative recurrence.

Level of evidence: Level IV.

Keywords: Solitary bone cyst, cystic fluid, bone turnover marker, tartrate-resistant acid phosphatase 5b, postoperative recurrence

Introduction

Solitary bone cysts are frequently discovered in the proximal humerus and proximal femur (both long bone cysts), calcaneus, and tibia during the age of skeletal growth.[1] Solitary bone cysts may induce various clinical problems following pathological fractures and subsequently lead to limb deformities, growth disorders, and postoperative recurrences.[2–4]

This lesion is classified as a non-true tumor in a strict sense, and it is also classified as a tumor-like lesion. Histopathological examination of the surgical specimens of solitary bone cysts confirmed that the lining membrane

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tissue of the cyst wall was mainly composed of fibrous membrane and chronic inflammatory tissue, including fibrin-like collagen, giant cells, and hemosiderin.[5] Another important component of solitary bone cysts is the cystic fluid. A bloody, serosanguineous, and straw-colored fluid is contained inside the cavity.[6]

The origin of the cystic fluid is unclear. Cohen[7] first reported that solitary bone cysts exhibit a venous return, after a contrast medium was injected into the cystic cavity. Subsequently, Ramirez et al.[8] and Yandow et al.[9] also discovered that rapid venous outflow from the cyst was evident through cystography examination. Therefore, the cystic cavity was believed to have a direct communication with the venous flow. The characteristics of the cystic fluid were considered similar to those of venous blood.

The pathogenesis of fluid storage in solitary bone cysts remains unknown. Several pathogeneses[7,10–18] have been proposed, but none of them gained complete acceptance. Cohen[10] evaluated the laboratory data of the cystic fluid in a solitary bone cyst and discovered that the fluid content was similar to that of the interstitial fluid. Later, he proposed that venous return obstruction was the etiology of solitary bone cysts.[7] In 1983, Chigira et al.[11] reported that the partial pressure of oxygen of the cystic fluid was lower than that of the venous blood, suggesting that venous obstruction in the bone is a possible cause of these cysts. In 1988, Marković et al.[12] reported increased levels of the bone turnover enzymes, such as acid and alkaline phosphatases (ALPs) in the cystic fluid. Gerasimov et al.[14] showed enhanced osmotic pressure of cystic fluid. Komiya et al.[15] discovered enhanced levels of prostaglandin E_2 and collagenolytic enzymes, promoting bone resorption. Subsequently, Komiya et al.[16] demonstrated oxygen free radicals in the cystic fluid. In addition, he showed elevated nitrate and nitrite.[17] Aarvold et al.[18] discovered elevated levels of pro-inflammatory cytokines, such as interleukin-6, macrophage inflammatory protein-1α, and monocyte chemotactic protein-1 in the cystic fluid. However, the definitive pathogenesis of the storage of this fluid has not been clearly elucidated.

Bone metabolism seems a logical explanation for the formation of solitary bone cysts. Marković et al.[12] demonstrated the high levels of acid phosphatase in the cystic fluid indicated that osteoblastic activity was related to cyst formation. Yu et al.[13] also suggested that the cells derived from the wall of solitary bone cysts expressed key factors for osteoblastic differentiation and had the capacity to induce osteoclastogenesis in vitro. Aarvold et al.[18] also proposed that the upregulation of osteoclasts might hold the key to the pathogenesis of cyst formation. Therefore, we focused on the osteoblastic and osteoclastic activities in solitary bone cysts.

Analysis of serum and cystic fluids is vital to elucidate the pathogenesis of solitary bone cyst generation. In this study, we performed biochemical analysis of the cystic fluid in solitary bone cysts and the serum of patients and discussed the clinical implications. In addition, we proposed a hypothesis for the pathogenesis of solitary bone cyst generation.

Methods

This was a retrospective observational study, approved by the institutional review board of our institution. Since this study was a retrospective chart review, the need of providing consent for participation was waived and approval of this waiver was obtained by the institutional review boards of our institution. Between April 2004 and August 2020, 35 patients with solitary bone cysts were evaluated. Patients who were diagnosed with solitary bone cysts in the resected specimens were studied. We focused on patients with solitary bone cysts in the typical location of long bones, such as the humerus and femur. We excluded patients with solitary bone cysts in uncommonly affected long bones, such as the tibia and fibula, and in irregular bones, such as the calcaneus.

The initial diagnosis of solitary bone cysts was based on plain radiographic findings. Solitary bone cysts showed radiolucent and well-circumscribed appearances. All cysts were evaluated using plain radiography, computed tomography, and/or magnetic resonance imaging.

Surgery was performed to confirm the diagnosis and to prevent pathological fractures, recurrence, disturbance of skeletal growth, and deformity. If a pathological fracture had occurred, immobilization and restriction of activities were prescribed for 4–6 weeks to achieve spontaneous bone repair. Subsequently, if radiological findings were suggestive of a low risk of fracture after spontaneous bone repair, we recommended non-operative treatment to the patients. However, after the conservative treatment of over 3 months, the patients were advised to undergo operative treatment for three scenarios: (1) if the persistent and expansive cyst was associated with a high-risk of pathological bone fracture,[19] (2) if the patients expected to prevent pathological fractures, or (3) if they desired operative treatment for definitive pathological diagnosis.

Twenty-seven males and eight females were included, and the median age at diagnosis was 11 (5–23) years. Clinical information, including sex, age, affected site, radiological findings of phase (active or latent), surgical procedure, and outcome was assessed from medical charts. The follow-up period was calculated as the interval between surgery and final follow-up. The mean follow-up was 60 months (range: 14–146 months). No patients were lost to follow-up in this study.

Radiologically, solitary bone cysts were classified as "active" when the distance between the cyst and the growth plate was < 5 mm and as "latent" when the distance was > 5 mm.[6,20] Radiological images were reviewed by three orthopedic surgeons.

During the surgery, following Kirschner wire puncture, the cystic fluid was collected from the thinning cortical

bone of the affected bone, and the characteristics were evaluated in all patients. The gross findings were classified as "bloody," "serosanguineous," and "straw-coloured."[10] More than three surgeons discussed the results. Curettage with burr drilling was conducted and then the bone defects were filled with bone substitutes.

The resected specimens of the surgeries were stained with hematoxylin and eosin. All resected specimens were examined by a pathologist specializing in bone tumor pathology and diagnosed according to the standard criteria for solitary bone cysts.[5]

Biochemical analysis

Biochemical analysis of blood samples from the patients taken within 2 weeks preceding surgery and of cystic fluid from the solitary bone cyst taken during surgery was performed. Laboratory data of total protein (TP), albumin (Alb), sodium (Na), potassium (K), calcium (Ca), aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactic acid dehydrogenase (LDH), ALP, bone-specific alkaline phosphatase (BAP), and tartrate-resistant acid phosphatase 5b (TRACP 5b) levels were assessed. Biochemical analysis of each sample was carried out immediately after surgery.

Clinical outcome after surgery for long bone cyst

Plain radiographs were used to evaluate healing at the last follow-up, and assessment was done based on the modified Neer classification system:[21] "healed," "healed with defect," "persistent cyst," and "recurrent cyst." The state of persistent and recurrent cysts was defined as "recurrence." The Kaplan–Meier method was used to evaluate the healing rate.

Comparison of biochemical analysis between serum and cystic fluid

Biochemical data of the serum and cystic fluid were compared. In addition, cystic fluid data were also compared between the active and latent phases of solitary bone cysts.

Correlation of bone turnover markers between serum and cystic fluid

To assess the correlation of bone turnover markers (ALP, BAP, and TRACP 5b) between serum and cystic fluid, Pearson's correlation coefficient (r) was applied.

Relationship of recurrence and bone turnover markers in cystic fluid

To determine the contribution of bone turnover markers (ALP, BAP, and TRACP 5b) with postoperative recurrence, receiver operating characteristic (ROC) curves were plotted.

Statistical analysis

The clinical outcome of healing rate was determined using the Kaplan–Meier method and the comparisons of cystic fluid data between the active and latent phases of solitary bone cysts were assessed using the log-rank test. The Mann–Whitney U test was used for statistical comparison between the two groups. The statistical significance was set at $p < 0.05$. The correlation of biochemical data of bone turnover markers between serum and cystic fluid was determined using Pearson's correlation coefficient (r). ROC curves were used to assess the relationship between postoperative recurrence and bone turnover markers. The optimum cut-off value was defined as the point on the ROC curve with a minimum distance from the 100% true-positive and the 0% false-positive rate.

Statistical analysis was performed with statistical software BellCurve for Excel (version 2022; Social Survey Research Information Co., Ltd., Tokyo, Japan).

Results

The demographic data are summarized in Table 1.

The locations of solitary bone cysts were humerus in 22 cases and femur in 13 cases. The locations in all 35 cases except one (Case 9: midshaft of humerus) were in the proximal region. Twenty-five cases were active (Figure 1(a)) and 10 were latent. Pathological fractures occurred in 23 of the 35 (65.7%) cases at the initial visit.

At the time of surgery, macroscopic findings of the cystic fluid were evaluated. The character was grossly judged as bloody in 10 cases, serosanguineous in 21 (Figure 1(b)), and straw-colored in four.

After curettage, the bonny defect was reconstructed with beta-tricalcium phosphate in 19 cases (Figure 1(c)), cannulated hydroxyapatite pin in nine cases, and hydroxyapatite in seven cases.[1,22]

Clinical outcome after surgery for long bone cyst

Healing evaluation indicated 20 healed cysts, four cysts healed with defects, three persistent cysts, and eight recurrent cysts (Figure 1(d)). The 5-year healing rate was 64.0%. The healing rates of patients in active and latent phases were 59.3% and 83.3%, respectively. The statistical significance between these two phases was not observed ($p = 0.53$). No adverse effects, such as poor wound healing, postoperative infection, and/or pathological fracture developed after surgery. Postoperative pathological fracture occurred in two cases during follow-up (Figure 2).

Biochemical analysis of serum and cystic fluid

The TP and Alb levels were statistically lower in the cystic fluid than in the serum. The ALP, BAP, TRACP 5b, AST,

Table 1. Demographic data of participants.

Case	Age/ sex	Side	Site	Phase	Pathological fracture	Surgery	Cystic fluid	Healing evaluation	Follow-up (months)
1	23/M	Right	Femur (proximal)	Latent	–	Curettage + HA	Serosanguineous	Healed	16
2	16/M	Left	Humerus (proximal)	Latent	+	Curettage + cannulated HA pin	Serosanguineous	Healed	36
3	15/M	Right	Humerus (proximal)	Active	+	Curettage + cannulated HA pin	Serosanguineous	Healing with defect	65
4	12/M	Right	Humerus (proximal)	Latent	+	Curettage + β-TCP	Serosanguineous	Healed	36
5	13//F	Right	Femur (proximal)	Latent	–	Curettage + cannulated HA pin	Bloody	Recurrent cyst	31
6	13//F	Right	Femur (proximal)	Active	+	Curettage + cannulated HA pin	Serosanguineous	Healed	30
7	12//F	Left	Femur (proximal)	Active	–	Curettage + β-TCP	Serosanguineous	Healed	79
8	13/M	Left	Humerus (proximal)	Active	+	Curettage + β-TCP	Serosanguineous	Healed	52
9	9/M	Left	Humerus (midshaft)	Latent	+	Curettage + β-TCP	Serosanguineous	Healed	70
10	6/M	Left	Humerus (proximal)	Active	+	Curettage + β-TCP	Serosanguineous	Recurrent cyst	24
11	15/M	Right	Humerus (proximal)	Active	+	Curettage + β-TCP	Bloody	Healing with defect	60
12	10//F	Left	Femur (proximal)	Active	–	Curettage + cannulated HA pin	Straw-colored	Recurrent cyst	28
13	9/M	Right	Femur (proximal)	Active	–	Curettage + HA	Serosanguineous	Healing with defect	49
14	6/M	Right	Femur (proximal)	Active	–	Curettage + cannulated HA pin	Straw-colored	Persistent cyst	10
15	17/M	Right	Humerus (proximal)	Active	+	Curettage + β-TCP	Bloody	Healed	14
16	11/M	Left	Humerus (proximal)	Active	+	Curettage + cannulated HA Pin	Bloody	Healing with defect	146
17	11//F	Right	Humerus (proximal)	Active	+	Curettage + cannulated HA Pin	Serosanguineous	Healed	60
18	12/M	Left	Humerus (proximal)	Active	+	Curettage + β-TCP	Serosanguineous	Persistent cyst	80
19	7/M	Right	Humerus (proximal)	Active	+	Curettage + β-TCP	Bloody	Recurrent cyst	13
20	11/M	Right	Humerus (proximal)	Active	+	Curettage + β-TCP	Bloody	Healed	12
21	11/M	Left	Humerus (proximal)	Active	+	Curettage + β-TCP	Serosanguineous	Healed	109
22	8/M	Left	Femur (proximal)	Active	–	Curettage + β-TCP	Straw-colored	Persistent cyst	19
23	12/M	Left	Humerus (proximal)	Latent	–	Curettage + β-TCP	Serosanguineous	Healed	13
24	9/M	Left	Humerus (proximal)	Latent	+	Curettage + β-TCP	Serosanguineous	Healed	29
25	9/M	Left	Humerus (proximal)	Active	+	Curettage + β-TCP	Serosanguineous	Recurrent cyst	40
26	9/M	Left	Humerus (proximal)	Active	+	Curettage + β-TCP	Bloody	Recurrent cyst	10
27	14//F	Left	Femur (proximal)	Latent	–	Curettage + β-TCP	Bloody	Healed	21
28	7/M	Right	Femur (proximal)	Active	+	Curettage + β-TCP	Serosanguineous	Healed	19
29	14/M	Left	Humerus (proximal)	Active	+	Curettage + β-TCP	Serosanguineous	Healed	60
30	7//F	Left	Femur (proximal)	Active	+	Curettage + cannulated HA Pin	Serosanguineous	Recurrent cyst	52
31	23/M	Left	Humerus (proximal)	Latent	+	Curettage + HA	Bloody	Healed	37
32	17//F	Left	Humerus (proximal)	Latent	–	Curettage + HA	Bloody	Recurrent cyst	80
33	7/M	Right	Femur (proximal)	Active	+	Curettage + HA	Straw-colored	Healed	21
34	8/M	Right	Humerus (proximal)	Active	–	Curettage + HA	Serosanguineous	Healed	13
35	5/M	Left	Femur (proximal)	Active	–	Curettage + HA	Serosanguineous	Healed	14

M: male; F: female; HA: hydroxyapatite; β-TCP: beta-tricalcium phosphate; healing evaluation: Chang's radiographic classification.

and LDH levels were significantly higher in the cystic fluid than in the serum. There were no significant differences between the two groups in Na, K, Ca, and ALT levels (Table 2).

Comparison of cystic fluid of solitary bone cyst between the active and latent phases

The ALP and BAP levels were statistically enhanced in the active phase compared to the latent phase, whereas the TP, Alb, Na, Ca, AST, ALT, LDH, and TRACP 5b levels were not significantly different (Table 2).

Correlation of bone turnover markers between serum and cystic fluid

Figure 3 shows the correlations of bone turnover markers (ALP, BAP, and TRACP 5b) between the serum and cystic fluid of solitary bone cysts. R values, which were calculated to determine the consistency between the serum and cystic fluid, were 0.127, 0.076, and 0.095 for ALP

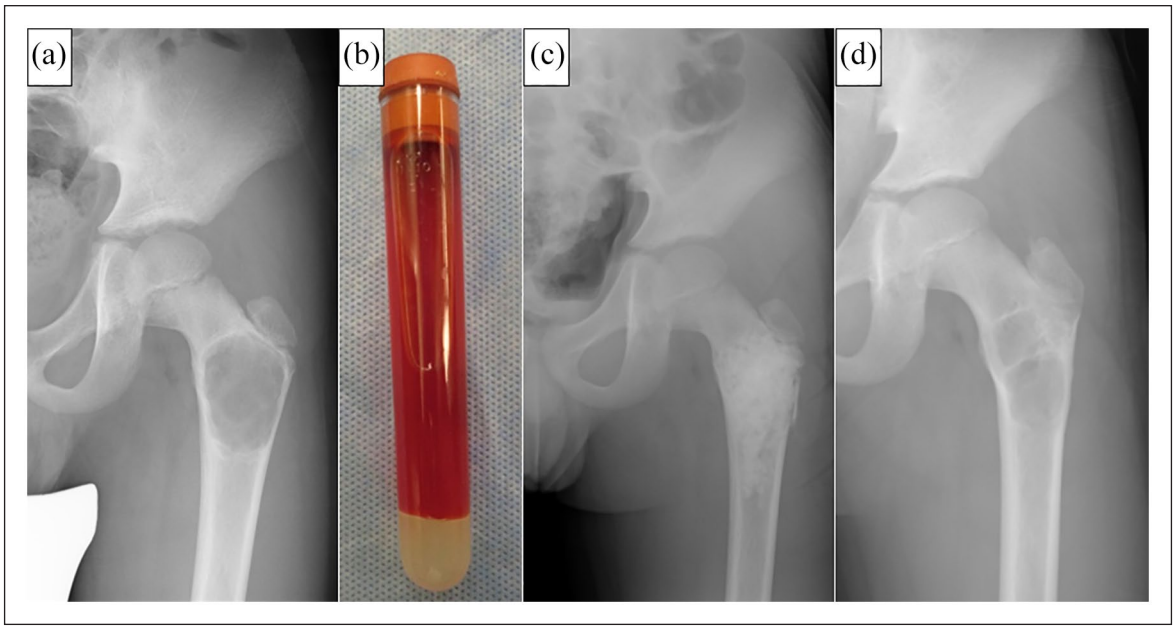

Figure 1. Case 22: An 8-year-old male patient. (a) Plain radiographs demonstrate an active-phase solitary bone cyst in the left proximal femur. (b) Gross finding of aspirated cystic fluid is serosanguineous. (c) At surgery, curettage and artificial bone grafting using beta-tricalcium phosphate (β-TCP) are performed. (d) Postoperative recurrence occurs 19 months after the surgery. Additional surgery is performed for this patient.

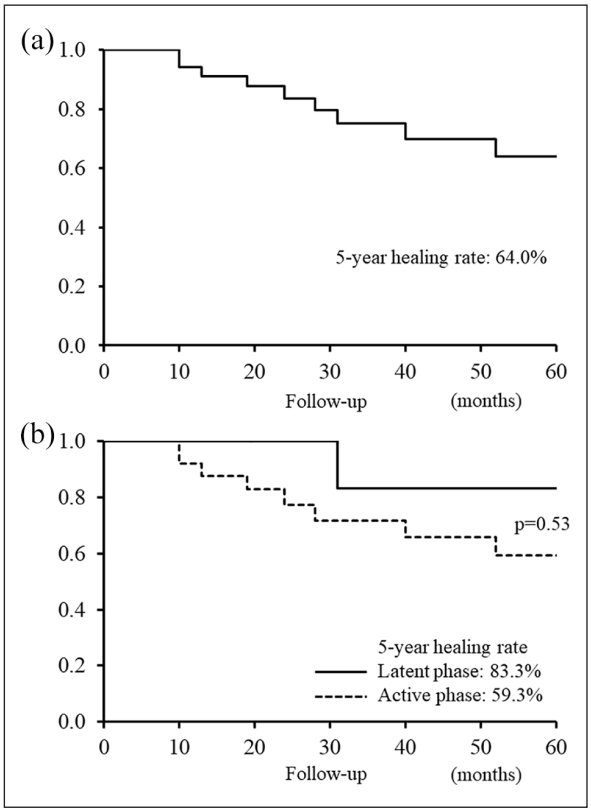

Figure 2. Five-year healing rate of solitary bone cysts. (a) Five-year healing rate in all patients is 64.0%. (b) Five-year healing rates are 59.3% and 83.3% in the active and latent phases, respectively. There is no significant difference between these two groups (log-rank test, $p = 0.53$).

(Figure 3(a)), BAP (Figure 3(b)), and TRACP 5b, respectively (Figure 3(c)). This result indicates that bone turnover marker levels in the serum were not correlated with those in the cystic fluid.

Relationship of postoperative recurrence and bone turnover markers in cystic fluid

To determine the relationship between postoperative recurrence and bone turnover markers, the area under the ROC curve was calculated and determined to be 0.57 (Figure 4(a)), 0.51 (Figure 4(b)), and 0.70 (Figure 4(c)) for ALP, BAP, and TRACP-5b, respectively. The cut-off values of ALP, BAP, and TRACP 5b were evaluated as 1661, 256.3, and 28,900, respectively. Specificity and sensitivity were 0.454 and 0.778 for ALP, 0.684 and 0.500 for BAP, and 0.636 and 1.00 for TRACP 5b, respectively. Elevated levels of TRACP 5b were found to be associated with postoperative recurrence of solitary bone cysts.

Discussion

Biochemical analysis is a relatively simple method to identify the characteristics of cystic fluid. The TP and Alb levels were lower in the cystic fluid than in the serum. The Na, K, and Ca electrolyte levels were not significantly different. This result was consistent with a previous report[10] that the composition of cystic fluid was similar to that of interstitial fluid.

Table 2. Biochemical analyses of solitary bone cysts.

Serum and cystic fluid						
Factor	Unit	Serum	Number	Cystic fluid	Number	*p*-value
TP	g/dl	7.3 ± 0.6	34	5.8 ± 0.6	24	< 0.01
Alb	g/dl	4.5 ± 0.3	34	3.9 ± 0.4	20	< 0.01
Na	mEq/l	139 ± 2	35	139 ± 3	27	0.17
K	mEq/l	4.2 ± 0.3	35	4.2 ± 0.9	23	0.55
Ca	mEq/l	9.6 ± 2.2	20	9.1 ± 2.0	27	0.13
AST	IU/L	25.0 ± 4.8	34	38.5 ± 17.7	24	< 0.05
ALT	IU/L	15.5 ± 14.2	34	12.5 ± 6.4	16	0.08
LDH	IU/L	271 ± 115	25	821 ± 472	21	< 0.01
ALP	IU/L	572 ± 273	34	1854 ± 1889	31	< 0.01
BAP	µg/L	95.2 ± 46.9	22	314 ± 333	27	< 0.01
TRACP 5b	g/dL	1665 ± 457	14	28,900 ± 18,826	15	< 0.01
Cystic fluid between active and latent phase						
Factor	Unit	Active	Number	Latent	Number	*p*-value
TP	g/dl	5.7 ± 0.6	17	6.1 ± 0.6	7	0.35
Alb	g/dl	3.9 ± 0.2	13	4.1 ± 0.5	7	0.06
Na	mEq/l	138.5 ± 2.8	20	140.0 ± 3.3	7	0.84
K	mEq/l	4.0 ± 0.5	16	4.3 ± 1.3	7	< 0.01
Ca	mEq/l	9.2 ± 1.8	19	8.8 ± 2.4	8	0.15
AST	IU/L	42.0 ± 12.1	17	35 ± 28	7	0.65
ALT	IU/L	12.5 ± 4.5	12	17 ± 9	4	0.22
LDH	IU/L	621 ± 312	15	1101 ± 605	6	0.09
ALP	IU/L	2876 ± 1876	22	996 ± 497	9	< 0.01
BAP	µg/L	476 ± 341	12	183 ± 177	9	< 0.05
TRACP 5b	g/dL	33,300 ± 1821	10	10,900 ± 17,690	5	0.22

TP: total protein; AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactic acid dehydrogenase; ALP: alkaline phosphatase; BAP: bone-specific alkaline phosphatase; TRACP: tartrate-resistant acid phosphatase.

The levels of bone turnover markers ALP, BAP, and TRACP 5b were remarkably increased in the cystic fluid in most cases, which is consistent with the results of a previous study.[12] Inside the cavity, bone turnover is speculated to be active. Considering the radiological findings of solitary bone cysts as bone resorption characteristics, osteoclastic activity would be predominant in expansive, residual, and postoperative recurrent solitary bone cysts.

In primary bone tumors, ALP and TRACP 5b levels in the serum are representative markers for monitoring the activity of osteosarcoma[23] and giant cell tumor of bone.[24] However, the biochemical marker for activity remains unclear in solitary bone cysts. In this study, bone turnover makers were examined to assess their correlation between the serum and cystic fluid. Pearson's correlation coefficient (r) was applied and the R-values were 0.127, 0.076, and 0.095 for ALP, BAP, and TRACP 5b, respectively. This indicated that no clear correlation of bone turnover enzymes was observed between the serum and cystic fluid.

Several studies have demonstrated that the healing rate of solitary bone cysts in the active phase is worse than that in the latent phase.[25,26] In contrast, Neer et al.[6] concluded that there was no significant difference in clinical outcomes between these two phases. In this study, the healing rate was not significantly different between the two phases. Bone turnover markers were compared between the active and latent phases. The TRACP 5b level was not significantly different, but the ALP and BAP levels were higher in the active phase than those in the latent phase. The reason for this is unclear. A further study with a larger sample size may lead to different results. The cysts in the active phase were adjacent to the growth plates. Jaffe and Lichtenstein[20] suspected aberrant growth plates function in active cysts. Further study is necessary to identify why enhanced osteoblastic activity is related to cyst formation, instead of bone formation.

It seems to be an attractive explanation that the increased levels of bone turnover markers might be associated with postoperative recurrence. Areas under the ROC curve were 0.56, 0.51, and 0.70 for ALP, BAP, and TRACP 5b, respectively. Osteoblastic markers of ALP and BAP were not related to postoperative recurrence, but the osteoclastic marker of TRACP 5b was associated with postoperative recurrence. Postoperative recurrence

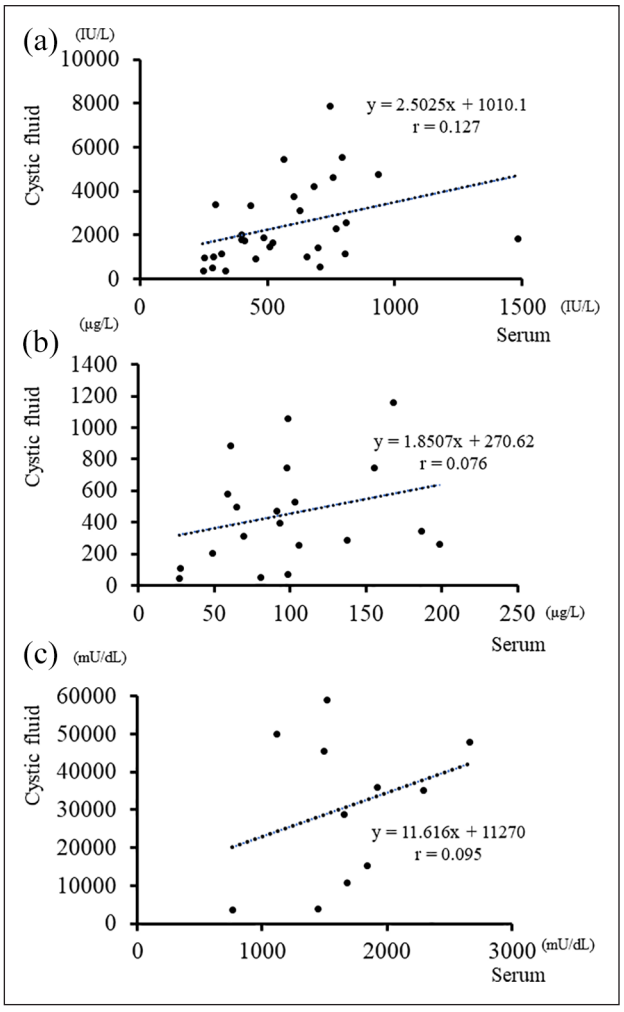

Figure 3. Correlation of bone turnover marker levels in the serum and in cystic fluid with Pearson's correlation coefficient (*r*). (a) Alkaline phosphatase (ALP): $r = 0.127$. (b) Bone-specific alkaline phosphatase (BAP): $r = 0.076$. (c) Tartrate-resistant acid phosphatase 5b (TRACP 5b): $r = 0.095$.

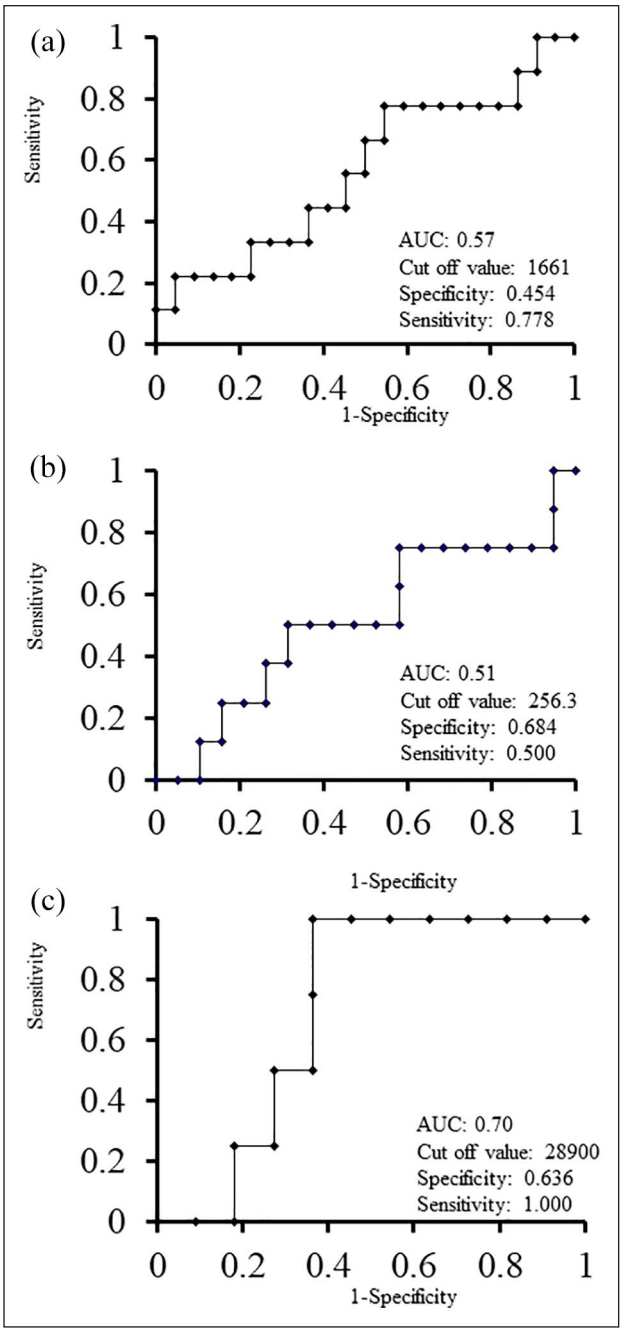

Figure 4. (a) The area under the receiver operating characteristic (ROC) curve (AUC) of alkaline phosphatase (ALP) to postoperative recurrence is 0.57. (b) The AUC of bone-specific alkaline phosphatase (BAP) to postoperative recurrence is 0.51. (c) The AUC of tartrate-resistant acid phosphatase 5b (TRACP 5b) to postoperative recurrence is 0.70.

of solitary bone cysts is likely to be associated with the marker of bone resorption.[26]

Garceau and Gregory[27] reported that ~64.9% of patients with solitary bone cysts experienced pathological fractures at the initial visit, but some solitary bone cysts spontaneously regressed after pathological fractures.[28,29] Pathological fractures sometimes contribute to cyst healing. In this study, 23 of the 35 (65.7%) patients experienced pathological fractures. We included cases with residual defects and ballooning cysts from conservative treatment for over 3 months following pathological fractures and excluded cases with recovered solitary bone cysts. As our hypothesis of the etiology of solitary bone cysts, the turnover markers in the cystic fluid might indicate an important role in cyst generation. When a solitary bone cyst is healed after a pathological fracture, osteoblastic activity is more predominant and bone remodeling results in spontaneous cyst healing. If solitary bone cysts are residual or expansive after pathological fractures or are recurrent after surgery, bone resorption is speculated to be predominant.

This study has several limitations. First, it was retrospective in nature. Second, this study included a small

number of patients and had low statistical power. Third, 23 of the 35 (65.7%) patients experienced pathological fractures. Although we performed surgery for solitary bone cysts more than 3 months after pathological fractures, it is likely that the pathological fractures may have affected biochemical data. Fourth, at surgery, three different kinds of bone substitutes, hydroxyapatite, beta-tricalcium phosphate, and cannulated hydroxyapatite pin were applied to the bone defects, and the anatomical sites included proximal and midshaft parts in the femurs and humerus. These factors might have influenced the healing evaluation. Fifth, to understand the effects of bone turnover markers in the cystic fluid on the host bone, comparison with the bone marrow fluid of the unaffected side would be meaningful, but this analysis was not performed in this study.

Conclusion

Biochemical analysis showed that TP and Alb levels in the cystic fluid were statistically lower than those in the serum, suggesting that the cystic fluid resembled the interstitial fluid. The bone turnover markers ALP, BAP, and TRAP 5b levels were remarkably increased in the cystic fluid, compared with those in the serum. However, no clear clinical correlation of these levels was observed between the serum and cystic fluid, implying that bone metabolism in the cyst cannot be predicted from serum. The high TRACP 5b level in the cystic fluid was associated with postoperative recurrence.

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Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

This study was carried out with approval from the Institutional Review Board of Osaka Metropolitan University Graduate School of Medicine (IRB number: 4394. Date: September 12, 2019). This work did not involve any active human or animal participants.

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