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Receiver operating characteristic (ROC) analysis of the ability of arterial ketone body ratio to predict graft outcome after liver transplantation – its sensitivity and specificity

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Abstract. To evaluate the ability of arterial ketone body ratio (AKBR; acetoacetate/3-hydroxybutyrate) to predict graft prognosis after liver transplantation, the diagnostic value as a predictive index was compared between AKBR and conventional liver function tests using receiver operating characteristic (ROC) analysis. The ROC curves were determined for AKBR, GOT, GPT, total bilirubin, serum lactate level, and prothrombin time, all of which were measured on the 1st and 2nd postoperative days in 88 cases of liver transplantation. Comparisons of the areas under the ROC curves between AKBR and other tests revealed the significant superiority of AKBR to other tests in predicting graft death within 1 month after transplantation. The present study suggests that AKBR can be used as an accurate index to predict graft prognosis after liver transplantation.

Key words: Liver transplantation, graft prognosis test – Prognosis, liver transplantation, ketone body ratio – Arterial ketone body ratio, prognosis liver graft

For successful recovery after liver transplantation, full and prompt restoration of function of the implanted graft is essential. In contrast, there is high mortality and morbidity in patients with poorly functioning or nonfunctioning grafts. To date, the only treatment for the initial nonfunctioning graft (INF) has been retransplantation in the immediate postoperative period. Thus, the accurate evaluation of graft function before critical conditions develop is of utmost clinical importance.

Taki et al. [15] have shown that arterial ketone body ratio (AKBR; acetoacetate/3-hydroxybutyrate), reflecting hepatic mitochondrial redox potential (NAD^+/NADH), provides an accurate means of assessing the metabolic function of the graft liver, and that the suppression of AKBR below 0.7 within 24 h after reperfusion of the graft is an early indicator of INF. Moreover, the Hannover [9] and Pittsburgh [1] liver transplantation teams have recently reported that there is a close relationship between long-term graft function and changes in AKBR in the immediate postoperative days. They have shown that restoration of AKBR to above 1.0 by the 2nd postoperative day (POD) is a prerequisite for graft survival with satisfactory patient condition at the end of the 1st postoperative month. Therefore, it is conceivable that AKBR can be used as an index to predict graft outcome in the postoperative course.

The purpose of this paper is to evaluate the predictive ability of AKBR for graft outcome using receiver operating characteristic (ROC) analysis. ROC analysis has become increasingly popular in the medical field [13, 14, 17, 18] and has been used to evaluate the discriminating ability of test results to detect disorders. The analysis is based on the ROC curve, which is a graph plotting the achievable combinations of sensitivity and specificity of a test with varying cut-off points [7, 8]. A comparison of the curves between two or more tests will show which one is superior to the other in diagnostic accuracy for a particular purpose. In addition, the areas under the curves (AUC) can be used for a quantitative analysis of the curves [3, 4].

In the present study using ROC analysis, the diagnostic validity of AKBR to predict graft death within 1 month is compared with other widely used liver function tests.

Patients and methods

Patients

From July 1988 to May 1990, AKBR was measured on the 1st and 2nd postoperative days (POD) in 88 liver transplantations (LTx) on 78 patients at the Department of Abdominal and Transplantation Surgery of the Medical School in Hannover. The patients consisted of 40 men and 38 women with a mean age of 42 years (range 14–64 years). Indications for the 88 LTx were liver cirrhosis ($n = 34$), graft failure after LTx ($n = 13$), hepatocellular carcinoma ($n = 11$), fulminant hepatitis ($n = 8$), Budd-Chiari syndrome ($n = 6$), sclerosing cholangitis ($n = 3$), and other ($n = 13$). Of these 88 cases, 71

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Table 1. Outcomes of the 17 patients in group 2. POD, Postoperative day

Outcome	No.	Day of death or reLTx
INF→reLTx	8	POD 1, POD 1, POD 1, POD 2 POD 3, POD 3, POD 4, POD 7
Died of sepsis	3	POD 6, POD 7, POD 21
Died of multiple organ failure	4	POD 2, POD 10, POD 20, POD 31
Died of liver failure due to portal thrombus	1	POD 23
Died of acute liver necrosis of unclear origin	1	POD 8
Total	17	

(group 1) were alive at the end of the 1st month after transplantation; the remaining 17 cases (group 2) died or required retransplantation (reLTx) within the 1st month due to various complications, as shown in Table 1.

The donor livers were harvested according to a standardized procedure [2], and preservation was performed using UW solution. Postoperative management, including infusion of fluid or blood derivatives [9] and immunosuppressive therapy [12], has been described elsewhere. Ketone bodies (acetoacetate and 3-hydroxybutyrate) in the arterial blood were measured enzymatically using a KETOREX Kit (Sanwa Chemical, Nagoya, Japan) and KETO-340 (a semiautomatic spectrophotometer designed for the measurement of ketone bodies; Ihara Electric, Kasugai, Japan) [6, 16, 19].

ROC analysis

In order to evaluate the ability to predict graft death within 1 month after transplantation, ROC curves for AKBR, GOT, GPT, total bilirubin, serum lactate level, and prothrombin time on POD 1 and 2 were constructed according to the frequency distributions of each test result in groups 1 (graft survival group) and 2 (graft death group) [7, 8]. The sensitivity is the ratio of the number of true-positive decisions to the number of actually positive cases (i.e., the number of group 2 cases) and the specificity is the ratio of the number of true-negative decisions to the number of actually negative cases (i.e., the number of group 1 cases). The ROC curve can be drawn by plotting the sensitivity (or "true-positive rate") on the vertical (Y) axis and one minus the specificity (or "false-positive rate") on the horizontal (X) axis with a given cut-off point and changing the cut-off points from more stringent to less stringent. Since the accuracy of a test depends on its sensitivity and specificity, the ROC curve of a test with higher discriminating ability is closer to the upper left corner than the curve of that with lower ability.

An area under the ROC curve (AUC) can be calculated using the trapezoidal method [3]. The AUC represents the probability of correctly ranking a randomly chosen pair of persons with and without disorder. For comparison of two areas under the curves, the nonparametric method developed by Hanley and McNeil [3, 4] was employed. A standard error of the estimated AUC was calculated from the following formula:

$$SE^2 = \frac{AUC(1-AUC) + (n_D - 1)(Q_1 - AUC^2) + (n_N - 1)(Q_2 - AUC^2)}{n_D\, n_N}$$

where SE represents the standard error of AUC, AUC is the estimated area under the ROC curve, $Q_1 = AUC/(2 - AUC)$, $Q_2 = 2AUC^2/(1 + AUC)$, n_D represents the number of patients with the disorder, and n_N the number of patients without the disorder. Finally, the Z statistic for the difference between two areas was calculated as:

$$Z = \frac{AUC_1 - AUC_2}{(SE_1^{\,2} + SE_2^{\,2} - 2rSE_1SE_2)^{1/2}}$$

where AUC_1 and AUC_2 are the estimated ROC areas for tests 1 and 2, and SE_1 and SE_2 are the corresponding standard errors. The correlation r between ROC areas was estimated using the Hanley and McNeil method [4].

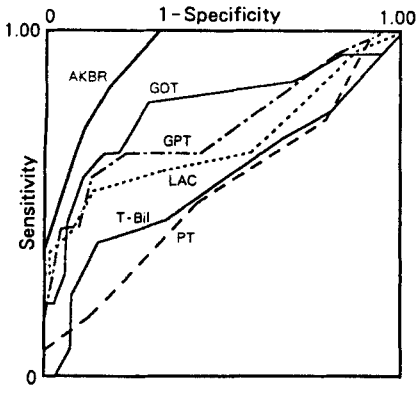
Statistical analysis

The differences in the means of each test between groups 1 and 2 were determined using Student's *t*-test. All comparisons used two-tailed tests of statistical significance and *P* values less than 0.05 were regarded as significant.

Results

The numbers, distribution ranges, and mean values of each test in groups 1 and 2 are shown in Table 2. Because the data were retrospectively analyzed, not all tests were equally measured at the same time in some patients. Thus, the number of test results differed. AKBR on POD 1 and 2 was significantly higher in group 1 than in group 2 (Table 2). Also, the differences in the means between groups 1 and 2 were significant for GOT (POD 1 and 2), GPT (POD 1 and 2), total bilirubin (POD 2), and serum lactate level (POD 1 and 2).

The empirical ROC curves for each test were constructed by changing the cut-off levels (Figs. 1, 2). For example, in the case of AKBR on POD 1, where the cut-off point is 0.7, assuming that AKBR < 0.7 indicates a case



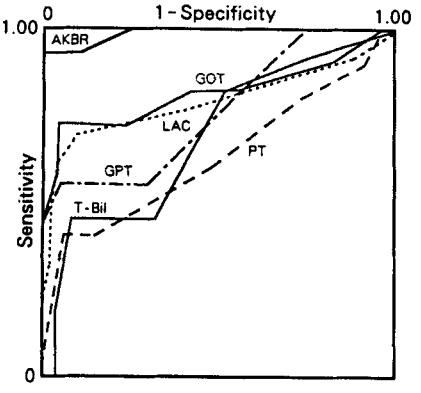


Fig. 1. Comparison of the empirical ROC curves among AKBR, GOT, GPT, total bilirubin *(T-Bil)*, serum lactate level *(LAC)*, and prothrombin time *(PT)* on POD 1

Fig. 2. Comparison of the empirical ROC curves among AKBR, GOT, GPT, total bilirubin *(T-Bil)*, serum lactate level *(LAC)*, and prothrombin time *(PT)* on POD 2

Table 2. Numbers, distribution ranges, and mean values of each test in groups 1 and 2

		POD 1		POD 2	
		Group 1	Group 2	Group 1	Group 2
AKBR	*n*	71	17	71	15
	Range	0.68–2.85	0.38–0.97	1.00–3.55	0.26–1.19
	Mean ± SD	1.24 ± 0.45	0.70 ± 0.17**	1.65 ± 0.63	0.64 ± 0.24**
GOT	*n*	63	14	62	11
(IU/l)	Range	50–2610	66–4334	32–1820	55–4752
	Mean ± SD	488 ± 547	1609 ± 1409*	299 ± 313	2023 ± 1567**
GPT	*n*	63	14	61	11
(IU/l)	Range	22–2322	197–3124	7–1805	272–3270
	Mean ± SD	495 ± 448	1287 ± 386*	463 ± 386	1634 ± 1222*
T-Bil[a]	*n*	61	13	63	11
(μmol/l)	Range	9–342	28–243	11–592	33–306
	Mean ± SD	103 ± 70	124 ± 72	100 ± 89	162 ± 95*
LAC[b]	*n*	66	17	58	13
(mmol/l)	Range	0.12–3.53	0.38–9.16	0.19–3.54	0.42–12.21
	Mean ± SD	1.28 ± 0.71	3.33 ± 3.15*	1.00 ± 0.51	3.55 ± 3.38*
PT[c]	*n*	62	12	62	10
(%)	Range	35–97	27–69	34–84	22–74
	Mean ± SD	53 ± 12	50 ± 13	52 ± 12	44 ± 17

* $P < 0.05$ and ** $P < 0.01$, compared with group 1
[a] Total bilirubin concentration
[b] Serum lactate level
[c] Prothrombin time

with disorder, there were 8 patients in group 2 whose AKBR was less than 0.7 and 68 patients in group 1 whose AKBR was more than 0.7. Accordingly, the sensitivity is 8/17 = 0.47 and one minus the specificity is 1–68/71 = 0.04; hence, a point of (0.04, 0.47) is plotted on the X-Y graph. Connecting the plotted points of such pairs obtained by changing the cut-off points from 0.6 to 1.0, the ROC curve for AKBR on POD 1 can be drawn. As shown in Figs. 1 and 2, the ROC curves of AKBR on both POD 1 and POD 2 are located higher than and to the left of those of the other five tests. In particular, the ROC curve for AKBR on POD 2 is closest to the upper left corner, indicating that AKBR on POD 2 is superior to other tests in both sensitivity and specificity.

The calculated results of areas under the ROC curves (AUC) for AKBR and other tests are shown in Table 3. On both POD 1 and 2, the AUC for AKBR was larger than that for any other test. For statistical comparison, Z statistics for the differences in AUC between AKBR and each of the other conventional tests are shown in Table 4. With the exception of the difference between AKBR and GOT on POD 1 not being significant, the areas of AKBR are significantly larger than those of any other test on both POD 1 and POD 2. This means that AKBR is more accurate than any other test in differentiating group 2 from group 1.

Table 3. Areas under the ROC curves

	Area under the ROC curve	
	on POD 1	on POD 2
AKBR	0.920	0.987
GOT	0.774	0.826
GPT	0.723	0.767
T-Bil[a]	0.621	0.696
LAC[b]	0.673	0.796
PT[c]	0.538	0.632

[a] Total bilirubin
[b] Serum lactate level
[c] Prothrombin time

Table 4. Statistical comparison of areas under the ROC curves between AKBR and each of the other liver function tests

	Z Statistic (*P* value)	
	vs AKBR on POD 1	vs AKBR on POD 2
GOT	1.775 (0.076)	2.049 (0.040)
GPT	2.253 (0.024)	2.519 (0.012)
T-Bil[a]	3.038 (0.002)	3.125 (0.002)
LAC[b]	2.975 (0.002)	2.634 (0.008)
PT[c]	3.783 (0.0002)	3.629 (0.0003)

[a] Total bilirubin
[b] Serum lactate level
[c] Prothrombin time

Discussion

Recently, Asonuma et al. [1] have shown that AKBR was elevated to above 1.0 by the 2nd POD in patients who survived longer than 1 month after LTx. Those whose AKBR failed to increase to over 1.0 by the 2nd POD had to stay in the ICU until the end of the 1st month or eventually required reLTx or died within 1 month. Also, Ozaki et al. [9] have suggested that restoration of AKBR to above 1.0 within 2 days after LTx is a prerequisite for graft survival at the end of the 1st postoperative month. Because hepatic mitochondrial function has been suggested to be a powerful predictor of the outcome of hepatic surgery [5, 10, 11, 20], it is reasonable to apply the AKBR technique in liver transplantation. With respect to the relationship between changes in AKBR within the 1st 2 POD and patient condi-

tion in the following postoperative days, it is thought that prolonged suppression of cellular function of the graft liver after reperfusion, as recognized by the incomplete recovery in AKBR, may contribute to a complicated postoperative course. In light of these reports, it is conceivable that suppression of AKBR below 1.0 during the 1st 2 POD will result in graft death within 1 month after LTx.

In the present study, designed to evaluate the ability of AKBR to predict graft death within 1 month, the ROC analysis was used to compare the diagnostic validity of AKBR with that of other conventional liver function tests. Since the ROC curves of AKBR, especially that on POD 2, are closer to the upper left corner of the graph than those of other tests and do not intercept one another, it can be concluded that the sensitivity and specificity of AKBR are higher than those of the others at any of the cut-off points. Moreover, the statistical analysis of the differences in the areas under the ROC curve reveals that AKBR can more accurately predict graft death within 1 month after LTx than any other test.

Because the differences in the means between groups 1 and 2 are regarded as significant using Student's *t*-test in some of the conventional liver function tests as well as in AKBR, these tests can differentiate between the two groups to some extent. However, such an analysis does not help us to compare the discriminating ability among these tests. On the other hand, using the ROC analysis, the diagnostic validity can be compared as described above. In addition, since the ROC curve is a graph of sensitivity versus specificity, both of which are independent of disorder prevalence, the analysis does not depend on the prevalence of disorder in the actual population to which the test may be applied [7]. Hence, the present study suggests that AKBR is one of the most optimal indices for the purpose of predicting graft prognosis in the early postoperative phase.

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