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Inter-laboratory difference among eleven clinical laboratories in the Okayama City area.

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Abstract

The aim of the present study was to find the cause of inter-laboratory differences in laboratory test data and to examine whether control assessment helps to reduce inter-laboratory differences. Blood and serum samples of one healthy subject and one subject with liver cirrhosis were analyzed by 11 laboratories in the Okayama City area. No differences were found in the assay units of 26 tests surveyed. However, considerable differences were observed in test data, reference interval, and clinical level (CL), though most laboratories pointed out that the test data for the normal subject was within the reference intervals and those for the patient with liver cirrhosis showed abnormalities in tests for liver function. The difference in reference intervals was serious in the tests of direct bilirubin (D-Bil), thymol turbidity test (TTT), alkaline phosphatase (ALP), gamma-glutamyltranspeptidase (GGTP) and choline sterase. Marked differences in CLs were found in the tests of D-Bil, TTT, ALP, GGTP, creatine phosphokinase, amylase, heavy density lipoprotein cholesterol and white blood cell count. However, three hepatologists independently suggested that such inter-laboratory differences would not seriously affect a clinical decision on the disease status of the cirrhotic patient. Most tests that showed a trend error in a recent quality control survey appeared to have the same trend in the present study. These results indicate that inter-laboratory differences occur at various levels and control assessment are helpful in establishing, and therefore reducing, the level of inter-laboratory differences.

KEYWORDS: inter-labpratory differrence, liver cirrhosis referrence interval, clinical level, control survey

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Inter-Laboratory Difference among Eleven Clinical Laboratories in the Okayama City Area

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The aim of the present study was to find the cause of inter-laboratory differences in laboratory test data and to examine whether control assessment helps to reduce inter-laboratory differences. Blood and serum samples of one healthy subject and one subject with liver cirrhosis were analyzed by 11 laboratories in the Okayama City area. No differences were found in the assay units of 26 tests surveyed. However, considerable differences were observed in test data, reference interval, and clinical level (CL), though most laboratories pointed out that the test data for the normal subject was within the reference intervals and those for the patient with liver cirrhosis showed abnormalities in tests for liver function. The difference in reference intervals was serious in the tests of direct bilirubin (D-Bil), thymol turbidity test (TTT), alkaline phosphatase (ALP), γ-glutamyltranspeptidase (GGTP) and choline sterase. Marked differences in CLs were found in the tests of D-Bil, TTT, ALP, GGTP, creatine phosphokinase, amylase, heavy density lipoprotein cholesterol and white blood cell count. However, three hepatologists independently suggested that such inter-laboratory differences would not seriously affect a clinical decision on the disease status of the cirrhotic patient. Most tests that showed a trend error in a recent quality control survey appeared to have the same trend in the present study. These results indicate that inter-laboratory differences occur at various levels and control assessment are helpful in establishing, and therefore reducing, the level of inter-laboratory differences.

Key words: inter-laboratory difference, liver cirrhosis, reference interval, clinical level, control survey

The quality of laboratory data and the suitability of the reference interval setting are of equal importance to an accurate clinical diagnosis. The development of an auto-analyzer system made it possible not only to perform many tests with a small-volume sample in one run, but also to manage the quality control. Quality control assessment such as the nation-wide program sponsored by the Japan Medical Association (1) helps to assess the quality of laboratory tests. For the past 13 years, we have been conducting an annual local quality control survey within a limited area of Okayama Prefecture (2). This survey is co-sponsored by the Okayama Medical Association and the Okayama Association of Medical Technologists. These surveys are contributing to the reduction of inter-laboratory differences.

It is a fact that the data for test results are rarely the same for any two laboratories, even when the same auto-analyzer and reagents are used. And even when the data are the same, different reference intervals can lead to different clinical diagnoses. These days, patients often visit more than one hospital. Thus it is of interest whether the same clinical results are obtained at different hospitals when a patient cross-visits the same day.

In the present study, we distributed two pairs of blood and serum samples to 11 laboratories around the Okayama city area and investigated the inter-laboratory differences in routine liver function tests. One pair of samples was from a subject with type C liver cirrhosis while the other was from a normal healthy subject. The effect of inter-laboratory difference among the 11 laboratories on

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clinical diagnosis was independently evaluated by three hepatologists authorized by the Japan Association of Study of Liver Diseases. We further investigated whether the error trend of the laboratory data observed during a local control assessment performed in this area 4 months earlier was reflected in the test data obtained in the current study.

Methods

Laboratories. Eleven laboratories within a 20 km square area around Okayama city participated in the study. They consisted of the laboratories of 8 hospitals with over 400 beds (A, B, C), 100–400 beds (D, E), and less than 100 beds (F, G, H), 2 commercial laboratories (I, J), and 1 public health center (K). Auto-analyzers used for blood tests and for biochemical tests (9 wet chemistry and 2 dry chemistry) are shown in Table 1. The time taken for the tests to be performed after sample collection is also shown.

Tests. Blood tests conducted were red blood cell (RBC) count, white blood cell (WBC) count, platelet (Plt) count, hemoglobin concentration (Hb), and hematocrit (Ht). Tests for biochemistry were the following: total bilirubin (T-Bil), direct bilirubin (D-Bil), thymol turbidity test, (TTT), zinc sulfate turbidity test (ZTT), aspartate aminotransferase (GOT), alanine aminotransferase (GPT), alkaline phosphatase (ALP), leucine amino peptidase (LAP), γ-glutamyltranspeptidase (GGTP), cholinesterase (ChE), lactate dehydrogenase (LDH), creatine phosphokinase (CPK), amylase (AMY), total protein (TP), albumin (Alb), cholesterol (CHO), triglyceride (TG), HDL-cholesterol (HDL), blood urea nitrogen (BUN), creatinine (CRN) and uric acid (UA). These tests were performed within 30 h after the sample was delivered. The data for the tests as well as the time of assay and the reference intervals were returned to our institute by FAX.

Samples. The subjects were a 50-year-old healthy male and a 66-year-old male with liver cirrhosis. Sixty milliliters of blood was drawn from each subject after obtaining informed consent. Two milliliter aliquots of blood sample were transferred to test tubes containing anticoagulant. After the separation of serum, 3 ml of serum sample was transferred to a test tube for biochemical assay. A pair of blood and serum samples was delivered to each laboratory and kept at 4 °C until the assay was carried out.

The healthy subject had shown no abnormalities on annual health checks performed for 10 years prior to this study, nor did he show any abnormalities on a physical examination performed just prior to the taking of the blood sample. The subject with liver cirrhosis has been an out-patient of Hospital E for 8 years, and his annual liver function test is shown in Table 2. His serological tests for hepatitis B virus are all negative, and those for hepatitis C virus have been positive since 1991. Autoantibodies: anti-nuclear antibody, anti-smooth muscle, and anti-mitochondria antibody, were all negative. IgG was 2,451 mg/ml, IgM 383 mg/ml, and IgA was 289 mg/ml. K_{ICG} was 0.076. Imaging examinations by abdominal ultrasonography and computed tomography revealed mild splenomegaly, cirrhotic liver, and no space-occupying lesions in the liver. Based on these findings, he has been diagnosed

Table 1 Laboratories participating in this study

	Laboratory	Number of beds	Auto-analyzer for biochemistry	Auto-analyzer for blood tests	Time until assay
A	Hospital laboratory	847	Hitachi 7350/7170/7070	Coulter STKR	1:30
B	Hospital laboratory	500	JEOL RX20	Coulter STKR	2:00
C	Hospital laboratory	428	Hitachi 7250	Sysmex SE9000	1:30
D	Hospital laboratory	150	EKTACHEM 950	Coulter JT	9:30
E	Hospital laboratory	100	Toshiba TBA-80FR	Coulter T-660	2:30
F	Hospital laboratory	93	EKTACHEM 700N	Coulter T-660	25:30
G	Hospital laboratory	88	Hitachi 7070	Coulter S-plus IV	7:00
H	Hospital laboratary	40	Hitachi 7050	Sysmex K-800	1:00
I	Commercial laboratory		Hitachi 7250/7150	Sysmex NE-8000	6:00
J	Commercial laboratory		Hitachi 7170	Sysmex E3000	2:30
K	Health check-up center		Hitachi 7170	Sysmex E3000	2:30

Table 2 Change in laboratory data of the liver cirrhosis subject

	Assay unit	Year						
		90	91	93	94	95	96	97
T-Bil	mg/dl	ND	0.6	0.8	1.1	0.7	0.9	1.0
D-Bil	mg/dl	ND	0.2	ND	0.3	0.3	ND	0.4
ZTT	K·U	12.2	ND	ND	12.8	13.4	17.9	15.0
TTT	K·U	11.8	ND	ND	9.7	13.1	ND	14.7
GOT	IU/L	32	43	53	71	103	69	136
GPT	IU/L	33	44	78	137	226	127	173
ALP	IU/L	64	74	65	119	130	168	220
LAP	IU/L	55	ND	ND	96	94	95	90
GGTP	IU/L	133	133	198	288	374	176	220
ChE	IU/L	304	ND	ND	335	302	213	175
LDH	IU/L	ND	289	ND	360	364	363	392
TP	g/dl	7.1	7.0	7.2	7.0	7.0	6.9	7.0
Alb	g/dl	4.0	4.0	3.8	3.7	3.6	3.5	3.4
CHO	mg/dl	206	189	185	164	162	178	169
TG	mg/dl	162	ND	157	ND	ND	278	ND
HDL	mg/dl	56	ND	56	ND	ND	56	56
BUN	mg/dl	15.2	17.2	18.7	16.8	16.3	15.5	16.1
CRN	mg/dl	0.7	0.8	0.7	0.7	0.7	0.7	0.7
UA	mg/dl	5.4	5.4	5.6	5.8	4.8	4.6	ND
RBC	$\times 10^4/\mu l$	432	454	448	452	491	450	425
WBC	$\times 10^3/\mu l$	6.1	5.2	4.1	4.3	5.3	4.8	4.3
Plt	$\times 10^4/\mu l$	10.1	10.6	7.7	10.9	8.7	6.9	4.6

ND: Not done.

with type C liver cirrhosis.

Indexes. Clinical level (CL) is an index indicating abnormal levels on laboratory tests and is calculated with the following formula: CL = test data/upper limit of reference interval. Standard deviation index (SDI) indicates the gap between test data and target value and is calculated with the following formula: SDI = (test data − target value)/|SD value|. Coefficient of variation (CV) indicates the extent of variation, and is calculated with the following formula: CV = |SD value| × 100/average value.

Comparison with control surveillance. The 12th annual local survey of quality control in Okayama prefecture was conducted in October 1997 using a pair of control samples, L-Suitrol® I for normal values and II for abnormal values (Nissui Co. Ltd.) (2). The study involved 154 laboratories. The results of the 11 laboratories were extracted from those of 154 laboratories and are illustrated as a twin-plot analysis (3) in Fig. 1. The two values of L-Suitrol® I and II were twin-plotted in the figure. The range given in the figure is within the average of registered laboratories ± 30 SDI, while the gray zone is the range within the average ± 20 SDI, and indicates good quality control (2).

Clinical evaluation of test data. Test data collected in the present study were independently evaluated by three hepatologists authorized by the Japan Association of Study of Liver Diseases. Other data including annual data of liver function tests for the past 8 years and recent imaging films were also reviewed. The hepatologists were requested to evaluate whether the present data are compatible with the present patho-physiological conditions for the normal healthy subject and the subject with liver cirrhosis.

Results

Reference intervals and the assay unit. The reference intervals and the assay units of 11 laboratories together with the test data for the two subjects are shown in Table 3. It appears that the assay units of the 26 tests were fully standardized among the 11 laboratories. Interestingly, those for enzyme tests were standardized to IU/L at 37°C, although the Karmen unit for

Table 3 Reference intervals and test data

T-Bil	RI	Unit	Nor	Lc
A	0.33-1.28	mg/dl	0.71	1.61
B	0.2 0.8	mg/dl	0.70	1.50
C	0 -1.0	mg/dl	0.50	1.33
D	0.2 1.0	mg/dl	0.80	1.50
E	0.2 -1.2	mg/dl	0.70	1.60
F	0.2 -1.2	mg/dl	0.79	1.52
G	0.2 -1.2	mg/dl	0.60	1.40
H	0.3 -1.1	mg/dl	0.68	1.54
I	0.2 -1.1	mg/dl	0.79	1.54
J	0.2 -1.2	mg/dl	0.50	1.40
K	0.33-1.28	mg/dl	0.70	1.50

TTT	RI	Unit	Nor	Lc
A	0.2-5.3	K·U	0.6	20.4
B	0 -5	K·U	ND	ND
C	0 -4.0	K·U	1.1	13.3
D			ND	ND
E	0 -5	K·U	1.5	19.8
F			ND	ND
G	0 -5	K·U	0.8	22.2
H		K·U	ND	ND
I	0.2-4.0	K·U	0.8	21.0
J	0 -0.4	K·U	0.8	18.1
K			ND	ND

ALP	RI	Unit	Nor	Lc
A	41-127	IU/L	94	202
B	30-120	U/L	107	208
C	60-220	IU/L	170	257
D	80-110	IU/L	72	164
E	70-290	IU/L	182	272
F	62-150	IU/L	94	210
G	87-250	IU/L	153	233
H	50-260	IU/L	205	318
I	40-150	IU/L	100	202
J	68-250	IU/L	165	238
K	41-127	IU/L	179	267

ChE	RI	Unit	Nor	Lc
A	104- 211	IU/L	161	62
B	180- 440	IU/L	343	139
C	175- 375	IU/L	307	122
D			ND	ND
E	185- 431	IU/L	324	127
F			ND	ND
G	2300-5300	IU/L	4077	1617
H	230- 470	IU/L	309	125
I			ND	ND
J			ND	ND
K			ND	ND

D-Bil	RI	Unit	Nor	Lc
A	0.08-0.28	mg/dl	0.21	0.70
B	0 -0.2	mg/dl	0.20	0.60
C	0 -0.4	mg/dl	0.25	0.77
D	0.09-0.3	mg/dl	0.30	0.60
E	0 -0.3	mg/dl	0.30	0.70
F	0 -0.3	mg/dl	0.37	0.75
G	0 -0.4	mg/dl		
H	0 -0.6	mg/dl	0.22	0.69
I	0.03 0.28	mg/dl	0.27	0.60
J	0 -0.4	mg/dl	0.25	0.68
K	0.08-0.28	mg/dl		

GOT	RI	Unit	Nor	Lc
A	11-32	IU/L	11	78
B	8 40	U/L	17	109
C	11-38	IU/L	17	94
D	8-40	IU/L	22	110
E	8-40	IU/L	18	99
F	9-38	IU/L	16	71
G	5-40	IU/L	17	91
H	0 45	IU/L	15	90
I	9-38	IU/L	16	90
J	5-40	IU/L	17	90
K	11-32	IU/L	18	98

LAP	RI	Unit	Nor	Lc
A	38-75	IU/L	56	105
B	7-41	U/L	34	64
C	25-75	IU/L	60	111
D			ND	ND
E	30-70	IU/L	56	104
F			ND	ND
G	27-66	IU/L	46	83
H			ND	ND
I	35-80	IU/L	50	95
J	28-77	IU/L	56	105
K			ND	ND

LDH	RI	Unit	Nor	Lc
A	236-455	IU/L	429	549
B	125-250	U/L	249	302
C	120-400	IU/L	430	538
D	100-430	IU/L	625	759
E	190-450	IU/L	430	523
F	203-442	IU/L	360	434
G	203-412	IU/L	428	533
H	180-463	IU/L	452	565
I	220-450	IU/L	429	547
J	200-450	IU/L	396	497
K	236-455	IU/L	450	561

ZTT	RI	Unit	Nor	Lc
A	3.8-14.9	K·U	2.2	26.1
B	4 -12	K·U	ND	ND
C	4.0-12.0	K·U	2.3	26.7
D			ND	ND
E	4 -12	K·U	3.0	17.9
F			ND	ND
G	4 -12	K·U	2.0	27.5
H			ND	ND
I	3 -12	K·U	2.1	21.2
J	2 13	K·U	3.0	25.8
K	3.8-14.9	K·U	2.0	28.0

GPT	RI	Unit	Nor	Lc
A	6-39	IU/L	13	109
B	5-35	U/L	18	122
C	6-35	IU/L	14	113
D	5-35	IU/L	28	152
E	5-35	IU/L	15	114
F	4-37	IU/L	16	98
G	1-28	IU/L	12	94
H	0-39	IU/L	11	100
I	5-40	IU/L	14	106
J	4-36	IU/L	13	100
K	6-39	IU/L	14	108

GGTP	RI	Unit	Nor	Lc
A	3-40	IU/L	13	292
B	0-40	U/L	23	295
C	0-50	IU/L	20	296
D	6-49	IU/L	25	403
E	*11-50	IU/L	16	273
F	8-45	IU/L	13	296
G	*11 50	IU/L	19	305
H	2-64	IU/L	13	211
I	*5-65	IU/L	23	354
J	0-80	IU/L	23	372
K	3-40	IU/L	12	201

CPK	RI	Unit	Nor	Lc
A	41-258	IU/L	109	210
A	38-176	U/L	117	222
C	30-200	IU/L	113	210
D	20-110	IU/L	104	199
E	*51-201	IU/L	114	214
F	3- 13	IU/L	110	191
G	*74 246	IU/L	101	191
H	22-222	IU/L	99	186
I	*60-250	IU/L	104	199
J	25-210	IU/L	102	192
K			ND	ND

Continued on the next page

AMY	RI	Unit	Nor	Lc
A	77-235	IU/L	124	137
B	43-155	U/L	67	74
C	50-200	IU/L	105	115
D	35-200	IU/L	54	62
E	50-228	IU/L	119	131
F	56-236	IU/L	79	104
G	42-120	IU/L	61	71
H	220 >	IU/L	122	137
I	40-130	IU/L	58	65
J	30 150	IU/L	55	60
K	77-234	IU/L	81	95

CHO	RI	Unit	Nor	Lc
A	125-259	mg/dl	133	183
B	130-219	mg/dl	142	193
C	150-225	mg/dl	127	173
D	130-220	mg/dl	139	195
E	130-220	mg/dl	131	177
F	130-220	mg/dl	134	185
G	120-230	mg/dl	133	177
H	130-220	mg/dl	135	184
I	130-220	mg/dl	132	181
J	120-220	mg/dl	137	186
K	125-259	mg/dl	137	187

BUN	RI	Unit	Nor	Lc
A	8.1-22.0	mg/dl	14.6	14.3
B	8 -18	mg/dl	14.4	13.1
C	8 -20	mg/dl	13.0	12.0
D	7 -22	mg/dl	14.0	12.8
E	8 -20	mg/dl	15.1	13.9
F	8 -20	mg/dl	13.0	12.0
G	8 -20	mg/dl	14.8	14.0
H	7 -23	mg/dl	14.0	13.0
I	8 -22	mg/dl	14.6	13.7
J	7.2-22.8	mg/dl	15.1	14.0
K			ND	ND

RBC	RI	Unit	Nor	Lc
A	*400-500	$\times 10^4/\mu l$	453	418
B	*410-530	$\times 10^4/\mu l$	449	421
C	*400-560	$\times 10^4/\mu l$	452	425
D	*431-565	$\times 10^4/\mu l$	457	426
E	*410 530	$\times 10^4/\mu l$	455	415
F	*410-530	$\times 10^4/\mu l$	447	418
G	*400-530	$\times 10^4/\mu l$	452	408
H	*410-530	$\times 10^4/\mu l$	451	418
I	420-560	$\times 10^4/\mu l$	465	428
J	411-550	$\times 10^4/\mu l$	472	434
K	*400-560	$\times 10^4/\mu l$	467	426

TP	RI	Unit	Nor	Lc
A	6.5-8.0	g/dl	6.5	7.3
B	6.5-8.0	g/dl	6.6	7.5
C	6.7-7.9	g/dl	6.5	7.3
D	6.6-8.4	g/dl	6.6	7.5
E	6.5-8.0	g/dl	6.3	7.0
F	6.0 8.0	g/dl	6.7	7.5
G	5.8-8.1	g/dl	6.1	7.0
H	6.7-8.3	g/dl	6.6	7.4
I	6.5-8.2	g/dl	6.5	7.4
J	6.2-8.2	g/dl	6.5	7.4
K	6.5-8.0	g/dl	6.5	7.4

TG	RI	Unit	Nor	Lc
A	17-198	mg/dl	106	262
B	30-149	mg/dl	116	284
C	60-160	mg/dl	100	232
D	28-160	mg/dl	104	243
E	28-160	mg/dl	103	244
F	50-130	mg/dl	105	240
G	50-130	mg/dl	109	250
H	32-153	mg/dl	98	237
I	35-175	mg/dl	109	260
J	38-160	mg/dl	98	237
K	17-198	mg/dl	106	249

CRN	RI	Unit	Nor	Lc
A	0.44-1.04	mg/dl	0.92	0.65
B	0.5 -1.2	mg/dl	1.10	0.80
C	0.7 -1.2	mg/dl	1.10	0.80
D	0.5 -1.4	mg/dl	1.00	0.70
E	0.4 -1.1	mg/dl	1.00	0.70
F	0.8 -1.77	mg/dl	1.00	0.70
G	0.4 -1.1	mg/dl	1.10	0.80
H	0.6 -1.2	mg/dl	0.81	0.53
I	*0.5 -1.1	mg/dl	0.97	0.64
J	0.8 -1.3	mg/dl	1.10	0.80
K	0.44-1.04	mg/dl	1.01	0.65

WBC	RI	Unit	Nor	Lc
A	3.0-9.4	$\times 10^3/\mu l$	7.0	3.4
B	4.5-8.5	$\times 10^3/\mu l$	7.0	3.3
C	3.0-9.4	$\times 10^3/\mu l$	6.5	2.9
D	3.5-8.0	$\times 10^3/\mu l$	7.7	3.5
E	4.5-8.5	$\times 10^3/\mu l$	7.7	3.2
F	3.0-9.0	$\times 10^3/\mu l$	7.3	3.4
G	4.0-8.0	$\times 10^3/\mu l$	7.5	3.8
H	4.5-8.5	$\times 10^3/\mu l$	6.7	3.2
I	3.5-9.0	$\times 10^3/\mu l$	7.1	3.0
J	3.6-9.1	$\times 10^3/\mu l$	6.9	3.0
K	3.0-9.4	$\times 10^3/\mu l$	6.8	3.4

Alb	RI	Unit	Nor	Lc
A	3.9-4.9	g/dl	4.1	3.2
B	3.8-5.3	g/dl	4.3	3.4
C	3.9-4.9	g/dl	4.4	3.4
D	3.9-5.3	g/dl	4.1	3.3
E	3.8-5.3	g/dl	4.1	3.2
F	3.7-5.1	g/dl	4.0	3.2
G	3.1-5.2	g/dl	4.2	3.1
H	3.8-5.3	g/dl	4.0	3.3
I	3.8-5.3	g/dl	4.3	3.2
J	3.7-5.2	g/dl	4.3	3.2
K	3.9-4.9	g/dl	4.4	3.2

HDL	RI	Unit	Nor	Lc
A	31-95	mg/dl	58	38
B	40-69	mg/dl	49	36
C	30-70	mg/dl	53	42
D			ND	ND
E	*37-60	mg/dl	57	43
F	*32-68	mg/dl	45	32
G	40-80	mg/dl	59	45
H	35-75	mg/dl	57	51
I	34-88	mg/dl	51	47
J	35-65	mg/dl	47	44
K	31-95	mg/dl	48	33

UA	RI	Unit	Nor	Lc
A	*3.9-8.3	mg/dl	5.1	3.5
B	2.3-6.6	mg/dl	4.8	3.4
C	2 -6.5	mg/dl	5.2	3.7
D	3.0-7.3	mg/dl	5.1	3.4
E	*3.6-8.1	mg/dl	5.1	3.4
F	*2.5-7.0	mg/dl	5.1	3.4
G	*3.6-7.9	mg/dl	5.0	3.4
H	2.6-7.5	mg/dl	5.4	3.8
I	*3.4-7.8	mg/dl	4.9	3.4
J	2.5-7.6	mg/dl	5.1	3.5
K	*3.9-8.3	mg/dl	5.3	3.6

Plt	RI	Unit	Nor	Lc
A	15 -40	$\times 10^4/\mu l$	27.5	3.5
B	14 -34	$\times 10^4/\mu l$	27.9	3.3
C	15 -40	$\times 10^4/\mu l$	31.0	3.3
D	*13.1-36.5	$\times 10^4/\mu l$	23.7	1.9
E	14 -34	$\times 10^4/\mu l$	28.2	3.1
F	13 -40	$\times 10^4/\mu l$	28.5	4.4
G	12 -36	$\times 10^4/\mu l$	33.1	3.8
H	14 -34	$\times 10^4/\mu l$	32.7	3.2
I	13 -40	$\times 10^4/\mu l$	32.3	3.4
J	12.3-35.2	$\times 10^4/\mu l$	33.5	3.0
K	15 -40	$\times 10^4/\mu l$	31.6	3.7

RI: Reference interval (*indicates the reference interval for men); Unit: Assay unit; Nor: Normal subject; Lc: Liver cirrhosis subject.

Table 4 Differences in reference interval among 11 laboratories

	Assay Unit	Lower limit of reference interval					Upper limit of reference interval				
		Ave	SD	CV	MAX	MIN	Ave	SD	CV	MAX	MIN
T-Bil	mg/dl	0.21	0.09	42	0.33	0.00	1.12	0.14	13	1.28	1.00
D-Bil	mg/dl	0.03	0.04	150	0.09	0.00	0.34	0.12	34	0.60	0.20
ZTT	K·U	3.3	0.7	19	4.0	2.0	13.0	1.4	11	14.9	12.0
TTT	K·U	0.1	0.1	138	0.2	0.0	4.0	1.8	46	5.3	0.4
GOT	IU/L	8	3	43	11	0	38	4	10	45	32
GPT	IU/L	4	2	47	6	0	36	3	9	40	28
ALP	IU/L	57	18	32	87	30	187	67	36	290	110
LAP	IU/L	29	9	33	38	7	69	13	19	80	41
GGTP	IU/L	4	4	93	11	0	52	13	24	80	40
ChE	IU/L	405	712	176	2300	104	1857	1747	94	5300	211
LDH	IU/L	183	47	26	236	120	422	60	14	463	250
CPK	IU/L	37	20	54	74	3	188	74	40	250	13
AMY	IU/L	45	21	47	77	0	192	45	23	236	120
TP	g/dl	6.4	0.3	4	6.7	6.0	8.1	0.2	2	8.3	7.9
Alb	g/dl	3.7	0.2	6	3.9	3.1	5.1	0.2	3	5.3	4.9
CHO	mg/dl	129	8	6	150	120	228	15	7	259	219
TG	mg/dl	35	14	39	60	17	161	23	14	198	130
HDL	mg/dl	35	4	11	40	30	77	13	16	95	60
BUN	mg/dl	7.8	0.5	6	8.1	7.0	21.0	1.6	8	23.0	18.0
CRN	mg/dl	0.6	0.2	27	0.8	0.4	1.2	0.2	17	1.8	1.0
UA	mg/dl	3.0	0.7	23	3.9	2.0	7.5	0.6	8	8.3	6.5
RBC	$\times 10^4/mm^3$	409	10	2	431	400	547	15	3	565	530
WBC	$\times 10^3/mm^3$	3.6	0.6	17	4.5	3.0	8.8	0.5	6	9.4	8.0
Plt	$\times 10^4/mm^3$	13.7	1.1	8	15.0	12.0	37.2	2.8	7	40.0	34.0

GOT and King King Unit for ALP had been used at some laboratories 6 years earlier (4). The reference interval for a test appeared to vary among the 11 laboratories. The upper and the lower limits of the reference interval for the 26 tests are summarized in Table 4. Relatively large variation in the upper limit of the reference interval was observed in the tests of D-Bil, TTT, ALP, GGTP and ChE; their CVs were greater than 20 %, the value beyond which misdiagnosis of clinical condition becomes possible. The CVs of the lower reference interval limit were much bigger than those of the upper limit for most tests, and those of T-Bil, D-Bil, TTT, GOT, GPT, GGTP and ChE appeared to exceed 40 %. The inter-laboratory difference in the reference interval for these tests may affect clinical diagnosis. It appears that the no serious differences in test data were observed among types of auto-analyzer and time before assay.

Compatibility with patho-physiological status. The test data and CLs of the 11 laboratories are listed in Table 5. Bases on their analyses, all the laboratories indicated that the subject with liver cirrhosis had mild hyper-bilirubinemia, positive for both TTT and ZTT, mild elevation of transaminase activity, mild hypoalbuminemia, hypocholesterolemia, and considerably low WBC and Plt counts. All of the laboratories also indicated that the patient had normal renal function and normal RBC count. Together with annual laboratory data and recent imaging films, the present test data were reviewed by 3 hepatologists to establish whether the diagnosis based on CLs was compatible with the present patho-physiological condition of the patient. They concluded that the judgments made by the 11 laboratories were valid in spite of apparent inter-laboratory differences. It was concluded, however, that the inter-laboratory difference in CLs for the tests of D-Bil, TTT, ALP, GGTP, CPK, AMY, HDL and WBC was large enough to affect the clinical diagnosis, since their CVs exceeded 20 %.

On the other hand, the CLs calculated by the laboratories for the healthy subject showed a greater inter-laboratory difference than those calculated for the liver cirrhosis subject. A relatively large difference was observed in tests of D-Bil, TTT, GOT, GPT, GGTP and

Table 5 Clinical level of the normal subject and patient with liver cirrhosis

	Clinical level of the normal subject															
	A	B	C	D	E	F	G	H	I	J	K	Ave	SD	CV	MAX	MIN
T-Bil	0.55	0.88	0.50	0.90	0.58	1.17	0.50	0.62	0.72	0.42	0.55	0.67	0.22	33	1.17	0.42
D-Bil	0.75	1.00	0.63	0.83	1.00	1.60	ND	0.37	0.96	0.63	ND	0.86	0.35	40	1.60	0.37
ZTT	0.15	ND	0.19	ND	0.25	ND	0.17	ND	0.18	0.23	0.13	0.19	0.04	23	0.25	0.13
TTT	0.11	ND	0.28	ND	0.30	ND	0.16	ND	0.20	2.00	ND	0.51	0.73	145	2.00	0.11
GOT	0.34	0.43	0.45	1.30	0.45	1.01	0.43	0.33	0.42	0.43	0.56	0.56	0.31	55	1.30	0.33
GPT	0.33	0.51	0.40	1.20	0.43	1.07	0.43	0.28	0.35	0.36	0.36	0.52	0.31	60	1.20	0.28
ALP	0.74	0.89	0.77	1.04	0.63	0.81	0.61	0.79	0.67	0.66	1.41	0.82	0.23	28	1.41	0.61
LAP	0.75	0.83	0.80	ND	0.80	ND	0.70	ND	0.63	0.73	ND	0.75	0.07	9	0.83	0.63
GGTP	0.33	0.58	0.40	1.23	0.32	0.80	0.38	0.20	0.35	0.29	0.30	0.47	0.30	64	1.23	0.20
ChE	0.76	0.78	0.82	ND	0.75	ND	0.77	0.66	ND	ND	ND	0.76	0.05	7	0.82	0.66
LDH	0.94	1.00	1.08	1.14	0.96	0.89	1.04	0.98	0.95	0.88	0.99	0.99	0.08	8	1.14	0.88
CPK	0.44	0.66	0.57	1.30	0.57	1.00	0.41	0.45	0.42	0.49	ND	0.63	0.29	47	1.30	0.41
AMY	0.53	0.43	0.53	0.99	0.52	0.99	0.51	0.55	0.45	0.37	0.35	0.57	0.22	39	0.99	0.35
TP	0.81	0.83	0.82	1.01	0.79	0.96	0.75	0.80	0.79	0.79	0.81	0.83	0.08	9	1.01	0.75
Alb	0.83	0.81	0.90	ND	0.77	0.86	0.81	0.75	0.81	0.83	0.90	0.83	0.05	6	0.90	0.75
CHO	0.51	0.65	0.56	1.10	0.60	1.05	0.58	0.61	0.60	0.62	0.53	0.67	0.20	30	1.10	0.51
TG	0.54	0.78	0.63	1.17	0.64	1.03	0.84	0.64	0.62	0.61	0.54	0.73	0.21	28	1.17	0.54
HDL	0.61	0.71	0.76	ND	0.95	1.25	0.74	0.76	0.58	0.72	0.50	0.76	0.21	28	1.25	0.50
BUN	0.66	0.80	0.65	0.98	0.76	1.16	0.74	0.61	0.66	0.66	ND	0.77	0.17	23	1.16	0.61
CRN	0.88	0.92	0.92	1.04	0.91	0.99	1.00	0.68	0.88	0.85	0.97	0.91	0.10	11	1.04	0.68
UA	0.61	0.73	0.80	1.30	0.63	0.79	0.63	0.72	0.63	0.67	0.64	0.74	0.20	27	1.30	0.61
RBC	0.81	0.85	0.81	1.00	0.86	1.06	0.84	0.85	0.83	0.86	0.83	0.87	0.08	9	1.06	0.81
WBC	0.74	0.82	0.69	0.93	0.91	1.31	0.94	0.79	0.79	0.76	0.72	0.85	0.17	20	1.31	0.69
Plt	0.69	0.82	0.78	1.13	0.83	1.07	0.92	0.96	0.81	0.95	0.79	0.89	0.13	15	1.13	0.69

	Clinical level of the patient with liver cirrhosis															
	A	B	C	D	E	F	G	H	I	J	K	Ave	SD	CV	MAX	MIN
T-Bil	1.26	1.88	1.33	1.50	1.33	1.27	1.17	1.40	1.40	1.17	1.17	1.35	0.20	15	1.88	1.17
D-Bil	2.50	3.00	1.93	2.00	2.33	2.50	ND	1.15	2.14	1.70	ND	2.14	0.53	25	3.00	1.15
ZTT	1.75	ND	2.22	ND	1.49	ND	2.29	ND	1.77	1.98	1.88	1.91	0.28	15	2.29	1.49
TTT	3.85	ND	3.33	ND	3.96	ND	4.44	ND	5.25	45.3	ND	11.01	16.79	152	45.25	3.33
GOT	2.44	2.73	2.47	2.75	2.48	1.87	2.28	2.00	2.37	2.25	3.06	2.43	0.34	14	3.06	1.87
GPT	2.79	3.49	3.23	4.34	3.26	2.65	3.36	2.56	2.65	2.78	2.77	3.08	0.53	17	4.34	2.56
ALP	1.59	1.73	1.17	1.49	0.94	1.40	0.93	1.22	1.35	0.95	2.10	1.35	0.37	27	2.10	0.93
LAP	1.40	1.56	1.48	ND	1.49	ND	1.26	ND	1.19	1.36	ND	1.39	0.13	10	1.56	1.19
GGTP	7.30	7.38	5.92	8.22	5.46	6.58	6.10	3.30	5.45	4.65	5.03	5.94	1.40	24	8.22	3.30
ChE	0.29	0.32	0.33	ND	0.29	ND	0.31	0.27	ND	ND	ND	0.30	0.02	7	0.33	0.27
LDH	1.21	1.21	1.35	1.77	1.16	1.01	1.29	1.22	1.22	1.10	1.23	1.25	0.19	15	1.77	1.01
CPK	0.84	1.26	1.05	1.81	1.06	14.69	0.78	0.84	0.80	0.91	ND	2.40	4.33	180	14.69	0.78
AMY	0.59	0.48	0.58	0.31	0.57	0.44	0.59	0.62	0.50	0.40	0.41	0.50	0.10	20	0.62	0.31
TP	0.92	0.94	0.92	0.89	0.88	0.94	0.86	0.89	0.90	0.90	0.93	0.91	0.02	3	0.94	0.86
Alb	0.65	0.64	0.69	ND	0.60	0.63	0.60	0.62	0.60	0.62	0.65	0.63	0.03	5	0.69	0.60
CHO	0.71	0.88	0.77	0.89	0.80	0.84	0.77	0.84	0.82	0.85	0.72	0.81	0.06	7	0.89	0.71
TG	1.32	1.91	1.45	1.52	1.53	1.85	1.92	1.55	1.49	1.48	1.26	1.57	0.23	14	1.92	1.26
HDL	0.40	0.52	0.60	ND	0.72	0.47	0.56	0.68	0.53	0.68	0.35	0.55	0.12	22	0.72	0.35
BUN	0.65	0.73	0.60	0.58	0.70	0.60	0.70	0.57	0.62	0.61	ND	0.64	0.06	9	0.73	0.57
CRN	0.63	0.67	0.67	0.50	0.64	0.40	0.73	0.44	0.58	0.62	0.63	0.59	0.10	17	0.73	0.40
UA	0.42	0.52	0.57	0.47	0.42	0.49	0.43	0.51	0.44	0.46	0.43	0.47	0.05	10	0.57	0.42
RBC	0.75	0.79	0.76	0.75	0.78	0.79	0.76	0.79	0.76	0.79	0.76	0.77	0.02	2	0.79	0.75
WBC	0.36	0.39	0.31	0.44	0.38	0.38	0.48	0.38	0.33	0.33	0.36	0.38	0.05	13	0.48	0.31
Plt	0.09	0.10	0.08	0.05	0.09	0.11	0.11	0.09	0.09	0.09	0.09	0.09	0.02	17	0.11	0.05

A-K: Laboratories; Ave: Average of clinical level; SD: Standard deviation; CV: Coefficiency of variance; MAX: Maximum value; MIN: Minimum value; ND: Not done.

CPK; the CVs for these tests were greater than 40 %. Nevertheless, for most of the laboratories, the values for the normal subject were within the reference intervals except for some tests of CHO, Alb and LDH. Comparison with the results of a control survey.

The results of a local control survey performed 4 months earlier that included the 11 laboratories are shown as twin-plots in Fig. 1. The tests with a systemic trend shifting to a lower value in the control survey were as follows: T-Bil for H, GOT for G, GPT for G and H, LDH for G, CPK for H, CHO for C, TG for A and H, and BUN for C. The same trend was found in the present study for the following tests: GOT for G, GPT for G and H, CHO for C, TG for H, BUN for C, and CPK for H. On the other hand, the tests with a systemic trend shifting to a higher value in the control surveillance were GOT for B and E, GPT for E, ALP for E and H, GGTP for C, LDH for H, CHO for D and H , AMY for A, B, C, E and H, UA for H and K. The same trend was found in the following tests in the present study: GOT for B and E, ALP for E and H, CHO for D, UA for H and K, AMY for A, B, C, E and H. These results suggest that the systemic trend error found in the control survey is well reflected in the present test data. Although a random error, a shift to the lower side only in the abnormal sample, was found in the tests of CRN for F, and Alb for H in the control assessment, we could not detect the same error in these tests in the present study.

Discussion

We examined the inter-laboratory differences in laboratory tests using blood samples obtained from a normal subject and a subject with liver cirrhosis. It is generally difficult from an ethical view point to collect blood in large volume from one individual and use it to examine inter-laboratory differences. For such a purpose, a blood sample pooled from multiple sources is commonly used, though this often gives rise to difficulties in estimating the diagnostic value for disease status and in handling as well. Using a sample from a cirrhotic subject we were able to evaluate not only the inter-laboratory differences in test data but also the effect of inter-laboratory differences on the clinical diagnosis. As shown in the results, the inter-laboratory differences in the test data of the patient had little influence on clinical assessment; the diagnosis of liver cirrhosis, the estimation of present disease status, and the selection of therapeutic methods, which were made independently by three hepatologists. However, apparent inter-laboratory differences were found in all of the tests examined; being much greater for enzyme than non-enzyme tests. Among the enzyme tests, ALP, GGTP, CPK and AMY showed inter-laboratory differences large enough to cause a misdiagnosis.

Relatively large inter-laboratory differences in these enzyme tests have been frequently revealed by the control assessments carried out by the Japan Medical Association (1) as well as our organization (2–4). To reduce these inter-laboratory differences, the use of a standardized method for each test has been recommended by the Japan Clinical Chemistry Association (5–10). Recently, enzyme reference materials (ERM) have been introduced for the quality control of enzyme tests (11) and become commercially available (12). These ERM consist of recombinant serum enzymes and are reported to be useful in calibrating enzyme activities for enzyme tests (13, 14). It has been widely noted that the inter-laboratory difference in reference intervals as well as the test data is much smaller for non-enzyme tests than enzyme tests (1–4). A similar result was obtained in the present study. This is probably due to the development of accurate methods for measuring non-enzymatic materials and the ready supply of reference materials. Therefore, the combination of a standardized method for enzyme assay and the use of ERM in quality control are expected to significantly reduce inter-laboratory differences in enzyme tests.

In addition to the standardization of enzyme tests, further efforts are necessary to reduce inter-laboratory differences. The sample from the subject with liver cirrhosis was effective for evaluating the inter-laboratory differences in the data out of reference interval. On the other hand, the sample from the normal subject was used to evaluate those within the reference interval. A few laboratories judged that the normal subject had hypocholesterolemia, hypoalbuminemia, or an abnormally high value of LDH. These mis-judgments are likely due to inter-laboratory differences in reference intervals, since there were no serious discrepancies among the test data. Frequent inspections following the improvement of the assay system at the respective laboratories have reduced the inter-laboratory differences in test data (1–4). However, there has been less effort to reduce the inter-laboratory differences in reference intervals.

Recently, laboratory tests have been used for health screenings. It is not uncommon for an individual judged

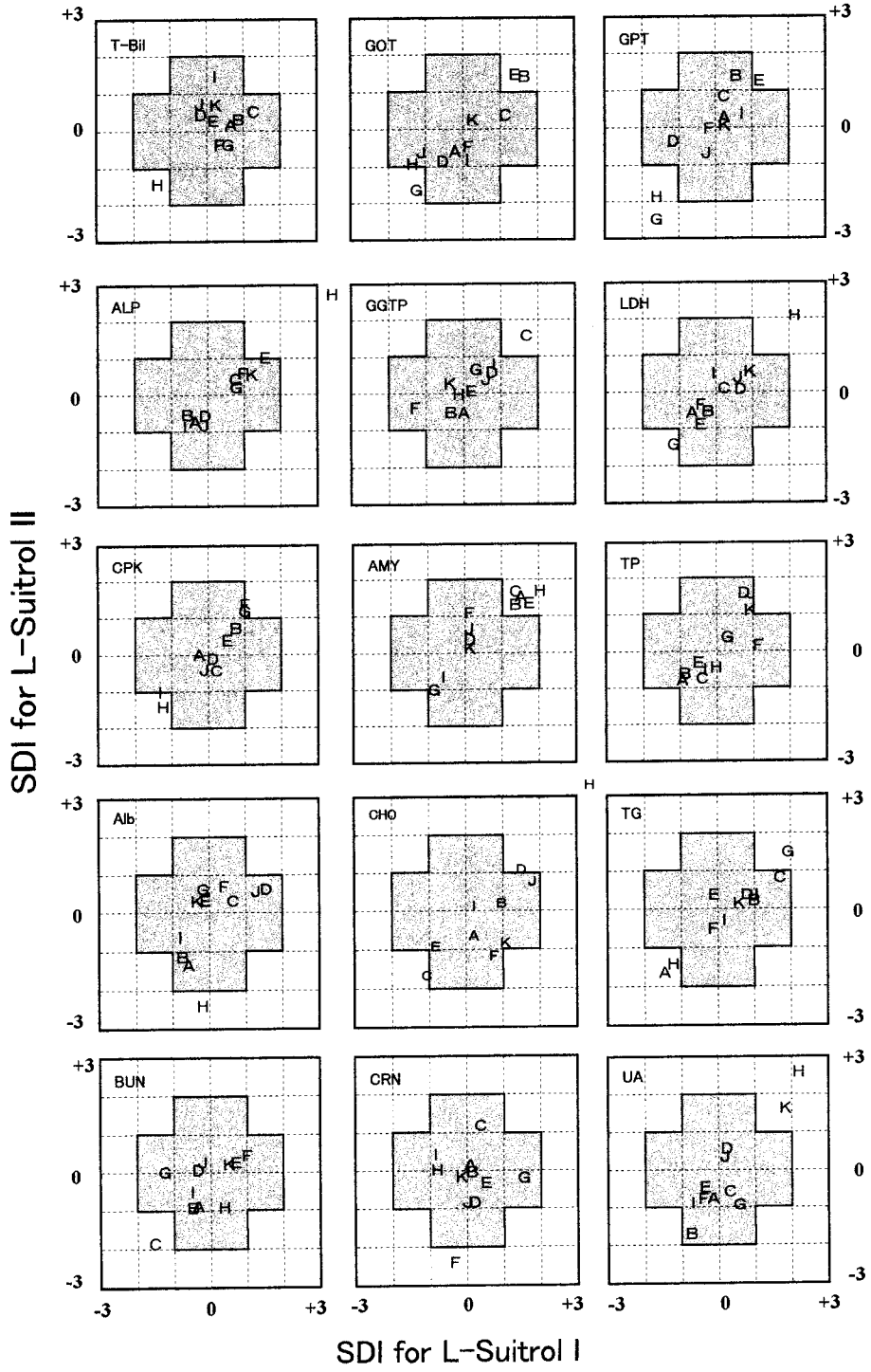

Fig. 1 Twin plot analysis of laboratory data obtained in a control survey. Laboratory data for L-suitrol I and II were obtained in a control survey performed 4 months prior. Standard deviation index (SDI) values of the laboratory data for a respective test were twin plotted. A-I indicates the 11 laboratories which participated in the present study.

as abnormal by one laboratory to be found normal by another laboratory. Laboratories used for health check-ups may intentionally lower the reference interval in order to improve their chances of detecting diseased individuals by screening tests, although there are several theories as to how to calculate reference interval (15–19). Organizations dealing with health care management may request laboratories to use unique reference interval values. However, a suitable value that can be used in all types of laboratories is needed. Thus, further effort is required to minimize the inter-laboratory differences in reference intervals as well as in test data.

It is natural that the trend errors revealed by the control assessment were well reflected in the actual test data. However, it is difficult to actually confirm that control assessment affects test data because of the problems described above. Thus, the results of the present study strongly suggest that frequent evaluation by control assessment following improvements in trend error helps to maintain the quality of the test data from medical laboratories.

In conclusion, to maintain the consistency of clinical diagnoses among laboratories, inter-laboratory differences must be reduced. The present study of 11 laboratories in Okayama City area suggests that the quality control assessment are useful in determining the level of inter-laboratory differences and that medical laboratory must make concerted efforts to minimize the inter-laboratory differences based on such assessments.

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