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PROGNOSIS OF HUMAN LIVER TRANSPLANTATION

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Abstract – The results of publications on liver transplantation were diverse since several years, without model prognosis. The impossibility was due to the international system of measurement. We resorted to vector functions for calculating the ratios of biological values. We studied 2 samples with the same total number (35patients) in the same conditions. We proposed 2 vector functions of transplants: αv_1 weight/age donor and recipient in proportion to obtain a medium coefficient; γv_2 ratio of biliary volume/700ml (minimum secretion); β was the coefficient of ratio ALT/AST (transaminases). After evaluation of 560 observations and mathematical control about 3000 cases, we compared the samples with 10 parameters without significant difference between variances, means, other values; with consented errors $\alpha = \beta = 0.05$; $\gamma < 10^{-7}$; means of relative errors = ± 0.03 negligible. The results were verified by diverse tests (standard deviation of differences, χ^2-test, relative risk, odds ratio, comparisons of distributions, parent population, equations of normality, partial correlations, partial regression coefficients, multiple regression, coefficient β. Final results : quantitative prognosis by grading ; ***right responders*** to immunosuppressive treatment without complications, **RR1** ***fast response*** (scores 3.5 ; 4) ; **RR2** ***slow response*** (scores 2 ; 2.5 ; 3). ***Partial responders***: ***very slow response*** (score 2; 2.5; 3) with transitory complications. Those patients were in recovery (81.5%). ***Wrong responders*** (score 2), ***4 deaths*** (5.5%) by ARS; score 2.5, ***1 death*** (1.5%) by ARS. ***We subtracted β from these scores to differentiate them***. ***Non-responders*** (score 1.5), 2 ***deaths*** (3%) by ARS.

Key words: Liver transplantation. Comparisons of samples. Parent population. Evaluation of parameters. Tests of control. Relationships and equations of vector functions. Model of calculation. Multiple regression. Acute Rejection Syndrome. Prognosis.

PROBLEMATIC OF HUMAN LIVER GRAFT PROGNOSIS

During a decade many authors had consecrated innumerable publications about liver transplant. Among all authors, each other according to his competence, attempted to establish a prognosis. The results of those texts were indeed as well interesting as diverse in many domains about the predictive probability of death after liver transplantation (6, 26, 29, and 35). And recently, a group of six authors (37) realized a single /multi-centre analysis of data coming from 65540 cases. Another of twenty three authors in Europe realized the analysis of data coming from 23644 cases (6). In all situations cited in references, the systematic review of the presented data was in no position to find a prognostic model to discriminate between patients who will die and those who may survive. Moreover these results did not allow any relationship between their different findings. This disappointment provoked the loss of the hope for several researchers, more than enough to find a solution, so that some of them wrote about this frustration: **'**Quest for the lost ark**'** (27). The research for a prognosis of liver transplantation looked impossible and bearing a lot of difficulties. The impossibility was to not be able to use directly the international system of measurement. As for main difficulties there were at least three of them. The first one was the unknown variable of the behaviour from transplants and patients if they were opposed or non-opposed or between them, to the immunosuppressive treatment.

The second one consisted in the selection of variables to evaluate the functional balance of transplants. The third one was to quantify at last the clinicophysiopathological status for each patient. In front of the complexity and of too many unknown variables or factors, we appealed to the vector functions. Then, we considered the liver transplant as a finite sequence of organic functions in correspondence with a finite space of vectors. From that it appeared possible to calculate for each basic vector its numeral module determined by a ratio in proportion between two values chosen among the biological results of the hepatic tests or from other physiopathological data.

PATIENTS AND METHODS

Selection of appropriate vectors

Despite our multiple methods of calculation, there were only two accessible modular values for the vector functions and particularly a coefficient β. All the useful data for these calculations were carried out in postoperative period on the fifth day of transplantation. The modular values were as following.

1) *The common medium coefficient* α was for the vector v_1. **e.g.** given the body weight of the donor 75kilogrammes (kg) with its age 32 years and the body weight of the recipient 71kg and its age 58 years. We grouped these equalities (75kg = α x 32) + (71kg = α x 58) given 75kg + 71kg = 2 α x (58+32), hence 146kg = α x 180. We obtained α = 146/180 = 0.81 ~ 0.80. It was a medium coefficient of the common body mass with the liver graft between donor and recipient relatively to their ages as a factor of physical wellbeing. It was certain that the values 1 or > 1 would be preferable as energetic benefit for the recipient. So we had 0.80 as α_1 $v_{1,1}$ vector function v_1 and so on till α_{70} $v_{1,70}$ (70 was the total number of patients).

2) *The biliary coefficient* γ was for the vector v_2 from the ratio of the daily volume in millilitres (ml) of biliary secretion: 700 ml (minimum of secretion per day) (32).

When **e.g.** given was daily volume of bile as 500 ml; then γ = 500 ml/700 ml = 0.70. We had 0.70 as $\gamma_1 v_{2,1}$ vector function v_2 and so on till $\gamma_{70} v_{2.70}$. The biliary secretion was more often an interesting visual indicator of the hepatic function.

3) *The enzymatic coefficient* β was the ratio ALT/AST of transaminase values taken from the hepatic test and expressed in the international units by litre (IU/l). The ratio was a number which gave, with a normal liver, a proportion varying from 0.80 to 1 with men and women. But with the liver transplants we obtained many values >>1. **e.g.** given for a patient was ALT/AST = 126 IU/l /184 IU/l ~ 0.70. β = 0.70. It was the coefficient β_1 and so on till β_{70}. To be right, we were restrictive about this coefficient because of its strong increase linked to apoptosis (28). In abeyance of its mathematical control below in the chapter discussion, we thought that the cellular renewal by apoptosis was assuring the homeostatic balance in the cellular metabolism of the liver grafts. It could constitute an elementary contribution to the calculation of the prognostic evaluation.

Sampling of patients (10)

We studied 70 patients with liver transplants since 1997 to 2005 from the Liver Transplantation Unit, Conception Hospital (Marseille, France). The patients were followed up during at least 5 years. However some patients caught our attention after 7 or 8 years. But unfortunately we lost sight from much of them. The total population was divided in two samples 1 and 2, each other with 35 patients for comparisons. We treated both the samples in the same conditions without arrangement or particular preference, and with random numbers for patients. That was to avoid a possible bias in check-in of men and women.

Model of calculation (table1)

We realized the products of each vector by a real number and their additions (15, 16). Then we could define the structure of the vectors functions in the set of hepatic functions with the real variables. That gave the common function $h(x) \rightarrow f(x) + g(x) + \beta$, where by application *h*, x had its image for each patient through the relationship $\alpha f(x) + \gamma g(x) + \beta = f(w)$. This dynamic function constituted a generator of pair vectors (v_1, v_2), (17). These vectors were combined with the real numbers of modules α, γ, given the vector functions $\alpha_1 v_{1,1} + \gamma_1 v_{2,1} + \beta_1 = f(w_1)$ from the first patient to the last as $\alpha_{70} v_{1,70} + \gamma_{70} v_{2,70} + \beta_{70} = f(w_{70})$, (18,19) (see general matrix, table1). Finally, a small number of vector functions in linear application was representative of the multiple others from their same set. Then, that set yielded a subset with a space for couples of vector functions from 1 to 70 relationships. But in this context, we could not add the times of cold ischemia preservation to the biological values of transplants for another vector. These times were disparate and very variable from one patient to the other, perhaps resulting from the long waiting times with the list of transplants. Multiplication and addition of the vector functions were in linear application with the matrix of results in an operational diagram. This model was applied for the database about 560 observations noted for all patients of samples 1 and 2, concerning weight/age of donors and recipients and of the volume of the daily biliary secretion and the dosage of ALT/AST.

RESULTS

Results of the vector functions (table 2, table 3)

In both tables of samples 1 and 2, we realized for each patient the ratios of proportions from the indications of database. At first we made easier the calculation of the scores for the prognosis. For that, we systematically rounded up or down, the modular coefficients of the vector functions and the coefficient β, to the integer, except the first half decimal number which was rounded to 0.5 or to the nearest integer.

Indications of the common code

We wrote as following. Retr: retransplantation. Surv : survival. ARS: acute rejection syndrome. D: death. Od: opportune disease. Rd: recurrent disease. TC: transitory

Table1. Model of calculation

$V_{1,1}$		α_1		$V_{2,1}$		γ_1		β_1
$V_{1,2}$		α_2		$V_{2,2}$		γ_2		β_2
.		.		.		.		.
.		.		.		.		.
.	x	.	+	.	x	.	+	.
.		.		.		.		.
.		.		.		.		.
$V_{1,n}$		α_n		$V_{2,n}$		γ_n		β_n

Multiplication, addition of vectors and coefficients β

$\alpha_1 V_{1,1}$	+	$\gamma_1 V_{2,1}$	+	β_1	$(\alpha_1 V_{1,1} + \gamma_1 V_{2,1} + \beta_1) = f(w_1)$
$\alpha_2 V_{1,2}$	+	$\gamma_2 V_{2,2}$	+	β_2	$(\alpha_2 V_{1,2} + \gamma_2 V_{2,2} + \beta_2) = f(w_2)$
.		.		.	
.		.		.	
.		.		.	
$\alpha_{70} V_{1,70}$	+	$\gamma_{70} V_{2,70}$	+	β_{70}	$(\alpha_{70} V_{1,70} + \gamma_{70} V_{2,70} + \beta_{70}) = f(w_{70})$

General matrix of results for linear functions of vectors and coefficients β given $f(w_1)$ to $f(w_{70})$

complications. NC: no complications or without complications.

Vector functions and clinical status

We checked-in for the two samples 1 and 2, for each patient, the values of the vector functions and the clinical information about each status of each patient.

Parameters of both distributions (table 4)

We elaborated 10 parameters which characterized each distribution. The table 4 had allowed to compare the values for drawing the conclusions of these ones. We also noted that the estimated values should be asymptotically unbiased (12). For that, we adopted the risk of consented errors at first $\alpha = \beta = 0.05$ of probabilities whereas the error γ was very negligible ($<10^{-7}$). As for the mean of the relative errors (5) between the comparative values of the parameters with both the samples, we obtained by the calculation of the arithmetic differences, with regardless of their designations, ± 0.03 like the margin of uncertainty. We calculated for all scores of each sample, their frequencies, their partial totals and both the general totals. Thus we identified each case of death as upper and other living with transitory complications or without complications.

Mathematical comparison

1) Between both variances $v_1 v_2$ (35) with their respective total numbers.

We applied the calculation of ε (epsilon) which was the standardized deviation of the difference $|v_1 - v_2|$. We obtained $\varepsilon = 1.64 < 1.96$ value corresponding to normality with $\alpha = 0.05$, (16). There was not a significant difference between the two variances. And P-value or degree of significance was close to 0.07 in the table of normality > 0.05.

2) Between the two means m_1, m_2 (34).

We applied a method close to the preceding one by the standard deviation ε of the difference $|m_1 - m_2|$. We obtained $\varepsilon = 1.40 < 1.96$ value corresponding to normality with $\alpha = 0.05$. There

Table2. Sample1. Vector functions, coefficient β and clinical status with coding

Patients N°	X αV_1	Y β	Z γV_2	W	Clinical status	Code
1	0.6	1	0.7	2.5		NC
2	0.6	1	0.1	1.5	Restr. Surv. 1 month. Hepatic occlusive disease	ARS, D
3	0.9	1.6	0.4	3	Cholangitis	TC
4	1	0.8	0.5	2.5	Respiratory deficiency, cholangitis, agitation	TC
5	1	0.4	0.6	2		NC
6	0.7	1	0.6	2.5	Surv. 2years, 3 months. Septicemia by CMV, lung and liver	Od, D
7	0.8	1	0.5	2.5		NC
8	0.8	0.8	0.4	2	Surv. 2 months, 9 days. Septicemia with liver shock	Od, D
9	0.8	1.6	0.4	2		NC
10	0.7	0.7	0.2	1.5		NC
11	0.7	1.6	0.6	3		NC
12	0.9	0.8	0.3	2		NC
13	0.9	0.7	0.1	1.5	Acute rejection, renal deficiency	TC
14	1	0.6	1	2.5	Acute rejection, under liver collection	TC
15	0.7	1	0.7	2.5	Renal deficiency	TC
16	0.9	1	0.6	2.5		NC
17	1	1	0.9	3		NC
18	0.7	1	0.1	2	Ascitis, embolism, sudden death	ARS, D
19	0.6	0.5	0.1	1	Ascitis, haemorrhage, renal deficiency, sepsis. Surv. 23 days	ARS, D
20	1	0.7	0.2	2		NC
21	1	1	1	3		NC
22	1	0.8	0.3	2		NC
23	0.8	1.7	0.1	2.5		NC
24	1	0.8	0.5	2.5	Haemorrhage, hepatic infarct, thrombosis of portal vein, surv. 5 days	ARS, D
25	1	0.8	0.9	2.5		NC
26	0.9	0.5	0.1	1.5	Renal deficiency	TC
27	0.9	0.7	0.6	2	Retr	NC
28	0.8	1	0.4	2		NC
29	1	0.6	0.4	2		NC
30	1	0.7	0.3	2	Under liver collection and cholangitis	TC
31	0.9	1	0.6	2.5	Cholangitis	TC
32	1	1	0.6	2.5	Cholangitis	TC
33	0.8	0.6	0.1	1.5	Acute rejection syndrome, fever at 43°7C, surv. 5 days	ARS, D
34	0.8	1	0.3	2	Arterial hepatic thrombosis	TC
35	0.9	0.9	0.4	2		NC

NB. The letters x, y, z were used in the formulae of partial correlations and multiple regression.

Table 3. Sample 2.Vector functions, coefficient β and clinical status with coding

Patients N°	X αV_1	Y β	Z γV_2	w	Clinical status	Code
36	1	1	0.5	2.5		NC
37	0.7	0.7	0.1	1.5	Sepsis on thrombosis of hepatic artery	ARS, D
38	1	1	0.7	3		NC
39	1	1	0.4	2.5	Retr. Hyper increase of platelets difficult to halt	NC
40	0.8	1	0.6	2.5	Pneumonia	TC
41	0.9	1.5	0.7	3		NC
42	0.6	0.9	0.9	2.5		NC
43	0.9	2	0.4	3.5		NC
44	0.8	1	0.9	3		NC
45	0.6	0.9	0.7	2		NC
46	0.9	1	1	3		NC
47	0.7	0.4	0.7	2		NC
48	0.9	1.5	0.3	2.5	Subhepatic collection, rheumatoid purpura	TC
49	1	0.7	0.7	2.5	Recurrence of lung cancer, surv. 2years, 3months	Rd, D
50	0.9	0.2	0.7	2		NC
51	0.8	0.2	0.6	1.5	Ascitis haemorrhage from immunoblastic lymphoma, surv. 1 month	Rd, D
52	0.5	0.8	0.7	2	Pneumonia and nervous disorders	TC
53	0.7	0.6	0.6	2		NC
54	0.8	0.7	0.6	2	Serious septicemia by hepatitis C virus, surv. 7 months	Rd, D
55	0.9	0.9	1	3	Psychic disorders	NC
56	1	0.4	0.6	2		NC
57	1	0.8	0.5	2.5		NC
58	1.5	0.7	0.7	3		NC
59	1	0.6	0.2	2	Secondary sepsis from ORL sphere, surv. 3 months, 15 days	Od, D
60	0.7	0.7	0.9	2.5		NC
61	0.9	1	0.3	2		NC
62	0.8	1.5	0.4	2.5		NC
63	0.8	0.9	0.6	2.5		NC
64	0.8	1	0.2	2	Retr. Thrombosis in fatty liver transplant, hepatic occlusive disease surv. 12 days	ARS, D
65	0.7	1.5	0.7	3		NC
66	1	0.9	0.4	2.5		NC
67	0.8	1.5	0.3	2.5		NC
68	0.8	0.5	0.5	2		NC
69	0.8	0.9	0.7	2.5		NC
70	1	1	0.2	2		NC

NB. The letters x, y, z, were used for in the formulae of partial correlations and multiple regression.

Table 4. Parameters of both the distributions with the mean of relative errors

Parameters	Sample 1		Sample 2	Mean of relative errors MRE	Rounding up
1. Total number of patients	35	—	35	0	0
2. Total values of scores	93	—	84	9/35 = 0.257	0.26
3. Mean m	2.6	—	2.4	0.2/35 = 0.0057	0.006
4. Average deviation of mean Dm	0.6	—	0.4	= 0.2/35 = 0.0057	0.006
5. Variance σ^2	0.5	—	0.22	= 0.28/35 = 0.008	0.01
6. Standard deviation of mean σ	0.7	—	0.5	= 0.2/35 = 0.0057	0.006
7. Standard error of mean SEM	± 0.1	—	± 0.08	= 0.02/35 = 0.00057	0.0006
Relationships of normality N					
8. Dm ÷ σ ≥ 0.75	0.81 (81% N)	—	0.80 (80% N)	= 0.01/35 = 0.000286	0.0003
9. 4/5 σ = Dm	0.6 = Dm	—	0.4 = Dm	= 0.2/35 = 0.0057	0.006
10. Extreme range w_n (scores)	$\frac{1.5\_\_\_4}{2.5}$	—	$\frac{1.5\_\_\_3.5}{2}$	= 0.5/35 = 0.01428	0.0143 ——— = 0.3092
MRE = 0.3092 / 10 = ± 0.03					

Table 5. Results of scores in both distributions

Sample 1			Sample 2		
Scores	Frequencies	Clinical status	Scores	Frequencies	Clinical status
1.5	1	1 ARS D	1.5	2	1ARS D 1 Rd D
2	10	3 ARS D 3 TC 4 NC		12	1 ARS D 1 Od D 1 Rd D 1 TC 8 NC
2.5	6	1 ARS D 1 Od D 1 TC 3 NC	2.5	13	1 Rd D 2 TC 10 NC
3	15	1 Od D 6 TC 8 NC	3	7	7 NC
3.5	1	1 NC	3.5	1 — 35	1 NC — 35
4	2	1 NC 1 NC — 35			

was not a significant difference between both means (m_1-m_2). The P-value was close to 0.07 in the table of normality > 0.05.

3) Between the scores of both samples.

We preferred, here, the use of the x^2-test (33) because it allowed to oppose the several group values 2x2 from both the samples, only with an operating calculation. Indeed we had 4 available groups from both the samples as following.

1) Group of 11 values	1 score	1.5	versus Group of 14 values	2 score 1.5
(sample1)	10 "	2	(sample 2) "	12 " 2
2) Group of 22 values	6 "	2.5	versus Group of 21 values	13 " 2.5
	15 "	3	" "	7 " 3
	1 "	3.5	" "	1 " 3.5

The results gave for 1 degree of freedom x^2 = 3.841 from the normal table of x^2 with $\alpha = 0.05$, without a significant difference between both samples. As for the score 4, there were only two values in the sample1. This score was indicated as being upper in the extreme range, like the highest value.

Evaluation of the distribution with the parent population

We considered the 35 patients of the sample 1 and the 35 others of the sample 2 as the integral parts of the parent population with its size of 70 patients. We determined at first its 10 parameters for understanding the interest of its distribution to draw up the quantitative prognosis.

Parameters of the distribution (table 6).

They were 10, but different from the preceding others.

Results of scores in the parent population (table7)

We calculated the frequency of the scores with their percents and their exact confidence limits at 95% for the total evaluation. Moreover we codified the clinical status of all 70 patients in order to classify their scores for the prognosis.

Table 6. Parameters of the distribution in the parent population

Total number of patients N	Designation	70
Total values of scores	T	177
Mean	m	2.5
Average deviations of mean	Dm	0.48
Variance	σ^2	0.37
Standard deviation of mean	σ	0.6
Standard error of mean	SEM	± 0.07
Relationships of normality	Dm / σ	0.8 (80% N)
	$4 / 5\ \sigma = Dm$	0.48 = Dm
Extreme range of scores	W_n	1.5 — 4.5 = 3

Table 7. Results of scores in the parent population

Score	Frequency	Percent	Exact Confidence limits at 95%	Clinical status
1.5	3	4%	2% — 14%	2 ARS, D - 1 Rd, D
2	22	31.5%	21% — 43%	4 ARS, D - 1 Od, D - 1 Rd, D - 4 TC - 12 NC
2.5	19	27%	17% — 39%	1 ARS, D - 1 Od, D - 1 Rd, D - 3 TC - 13 NC
3	22	31.5%	21% — 43%	1 Od, D - 6 TC -- 15 NC
3.5	2	3%	1% — 10%	2 NC
4	2 — 70	3% — 100%	1% — 10%	2 NC — 70

Table 8. Evaluation of the clinical status in the parent population

Diagnostic	Score	Case	Frequency	Percent	Exact Confidence limits at 95%
ARS, D	1.5 2 2.5	2 4 1	7	10%	4% — 20%
Od, D	2 2.5 3	1 1 1	3	4.25%	1% — 12%
Rd, D	1.5 2 2.5	1 1 1	3	4.25%	1% — 12%
TC	2 2.5 3	3 1 6	10	14.5%	7% — 25%
NC	2 2.5 3 3.5 4	13 15 15 2 2	47	67%	55% — 78%
		— 70	— 70	— 100%	

DISCUSSION

Comparison between both the two samples 1 and 2 (table 4)

Distributions

The distributions of the both samples were normal with discrete probabilities (11) as indicating upper from their parameters. These distributions were expressed by the general equation of Laplace-Gauss (30) from which it was possible to compare directly the respective values of the 10 parameters in each sample. Concerning the main values characterizing their distributions (variances, means and standard deviation of means), the comparisons made with the mathematical relationships, indicated clearly the absence of significant differences. These results, with the negligible errors, translated really the proximity of both distributions.

Comparison between the scores of the samples 1 and 2 (table 5)

The sample 1 appeared the most frequent with the levels 3; 3.5; 4 (18 scores), whereas the sample 2 was the most frequently with the levels 2; 2.5 (25 scores). The total *numbers* of scores were: 93 for the sample 1 and 84 for the sample 2. The difference of 9 points came from the sample 1 because of its highest values. In fact, the sample 1 was more scattered (σ =0.7), whereas the sample 2 was more concentrated and more homogeneous with a weak scattering (σ =0.5), the sample 1 contained 10 TC and 18 NC = 28 in recovery. While the sample 2 had 3 TC and 26 NC = 29 in recovery. The sample 2 was certainly the best model of distribution with

nearly two groups: deaths and living. Concerning the deaths, the sample 1 had 5 ARS, whereas the sample 2 had only 2 ARS. Of course we excluded the 6 deaths by Od, D and Rd, D of this count. Therefore we observed very few scores with death by ARS and many others with living by recovery. To distinguish these same scores we used their frequencies and their percents as following. But to differentiate them mathematically we required an ultimate adjustment of the prognosis.

Score 1.5: 2 D by ARS (3%) without cases of recovery
Score 2: 4 D " " (5.5%) versus 16 cases " (23%)
Score 2.5: 1 D " " (1.5%) versus 16 cases " (23%)

Lastly we could not mention any significant difference between both samples. But they had rather some few nuances in the scores. Indeed in the sample1 the scores were diverse from each other. Then it was not excluded to conceive a problem of non-response to the immunosuppressive treatment.

Distribution of the parent population Parameters (table 6)

Outside of the total number of patients (70) and the total values of score (177), the other parameters were between the values corresponding to the two samples 1 and 2. Moreover, this distribution was normal as indicating in the table 6.

Results of weak scores (table 7)

The most important weak scores were the level 2 with 31.5% of frequency accompanied by the level 3 with the same 31.5%. Then we noted the level 2.5 with 27% of frequency and finally the level 1.5 with 4% of frequency. These values were exposed with their confidence limits at 95%, (13).

Evaluation of the clinical status (table 8)

The cases of recovery were the most frequent with a total number of 57 patients given 10 TC (14.5%) and 47 NC (67%) yielding 81.5% of recovery. The deaths by ARS were 7 (10%). These values were exposed with their confidence limits at 95%. But if we excluded 6 other deaths by 3 cases of the opportune diseases and 3 cases of the recurrent diseases which were not linked directly in relation with the liver transplantation, we obtained with 64 patients (70-6), 89% of success by recovery. If we accepted only the 3 cases of the opportune diseases, even if one patient of them came back (after 2 years on the 3 months since the transplantation, from a very distant continent) in state of septicemia by the cytomegalovirus in lung and liver, then we would have 85% of success as the mean world scores of liver transplantation.

Equations of the distribution with normal adjustment (30, 31)

The general exponential equation centred and standardized by a variable t, was $\Phi(t) = 0.4^{-t^{2/2}}$. It was the variable rounding more or less about zero. t was linked to x original variable by the relationship $t = x - E(x) / \sigma$ where E(x) was the expected value of the mean estimated at 2.5 and σ the standard deviation of the mean estimated at 0.6.

That gave $t = 1/0.6x - 2.5/0.6$. Hence we obtained $t = 1.66x - 4.16$. The aim of this calculation was to verify the fitting of a straight line two points for this equation. This line showed the lowest scores which were corresponding only to the death patients by ARS. So we obtained: for x = score 1.5, t = -1.66 The scores were really negative and the lowest values of the for x = " 2, t = -0.84 distribution were corresponding to the wrong prognosis. for x = " 2.5, t = -0.01

Relative risk (RR) and odds ratio (OR) (22)

The table 8 showed a clear predominance from the scores of recovery. But we asked ourselves if this tendency was really confirmed by the relative risk and the odds ratio or not.

For the relative risk, the contingency table (exposed versus non-exposed and death versus living) gave RR = 0.319 < 1, indicating that RR was here a protective factor instead of a risk factor in other conditions.

For the odds ratio with the same contingency table, it appeared to be more precise and interesting than RR. It was compared to a mathematical test given OR = 0.228. It was also of interest by its confidence limits (CL) at 95%, its variance 0.25 and its standard deviation of the mean 0.05. Then we obtained OR = 0.228, CL = 0.228 ± 0.098 when OR (0.228) CL 95% = ⎪0.13 —— 0.326⎪. Its superior bounds were << 1. It was a right protective factor and it confirmed the results of the table 8 with P-value given $\alpha = 0.09$ as the level of significance far from $\alpha = 0.05$. This method was considered as a valid test. Besides OR gave 4.5 chances of recovery for living patients in proportion to the number of

deaths by ARS and also by the Od, D and the Rd, D.

Other considerations

They were qualitative or semi-quantitative and interesting concerning the position of the prognosis.

Ideal age of liver donor

In our work published in June 2003 (9), we wrote about the evolution of glycogen loss in cold ischemia and reperfusion: **'**The logistic regression allowed to establish 4 models of log its, for evaluating glycogen losses under shapes of affine functions. The models could be corresponding respectively to periportal and pericentral zones, during cold ischemia and reperfusion. The losses worsened over the age of 28 years, on weighted average of age in the sample more exactly above 28 years, 3 months and 18 days, median point of age. This point was located on the abscissa axis (9, fig 2, *p*512) where the straight lines representing the models were concurrent at a point of nil common ordinate at origin. The logistic regression showed thus evidently, the interaction between donor age and glycogen loss aggravating beyond the median point**'**. Otherwise, the best liver transplant was corresponding to the donor age round of 28 years. In conclusion, the hepatic allograft from a young donor was functionally better than from an old donor (38).

Glycogen depletion of liver transplant

Many authors concluded that the depletion of glycogen in the hepatic graft was associated with an increase of the risk of lesions from the preservation and the initial hepatic dysfunction (1). The global survival of the graft could be considered as the best survival factor from a graft rich in glycogen (1).

Glucose and perfusion

The preservation of the hepatic graft under continued hypothermia perfusion was deleterious when the liver became depleted in glycogen because it could not use the glucose for its survival. That was the glucose paradox (4).

Perfusion

The intraoperative perfusion below 60 ml/100g per minute was associated with a weak liver function and a primary graft failure after orthotopic liver transplantation (2).

Cold ischemia

The histologic lesions had significantly the same time as the cold ischemia from 13 to 14 hours. In opposite from 10 hours to < 11, there was generally no lesion (2). But from older donor, the liver transplant in cold ischemia during over 12 hours was subject to deleterious effects. It usually recommended 9 hours safely of cold ischemia duration (25).

Transaminase findings

The transaminases were subject of discord 10 years ago. Already in 1994 some authors thought that increasing of transaminase levels (out of infections or necrosis) was a serious preoperative dysfunction of the liver transplant (8). Then since 1996 other authors competent in liver transplantation said **'**we can see high transaminases with little histologic damage when transplanting a large-for-size liver in the small child**'** (14). In 1997, others asserted that the transaminase values were not useful in predicting presence or absence of preservation injury of liver graft (20). It was for that reason that we considered a possible correlation between apoptosis and increase of transaminase levels out of infections or necrosis (3).

Sex mismatch

A work was realized on this subject (7). The transplantation of liver from a male donor into a female recipient was also associated with an increased probability of chronic rejection. For our work we unfortunately had very little available information about the sex of the donors. However we observed surgeons who preferred transplanting woman's liver to other one's when it was possible.

Prognosis by grading

We specified the prognosis by grading, after exclusion of the opportune and the recurrent diseases.

1) *The right responders* to the immunosuppressive treatment *without complications*, including 2 categories:

a) *the grade RR1* with a *fast response* (scores 3.5; 4) corresponding to 27% of the total number.

b) *the grade RR2* with a *slow response* (scores 2; 2.5; 3) corresponding to 40% of the total number.

2) *The partial responders* with a *very slow response* (scores 2; 2.5; 3) and *with transitory complications*, corresponding to 14.5% of the total number.

All the patients of the both categories were in recovery (81.5%). It was clinically easy to distinguish them.
3) *The wrong responders* had the right scores (2; 2.5) as the preceding but they were deaths by ARS in a few numbers: score 2, 4 deaths (5.5%); score 2.5, 1 death (1.5%). Here we had to consider the folowing question: how to discriminate these values? For the answer see below.
4) *The non-responders* had *only the score* 1.5 with 2 deaths (3%) by ARS. This score was corresponding to *the darkening prognosis*.

Research of a discriminant factor for the wrong responders.

The trustworthy information was obtained from the model of the vector functions. This model could determine the adequate solution. We began by identifying the random variables and the supplementary coefficient β of transaminase factor. These values led to the explained variable corresponding to the sums of the quantitative prognostic grading. The first method with the vector functions was deductive from the initial hypothesis. The second method was inductive by comeback to verify the results of the first one. With respect to the designation of the mathematical formulae in the partial correlations and the multiple regression, we indicated the coefficient weight/age by x; the coefficient bile by z and the coefficient of transaminase ratio by y. The applied procedure consisted to exclude the factors of confusion along the calculations and to carry out the successive adjustments till the final result. Such was the scientific progressive method which we followed up. The calculation of the total correlations (binary) and the partial correlation (tertiary) (36), finally of the partial regression, was really indicated. That allowed to obtain the means of access to the multiple regression which was the field of the multidimensional analysis identifying the random variables (23), given the groups of both values as like: x,y ; y,z ; z,x.
1) *Group* x,y (weight, age/transaminases). We had the partial correlation r = 0.2158. That was a deleted value because it appeared < 0.2369 of the normal table at 95% with 3 degrees of freedom. This group was not significant, what allowed to exclude it as a factor of confusion.
2) *Group* y,z (transaminases/bile). We had r = 0.57. That was a strong value >> 0.2369 of the normal table at 95% with 3 degrees of freedom. This group was very significant. Its confidence limits were CL 95% = $\left|0.40 \text{——} 0.89\right|$.
3) *Group* z,x (bile/weight, age) we had r = 0.45. That was a moderate value >> 0.2369 of the normal table at 95% with 3 degrees of freedom. This group was significant enough. Its confidence limits were CL95% = $\left|0.24 \text{——} 0.73\right|$.
The group values remaining, after this selection, by eliminating the factor of confusion x,y, became y,z and z,x. The comparison between them by the calculation of the partial regression coefficients varying from -1 to 1, was imperative. It allowed to detect the right random explanatory variables.

Coefficients of the partial regression (24)

From the partial correlation (36) y, z; x *constant* = 0.57. z, x; y *constant* = 0.45 and the respective standard deviation of means $\sigma_x = 0.17$; $\sigma_y = 0.5$ and $\sigma_z = 0.19$, we obtained the coefficients of the partial regression which was essential to discover the random variables. We obtained the following:
1) y,z (transaminases / bile) given $0.57 \times \sigma_y / \sigma_z = 0.57 \times 0.5/0.19 = 1.5$. That was a wrong number > 1, consequently excluded as another factor of confusion. But the alternative z,y by inversion, was agreed and given valid $0.57 \times 0.19/0.5 = 0.22$. z was a true value with a real function as a random explanatory variable.
2) z,x (bile/weight, age) given $0.45 \times \sigma_z / \sigma_x = 0.45 \times 0.19/0.17 = 0.5$. z was also a true value, the most important, with a main function as another random explanatory variable. Then the multiple regression allowed adding these coefficients to define the linear equation of these variables as such the model $\alpha_x + \gamma_z + y = s$ where s was the sum of these variables with the coefficient y.

Final result

These variables and the coefficient y led to the final implementation where:
α_x was corresponding to $\alpha\ v_1$ vector function (weight / age);
γ_z …..... "……. $\gamma\ v_2$ " "
(bile / minimum secretion);
y ……. "…… β adjustment coefficient (transaminase ratios);
s ……. "…… w explained variable as the sum of the vector functions,
Thus we regained the original equation of vector functions: $\alpha\ v_1 + \gamma\ v_2 + \beta = f(w)$

The coefficient β had not any active relationship with other vector functions, certainly because of its very great variation due to apoptosis. But it was relative to each patient of the parent population. Thus we verified the initial linear application of the vector functions. From these findings, it appeared that the coefficient β could be the best discriminant factor for the wrong responders. For the scores of recovery β was normally added to the vector functions. But for the scores of the wrong responders we proposed its subtraction from the vector functions to discriminate them by approaching the fatal score 1.5.

The normal method by addition was applied right away for all cases of recovery. The rest of the few patients remained under medical surveillance to detect the first symptoms of ARS, to specify the prognosis and to define the appropriate treatment. We thought we had found the key of the prognosis of liver transplantation. For that, we thanked the mathematics which, when we introduced them skilfully in biomedical sciences, they answered our expectation. Although the mathematicians-biologists were not many of us to be agreed in the world. Of course, the application of mathematical reasoning for a model of observations could help to find the solution. But it was essential to simplify the mathematical expressions with a view to the best understanding for everyone. This method could reasonably be applied by extension to other organs of transplantation, but in required conditions. Finally, we hoped for an ideal model of prognosis of liver transplantation with the best qualities as at once: pertinence, validity, simplicity, quantifiability with precision (here from about 3000 numbers submitted to control), harmlessness, reproducibility and accessibility for the clinician near his patients.

Implications

The realization of that prognosis requires the respect for some conditions which exclude the external biases and the factors of error or confusion. For that we propose an algorithm that defines the operations to apply.

1) Take the total number N of patients as 30<N<100 for a Transplantation Unit which is easy to manage, then to control the patients and to avoid the postsurgical infections or the secondary contaminations from the hospital environment.

2) Check each patient and number him according to the international table of the random numbers.

3) Examine and follow up the patients with the same team of doctors and their aids in the same conditions.

4) Test all patients with liver grafts at the fifth day after surgical transplantation, with the same team of doctors and aids in the same conditions.

5) Detect and insulate urgently the patients with opportune diseases and others with recurrent diseases for their specific treatment.

6) Calculate the scores of the prognosis like they are evaluated in the copy.

7) Compare for each patient his score and his clinical status with the database of section “other considerations”, to confirm the level of the qualitative agreement.

8) Supervise the patients with a minimal score, to detect the possible first clinical signs of acute rejection syndrome which can be fatal. Those patients need urgently more intensive care or a new transplantation.

9) Identify the rest of the patients who appear evidently with some of them without complications and others with transitory complications.

REFERENCES

1. Adam, R., Reynes, M., Bao, Y.M., Astarcioglu, D., Azoulay, D., Chiche, L., and Bismuth, H. Importance clinique du contenu en glycogène du greffon hépatique. *Gastroenterol.Clin.Biol.* 1993, **17** (A)**:** 241.

2. Angelescu, M., Hofmann, W., Zapletai, C., Bredt, M., Kraus, T., Herfarth, C., and Klar, E. Histomorphological analysis of preservation injury as determinant of graft quality in clinical liver transplantation. *Transplant. Proc.* 1999, **31:** 1074-1078.

3. Barry, G., Rosser and Gregory, J., Gores, G.J. Liver cell necrosis: cellular mechanisms and clinical implications. *Gastroenterology* 1995, **108** (1)**:** 252-273.

4. Boidin, Ph., Boudjema, K., Lima, S., Brua, C., Alexandre, E., Cinqualbre, J., and Jaeck, D. Restauration des réserves énergétiques du greffon hépatique au cours de sa conservation par perfusion hypothermique continue. *Gastroenterol.Clin.Biol.* 1993, **17** (A)**:** 169.

5. Buisson, P. Ensemble et nombres entiers : erreur. In : Encyclopédie, les mathématiques. Nouvelle édition : Bibliothèque Retz - CEPL, Paris 1975, *p* 302.

6. Burroughs, A.K., Sabin, C.A., Rolles, K., Delvart, V., Karam, V., Buckels, J., O’Grady, J.G., Castaing, D., Klempnauer, J., Jamieson, N., Neuhaus, P., Lerut, J., De Ville de Goyet, J., Pollard, S., Salizzoni, M., Rogiers, X., Mühlbacher, F., Garcias Valdecassas, J.C., Broelsch, C., Jaeck, D., Berenguer, J., Moreno Gonzalez, E., Adam, R., and on behalf of the European Liver Transplant Association. 3-month and 12-month mortality after first liver transplant in adults in Europe: predictive models for outcome. *The Lancet* 2006, January, 225-232.

7. Candinas, D., Gunson, D.K., Nightingale, P., Hubscher, S., McMaster, P., and Neuberger, J.M. Sex mismatch as a risk factor for chronic rejection of liver allografts. *The Lancet* 1995, **346:** 1117-1121.

8. Carles, J., Fawaz, R., Neaud, V., Hamoudi, N.E., Bernard, P.H., Balabaud, C., and Bioulac-Sage, P. Ultrastructure of

human liver grafts preserved with UW solution. Comparison between patients with low and high postoperative transaminases, levels. *J. Electr. Microsc. Cytol. Pathol*. 1994, **26** (1)**:** 67-73.
9. Cherid, A., Cherid, N., Chamlian, V., Hardwigsen, J., Nouhou, H., Dodero, F., Benkoel, L., Letreut, Y.P., and Chamlian, A. Evaluation of glycogen loss in human liver transplants. Histochemical zonation of glycogen loss in cold ischemia and reperfusion. *Cell. Mol. Biol.* 2003, **49**(4)**:** 509-514.
10. Diem, K., and Seldrup, J. Population and sample. In: Geigy Scientific Tables. Eighth revised and enlarged edition by Ciba-Geigy, Basle, October 1982, **2:** 182-183.
11. Diem, K., and Seldrup, J. Discrete probability distribution. In: Geigy Scientific Tables. Eighth revised and enlarged edition by Ciba-Geigy, Basle, October 1982, **2:** 184-186.
12. Diem, K., and Seldrup, J. Estimates. In: Geigy Scientific Tables. Eighth revised and enlarged edition by Ciba-Geigy, Basle, October 1982, **2:** 189.
13. Diem, K., and Seldrup, J.Confidence limits for continous and discrete distribution. In: Geigy Scientific Tables. Eighth revised and enlarged edition by Ciba-Geigy, Basle, October 1982, **2:** 190-191.
14. Edmond, J.C., Renz, J.F., Linda, D., Ferrell, D., Rosenthal, P., Lim, R.C., Roberts, J.P., Lake, JR., and Asher, N.L. Functional analysis of grafts from living donors. Implications for the treatment of older recipients. *Ann. of Surgery* 1996, **224** (4)**:** 544-554.
15. Fèvre, D., L'algèbre linéaire : produit d'un vecteur par un nombre réel. In: Encyclopédie, les mathématiques. Nouvelle édition : Bibliothèque Retz - CEPL, Paris 1975, *pp* 57-59.
16. Fèvre, D., Somme de deux applications *f* et *g*. In: Encyclopédie, les mathématiques. Nouvelle édition : Bibliothèque Retz - CEPL, Paris 1975, *pp* 61-62.
17. Fèvre, D., Systèmes générateurs. In: Encyclopédie, les mathématiques. Nouvelle édition : Bibliothèque Retz - CEPL, Paris 1975, *pp* 65-68.
18. Fèvre, D., Applications linéaires. In: Encyclopédie, les mathématiques. Nouvelle édition : Bibliothèque Retz - CEPL, Paris 1975, *pp* 75-76.
19. Fèvre, D., Ecriture matricielle. In: Encyclopédie, les mathématiques. Nouvelle édition : Bibliothèque Retz - CEPL, Paris 1975, *pp* 81-82.
20. Gaffey, M.J., Boyd, J.C., Traveek, S.T., Ashraf, M.A., Rezeig, M., Caldwell, S.H., Iezzoni, J.C., McCullough, C., Stevenson, W.C., Khuroo, S., Nezamuddin, N., Ishitani, M.B., and Pruett, T.L. Predictive value of intraoperative biopsies and liver function. Tests for preservation injury in orthotopic liver transplantation. *Hepatol.* 1997, **25** (1)**:** 184-189.
21. Huguier, M., et Flahaut, A. Comparaison entre deux échantillons, risques d'erreur, tests statistiques. In: Biostatistique au quotidien. *Elsevier Science*, Amsterdam, Lausanne, New York, Oxford, Paris, Shannon, Tokyo 1998, *pp* 45-52.
22. Huguier, M., et Flahaut, A. Risque relatif, les odds. In: Biostatistique au quotidien. *Elsevier Science*, Amsterdam, Lausanne , New York , Oxford , Paris , Shannon , Tokyo 1998, *pp* 80-83.
23. Huguier, M., et Flahaut, A. Les analyses multidimensionnelles. In: Biostatistique au quotidien. *Elsevier Science*, Amsterdam, Lausanne, New York, Oxford, Paris, Shannon, Tokyo 1998, *pp* 155-161.
24. Huguier, M., et Flahaut, A. La régression multiple. In: Biostatistique au quotidien. *Elsevier Science*, Amsterdam, Lausanne, New York, Oxford, Paris, Shannon, Tokyo 1998, *pp* 161-163.
25. Ikegami, T., Nishizaki, T., Yanaga, K., Shimada, M., Kishikava, K., nomoto, K., Ushiyama, H., and Sugimachi, K. The impact of donor age on living donor liver transplantation. *Transplant.* 2000, **70** (12)**:** 1703-1707.
26. Jacob, M., Lewsey, J.D., Sharpin, C., Gimson, A., Rela, M., and Van der Meulen, J.H.P. Systematic review and validation of prognostic models in liver transplantation. *Transplantation* 2005, **11** (7)**:** 814-825.
27. Melendez, H.V., Rela, M., Murphy, G., and Heaton, N. Assessment of graft function before liver transplantation. *Transplantation* 2000, **70** (4)**:** 560-565.
28. Muller, H., K. Genesis of apoptosis *Brit.Med.J.* 1994, 308, *p* 1441.
29. Onaca, N.N., Levy, M.F., Sanchez, E.Q., Chinnakotla, S., Fasola, C.G., Thomas, M.J., Weinstein, J.S., Murray, N.G., Goldstein, R.M., and Klintmalm, G.B.A. A correlation between the pretransplantation MELD score and mortality in the first two years after the liver transplantation. *Liver Transplant.* 2003, **9** (2)**:**117-123.
30. Pascal, M. La statistique mathématique : loi normale. In: Encyclopédie, les mathématiques. Nouvelle édition : Bibliothèque Retz - CEPL, Paris 1975, *pp* 494-495.
31. Pascal, M. La statistique mathématique : ajustement d'une série statistique à une loi normale.
In: Encyclopédie, les mathématiques. Nouvelle édition : Bibliothèque Retz - CEPL, Paris 1975, *pp* 502-505.
32. Popper, H., and Schaffner, F. Daily production of bile. In Liver: Structure and function, bile formation. McGraw-Hill Company Inc, New York, Toronto, London 1987, *p* 80.
33. Schwartz, D. Le test X^2 et la comparaison de plusieurs répartitions observées. In: Méthodes statistiques à l'usage des médecins et des biologistes. 4è édition Médecine-Science Flammarion, Paris 1995, *pp* 74-88.
34. Schwartz, D. Comparaison de deux moyennes observées. In: Méthodes statistiques à l'usage des médecins et des biologistes. 4è édition Médecine- Science Flammarion, Paris 1995, *pp* 142-143.
35. Schwartz, D. Comparaison de deux variances à partir de leur différence. In: Méthodes statistiques à l'usage des médecins et des biologistes. 4è édition Médecine- Science Flammarion, Paris 1995, *pp* 168-169.
36. Schwartz, D. Liaison entre plusieurs caractères quantitatifs ; corrélations partielles. In: Méthodes statistiques à l'usage des médecins et des biologistes. 4è édition Médecine- Science Flammarion, Paris 1995, *pp* 247-249.
37. Thuluwath, P.J., Yoo, H.Y., and Thompson, R.E. A model to predict survival at one month, one year and five years after liver transplantation based on pretransplant clinical characteristics. *Liver Transplant.* 2003, **9** (5)**:** 527-532.
38. Totsuka, E., Fung, J.J., Ishii, T., Urakami, A., Moras, N.P., Hakamada, K., Narumi, S., Watanabe, N., Nara, M., Hashimoto, N., Takigushi, M., Nazaki, T., Umehara, Y., and Sasaki, M. Influence of donor conditions on postoperative graft survival and function in human liver transplantation. *Transplant. Proc.* 2000, **32:** 322-326.