Factors Predicting Survival After Portacaval Shunt:

A Multiple Linear Regression Analysis

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The predictive value of 15 pre- and peroperative parameters upon survival after portacaval shunt was analyzed in a retrospective investigation of 134 elective operations. A multiple linear regression model was used. Survival was measured at three different points of time: one month, one year and five years after the operation. Survival at one month was influenced by the parameters bilirubin/s and ascites only. Survival at one year was influenced by albumin/s, sex, bilirubin/s, BSP, heart disease history and ascites. Survival at five years was influenced by albumin/s, alkaline phosphatase/s, history of alcohol abuse, and globulin/s. These findings indicate that prediction of survival after portacaval shunt is an intricate process and that considerable improvement of the Child criteria is possible.

MANY ATTEMPTS TO IDENTIFY preoperative factors influencing survival after portacaval shunt have been made. The importance of hepatic function measured in different ways has been clearly established.[3,5,11,14] A notable lack of correlation between survival and preoperative portal pressures as well as other hemodynamic parameters has also been found.[2,4]

One of the difficulties in such studies is that the preoperative parameters very often vary together which makes it difficult to identify the predictive value of the individual factors. For instance there is a negative correlation between albumin/s and bilirubin/s in patients with liver cirrhosis. There is probably an association between presence of ascites and high bilirubin/s, but probably not between presence of ascites and portal pressure. To overcome this difficulty in evaluating the predictive value of a specific preoperative factor, statistical methods like cluster analysis, discriminant analysis, and multiple linear regression can be used. The last mentioned method is probably the best as it makes it possible to calculate a direct death risk for patients with certain risk factors.

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We are not aware of any investigations applying this method to a group of patients with portocaval shunts with the intention of identifying factors predicting the death risk, short-term or long-term. For these reasons we have used multiple linear regression analysis to evaluate the predictive value of 15 preoperative factors in a retrospective investigation of 134 portacaval shunts.

Materials and Methods

Three hundred fifteen patients were operated with end-to-side portacaval shunts in Lund 1951–1973. Only patients with true elective shunts were included in this investigation as very few records in patients with acute or subacute shunts fulfilled the criterion of having recorded values in all the preoperative parameters.

Records of 134 patients fulfilled this criterion, and the following preoperative parameters were used and defined:

1. Sex
2. Heart disease. This was defined as history of heart failure necessitating digitalis treatment and/or previously diagnosed coronary heart disease. Two categories were used: present or nonpresent.
3. Alcoholism. No strict definition was possible in this retrospective investigation. If the record considered the cause of the cirrhosis to be alcohol, this was defined as a positive statement, if not as a negative.
4. Ascites. Present in history or preoperative investigation or at operation, otherwise not present.
5. Edema. Present in the preoperative investigation, otherwise not present.

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6. Protein in serum recorded in two classes, above or below 68 g/l.
7. Albumin in serum (a). Divided into three classes: 1) a < 30 g/l, 2) 30 ≤ a < 38 g/l, 3) a ≥ 38 g/l.
8. Globulin/s (g) defined as the difference between protein/s and albumin/s. The values were divided into three classes: 1) g < 29 g/l, 2) 29 ≤ g < 37 g/l, 3) g ≥ 37 g/l.
9. Alkaline phosphatase (a) measured in Buch-Buch units. a) a < 9, b) 9 ≤ a < 16, c) 16 ≤ a.
10. Bilirubin/s (b) divided into three classes: 1) b < 1, 2 mg/100 ml, 2) 1.2 ≤ b < 3.1 mg/100 ml, 3) 3.1 ≤ b.
11. Bromsulphthalein retention test (b). The values were divided into three classes: 1) b < 21, 2) 21 ≤ b < 31, 3) 31 ≤ b.
12. Portal pressure (pp) measured with a catheter during operation recorded in cmH_2O. The values were divided into three classes: 1) pp < 33, 2) 33 ≤ pp < 39, 3) 39 ≤ pp.
13. Portal pressure after shunt (pa) measured in cmH_2O divided into three classes: 1) pa < 18, 2) 18 ≤ pa < 23, 3) 23 ≤ pa.
14. Fall in portal pressure (pf) defined as portal pressure before shunt minus portal pressure after shunt measured as described above. The values were divided into three classes: 1) pf < 11, 2) 11 ≤ pf < 21, 3) 21 ≤ pf.
15. Year of operation: a) before 1960, b) 1960–1965, c) 1966–1973.

Notable variables not possible to evaluate in this retrospective investigation were muscular wasting and encephalopathy prior to operation. These points were not always included in records.

The reasons for not using laboratory values in their absolute form but dividing them into classes were two: 1) A closer resemblance to the idea of Child classification was obtained. 2) During the years laboratory methods of estimating especially the serum proteins have changed, making values not exactly comparable. However, the maximum deviation is not more than ten per cent. By classification into a few classes "wrong values" were reduced at the expense of the information obtained. The division between classes has been chosen rather arbitrarily in order to obtain fairly equal sized groups. Dependent variables were patient survival (1 if alive, 0 otherwise) at three different points of time: one month after operation, one year after operation, and five years after operation.

The computations were performed on a Hewlett-Packard 9830 computer with a program especially written for this investigation but in accordance with the usual principles for multiple regression. This statistical method (for reference see most statistical handbooks e.g. Snedecor and Cochran 1968) consists in finding the best linear relation between the dependent variable (one at a time) and the independent variables. This corresponds to finding that (n-l)-dimensional plane in an n-dimensional space which lies closest to all the observed data points, if the deviation between the points and the plane is measured parallel to the axis corresponding to the dependent variable. The goodness of fit obtained is usually measured by the multiple correlation coefficient R^2 which can be interpreted as SS_{reg}/SS_{tot}, (where SS_{tot} is the sum of squares around the mean for the dependent variable y and SS_{reg} the sum of squares of the predicted values $\hat{y}$ around their mean), or equivalently, as the square of the correlation coefficient between the y's and the corresponding $\hat{y}$'s. The technique employed was "backward regression", *i.e.*, first a model including all the independent variables was constructed. For each variable in the model an F-test was made in order to decide whether the corresponding regression coefficient was significantly different from zero. The variable with the smallest F-value was then excluded from the set of independent variables and new model was constructed with the remaining ones. This procedure was repeated until all variables remaining in the model had an F-value exceeding the critical value for p = 5%.

TABLE 1. *Survey of Different Parameters Influencing Survival at Different Times After a Portacaval Shunt*

Variable	One Month Survival	One Year Survival	Five Years Survival
Albumin/s		+	+
Bilirubin/s	+	+	
Ascites	+	+	
Bromsulphthalein retention		+	
Sex		+	
Alkaline phosphatase			+
Heart disease		+	
Alcohol			+
Serum globulin			+

Results

Five-year Survival

One hundred thirty-two patients were included in this analysis since two were lost to follow-up within the observation time. Of these 132 patients 78 died within the observation interval and five years survival rate was 41%.

The analysis showed when considering all investigated independent variables a multiple correlation coefficient (r) of 0.45. This corresponds to a r^2 value of 0.20; in other words all the measured variables "explained" 20% of the variation in mortality within five years. However, in studying the separate parameters four of them were found to give a significant contribution to the correlation coefficient. These were when ordered according to decreasing F-value (high F-value indicates roughly speaking higher degree of correlation) albumin/s, alkaline phosphatase/s, history of alcohol abuse and serum globulin. The significant multiple correlation coefficient (r) based on these four parameters was 0.41 corresponding to a r^2 value of 0.17. These four variables alone thus explained 17% of the total variation of five year mortality in the group.

One Year Survival

One hundred thirty-three patients were included in this part of the study. One was lost to follow-up within the observation interval. Of these 133 patients 33 died giving a one year survival rate of 75%. Six parameters gave a significant addition to the correlation coefficient being in order of decreasing F-value: albumin/s, sex, bilirubins/s, bromsulphtalein retention, heart disease, ascites. The significant multiple correlation coefficient (r) reached was 0.55 corresponding to an "explained" part of the variation around the group mean of death rate (r^2) of 30%. The multiple correlation coefficient (r) reached with all the variables included was 0.59 corresponding to a r^2 of 0.35.

One Month Survival

One hundred thirty-four patients were included. Thirteen died within the observation time, giving a hospital mortality of ten per cent. Two parameters gave a significant addition to the multiple correlation coefficient and they were in order of magnitude bilirubin/s and ascites. The significant multiple correlation coefficient (r) reached was 0.26 corresponding to an "explained" part of variation around the group mean of death rate (r^2) of seven per cent. The multiple correlation coefficient reached with all the variables included was 0.41 corresponding to an r^2 of 0.17.

Discussion

Before making a more detailed discussion of results of the study we would like to point out some limitations of the method used in this investigation. The number of patients studied is small for the statistical model used. Most multiple linear regression analysis in medical statistics use patient numbers ten and 20 times this size although a few exist of comparative size.

It should also be noted that, in a regression model like this, where survival is measured on a 0-1-scale, a multiple correlation coefficient (r) near 1 is *not* to be *expected*, unless all, or nearly all, of the independent variables of interest have an approximately two point distribution. For instance, it can be shown mathematically, that in a model with one independent variable x, which is uniformly distributed over the interval (0, 1), the explained part of variation (r^2) will be about 0.33 (irrespective of the sample size) *even if* the survival chance is *exactly* equal to x. If x were uniformly distributed over the three values 0, ½, 1 (which resembles the situation for many of the independent variables considered in this paper), and the survival chance still were equal to x, we would get $r^2 = 0.67$. Most distributions, however, seem to give much lower r^2 values.

Andersen[1] in an extensive study of predicting postoperative complications and death risk in geriatric patients using 7,922 patients and 43 independent preoperative variables could get higher but not too impressive multiple correlation coefficients. For instance in the group with deaths within one month the correlation coefficient was for "abdominal operation" 0.63, which corresponds to an "explained" part of the variation of 40% and for prostatic operations 0.36 corresponding to an "explained" part of the variation of 13%.

Since our investigation only deals with elective shunts the patients with very poor liver function were excluded. If included, a larger amount of extreme values of the parameters would have entered the calculations. This would probably have increased the partial correlation coefficient for specific parameters and thereby also the explained part of the variation in mortality.

The main objective of this investigation is however not to give an estimate of the part of postoperative deaths among portacaval shunts that can be predicted preoperatively but more to point out which factors that can be of major importance in such a prediction. The investigation lists the parameters giving significant contribution to the correlation coefficient contra those that do not. It does not tell that any specific parameter is significantly better than another.

There are many investigations concerning the prediction of survival after portacaval shunt. The importance of hepatic function for survival after portacaval shunt has been emphasized by Child and Turcotte.[5] Repeated investigations have reached the same results.[3,6,14] The value of the Child criteria is thus

firmly established. However, the Child criteria reflect only part of the liver dysfunction and the laboratory values chosen were those easily measured during the 1950's. Little is known of the result of using other parameters of liver function such as alkaline phosphatase or prothrombin index. Bromsulphthalein retention has in one investigation[8] been shown to be a good predictor of survival but if it would increase the precision of survival prediction if added to the Child criteria is not known. Turner et al.[15] have claimed better prediction results for their improved version of the bromsulphthalein test than when using other laboratory signs of hepatic function. The exact value of this test is not yet known. Success in improving the Child criteria by adding other parameters has been generally lacking.[3,10,14] However, Leger et al.[9] found the age and general condition of the patients of importance for short time survival, sex and etiology of the cirrhosis of importance for long time survival. The possibility of short time and long time survival being influenced by different parameters is otherwise seldom considered in the various investigations in this field.

In this investigation we found that the only significant factors predicting *hospital mortality* were presence or history of ascites and the value of bilirubin/s. This is in accordance with the general theory of hepatic function reserve being of prime importance for short time survival after portacaval shunt. Worth noting is that the otherwise important liver function parameter albumin/s gave no significant addition to the result, because of covariance with bilirubin/s and ascites, which in this analysis gave major contributions to the correlation coefficient. This is in good accordance with the results reported by Malt and associates using discriminant analysis in a comparative study of portacaval and splenorenal shunts.[11]

Woodard and Webster[16] found that patients with alcohol cirrhosis had a higher mortality than nonalcoholics. This could not be confirmed by Foster et al.[7] In the present investigation no effect of alcohol could be seen on the hospital mortality. However, the exclusion of patients with acute operations could have reduced the influence of this factor as in the investigation of Woodard and Webster the largest difference between the groups was found in the acute operations.

One year survival was influenced by six parameters. Of these no less than four different liver parameters albumin, bilirubin, bromsulphthalein retention and ascites gave significant additions to the correlation coefficient despite the covariation existing between them. Therefore the formula for predicting risk in this situation necessarily has to be rather complex.

It has seldom been claimed that the sex of the patients has predictive value for the outcome. Leger et al.,[9] however, found, that men had longer survival than women, but they stated that women, when operated, generally had worse liver function than men. In our investigation being a female had a positive influence on survival. The reason for this is not easy to understand. It is possible that the difference in etiology of the cirrhosis between the sexes may in part explain the different prognosis.

History of heart failure also contributes significantly to the correlation coefficient. This is an expected finding in investigations of this kind (For instance B Andersen[1]). The interest for evaluation of this parameter in patients with porta-caval shunt seems to have been low.

Five years survival was significantly influenced by albumin/s, alkaline phosphatase, serum globulin and history of alcohol abuse. This time three parameters concerning liver function have been found to give a significant contribution. Why alkaline phosphatase now has substituted bilirubin and BSP is not clear, but it indicates that evaluation of liver function and liver function deterioration is a very complex problem. The high serum globulin associated with increased risk of dying within five years after the operation can be an indication of active progressive liver disease. As far as we know this parameter has never before been considered as a possible predictive factor. That alcohol abuse can be a parameter influencing long time survival after portacaval shunt has been well known. Especially bad is the prognosis for alcoholics who continue drinking.[7] The increased death risk for patients with alcohol cirrhosis in this investigation can probably be explained in that way.

Finally we can also with this method support the findings of several investigators[2,4] of the complete lack of correlation between portal pressures during the operation and survival after the shunt.

This study has shown that only part of the variation in mortality after portacaval shunt could be predicted when using standard Child criteria of operability. In predicting hospital mortality the Child criteria may be too complex as we could find that only two of the investigated parameters bilirubin/s and ascites influenced survival. In predicting other survival periods parameters outside the Child criteria played an important role.

From the figures in our investigation it is possible to calculate quotients which might be used as predictive help figures in the future, but we feel that the number of patients studied is too small to justify such a calculation. The precision in the prediction is seriously impaired when using small patient numbers. If the patients are separated into groups according to certain points (as done for instance by Malt et al.[11])

the number of patients in individual groups is often very low. If for example a predicted figure of ten per cent mortality is based on 20 patients in such a group the 95% confidence interval for this ten per cent is 1–32%. The usefulness of such a predictive figure is further reduced by the fact that the very important corresponding calculations have not been made for patients being in the same situation but not receiving a portacaval shunt.

References

1. Andersen, B.: Praeoperativ Vurdering af Operativ Risiko. F.A.D.L.'s Forlag A. S. Copenhagen, 1971.
2. Burchell, A. R., Moreno, A. H., Panke, W. F. and Nealon Jr. T. F.: Hemodynamic Variables and Prognosis Following Portacaval Shunts. Surg. Gynecol. Obstet., 138:359, 1974.
3. Campbell, D. P., Parker, D. E. and Anagnostopoulos, C. E.: Survival Prediction in Portacaval Shunts: A Computerized Statistical Analysis. Am. J. Surg., 126:748, 1973.
4. Charters, A. C., Brown, B. N., Sviolka, S. C. et al.: The Influence of Portal Perfusion on the Response to Portacaval Shunt. Am. J. Surg., 130:226, 1975.
5. Child, C. G. and Turcotte, J. G.: The Liver and Portal Hypertension Chapter 1 (Child, C. G., (ed), Philadelphia: W. B. Saunders, 1964.
6. Edmonson, H. T., Jackson, F. C., Juler, G. L. et al.: Clinical Investigation of the Portacaval Shunt: IV. A Report of Early Survival from the Emergency Operation. Ann. Surg., 173:372, 1970.
7. Foster, J. H., Ellison, L. H., Donovan, T. J. and Anderson, A.: Quantity and Quality of Survival After Portosystemic Shunts. Am. J. Surg., 121:490, 1971.
8. Hsu, K. Y.: Portal Systemic Shunt for Portal Hypertension: Importance of Bromsulphtalein Retention for Prediction of Survival. Ann. Surg., 175:569, 1972.
9. Leger, L., Lenriot, J.-P., Duclos, J.-M., Lemaigre, G.: Bilan de 187 Dérivations Porto-caves Tronculaires. Analyse Statistique des Facteurs Pronostiques. J. Chir., 108:31, 1974.
10. Maillard, J. N., Clot, P. and Coste, T.: Preoperative Parameters Influencing Survival in Patients with Elective Portacaval Shunts. Digestion, 10:129, 1974.
11. Malt, R. A., Szczerban, J., and Malt, R. B.: Risks in Therapeutic Porta-caval and Spleno-renal Shunts. Ann. Surg. 184:279, 1976.
12. Nordlund, S.: The Influence of some Pre- and Peroperative Factors on Postoperative Mortality and Renal Function in Open-Heart Surgery. Dissertation Uppsala, Sweden, 1966.
13. Snedecor, G. W. and Cochran, W. G.: Statistical Methods. 6th edition. Iowa State Univ. Press, Ames Town, 1968.
14. Turcotte, J. G. and Lamberg, M. J.: Variceal Hemorrhage, Hepatic Cirrhosis and Portocaval Shunts. Surgery, 73:810, 1973.
15. Turner, J., Cuschieri, A. and Shields, R.: The Prediction of the Outcome of Portacaval Shunt Using Bromsulphtalein (BSP): A Retrospective Aspect. Br. J. Surg., 61:828, 1974.
16. Woodard, J. C. and Webster, P. D.: Comparison of Portocaval Shunts in Patients with Alcoholic and Nonalcoholic Liver Disease. Dig. Dis., 17:997, 1972.