Clinical Chemistry 46:8
1114–1120 (2000)

Prognostic Significance of Low Serum Cholesterol after Cardiothoracic Surgery

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Background: **The precise prognostic significance of critically low cholesterol concentrations in patients undergoing cardiothoracic surgery is unknown.**

Methods: **In a retrospective case-control study, we analyzed the database of 2074 patients, of whom 87 died postoperatively in hospital. All patients underwent cardiothoracic surgery using a heart-lung machine. Age, sex, body mass index, preoperative ejection fraction, smoking, diabetes mellitus, type of operation, emergency surgery, renal deficiency, pulmonary hypertension, and endocarditis were considered together with serum concentrations of cholesterol, C-reactive protein, alanine aminotransferase, and triglycerides. The statistics included sensitivity, specificity, predictive value, odds ratio, and the ROC curve.**

Results: **Cholesterol decreased sharply immediately after surgery in both the deceased and the survivors. In the deceased, the mean cholesterol concentration (± SE) remained rather low between days 4 and 7 after surgery [2.46 ± 0.16 mmol/L (95 ± 6 mg/dL)]. In the survivors at that time, the mean cholesterol concentration was significantly (P <0.001) higher [4.37 ± 0.03 mmol/L (169 ± 1 mg/dL)]. The positive predictive value of a critically low cholesterol concentration [<3.10 mmol/L (<120 mg/dL)] was 25.4%, increasing to 66.6% at a cutoff value of 1.55 mmol/L (60 mg/dL). The odds ratio under those circumstances was 15.5, and the area under curve (*C*-statistic) was 0.90.**

Conclusions: **The cholesterol concentration between days 4 and 7 after cardiothoracic surgery possesses a high prognostic significance in terms of in-hospital mortality.**

Rather low serum cholesterol concentrations have often been reported in patients suffering from a variety of severe diseases *(1–10)*. The poor prognosis of such low cholesterol concentrations has been documented in several epidemiological studies *(11–16)*. Therefore, among other established indicators, it has been suggested that serum cholesterol might also be a valuable prognostic factor for critically ill patients *(8, 17–19)*. However, as yet little is known about the precise postoperative course of serum cholesterol. In particular, still unknown is the time after surgery at which the measured cholesterol might have the highest predictive value regarding in-hospital mortality.

In a retrospective case-control study, we evaluated cholesterol concentrations measured in patients who had undergone cardiothoracic surgery using a heart-lung machine. We were especially interested in the postoperative time at which the cholesterol value was highly predictive of death. Furthermore, we compared in more detail the prognostic power of cholesterol with that of other laboratory indicators such as C-reactive protein (CRP), triglycerides, and alanine aminotransferase (ALT) as well as with already known clinical prognostic factors. Finally, the laboratory findings were correlated with the cause of patient deaths.

Our study revealed that a postoperative serum cholesterol concentration below 3.10 mmol/L (120 mg/dL) between days 4 and 7 is highly predictive of death, the odds ratio being 15.5.

Materials and Methods

SUBJECTS AND PROTOCOL

The records of 2092 patients from the Clinic of Cardiac and Thoracic Surgery, Berufsgenossenschaftliche Kliniken Bergmannsheil, Ruhr-University, Bochum, were retrospectively reviewed. All patients underwent cardiothoracic surgery using a heart-lung machine between January 1996 and March 1998. The review revealed that 18 patients died on the day of surgery. Their database entries were empty regarding the postoperative laboratory findings in question. Therefore, they were excluded from this study.

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Received March 1, 2000; accepted June 6, 2000.

From the remaining records of 2074 patients, the following preoperative clinical data were considered: age, sex, body mass index, preoperative ejection fraction, smoking, diabetes mellitus, type of operation, emergency surgery, renal deficiency, pulmonary hypertension, and endocarditis.

In addition to cholesterol, preoperative and postoperative serum concentrations of CRP, ALT, and triglycerides were considered. Preoperatively, laboratory findings up to 4 days before surgery were reviewed; in case of more than one determination per patient, only the last value before the operation was taken into consideration. Postoperatively, in case of more than one determination per patient within the selected periods, either the lowest (cholesterol, triglycerides) or highest (CRP, ALT) value was considered.

LABORATORY TESTS

All tests were performed routinely in the Institute of Clinical Chemistry, Transfusion and Laboratory Medicine, Berufsgenossenschaftliche Kliniken Bergmannsheil, Ruhr-University, Bochum. Cholesterol, ALT, and triglycerides were measured with a CHEM 1 analyzer (Bayer Vital), and CRP with an ARRAY 360 (Beckman Coulter) according to the recommendations of the manufacturers. The quality assurance of quantitative determinations was strictly performed according to the German Norm: Quality Assurance in Medical Laboratories (DIN 58936 part 1, 1989). The criteria of acceptance were fulfilled throughout.

STATISTICAL ANALYSIS

Data are presented as the mean ± SE. For analysis, patients were divided into two groups: patients who died in hospital after surgery (deceased), and those who survived, i.e., left the hospital alive (survivors). The statistical significance of differences between survivors and deceased was calculated by the Student *t*-test and the χ^2 test. The predictive value "deceased" was calculated according to the following formula: prevalence × sensitivity × 100/[prevalence × sensitivity + (100 − prevalence) × (100 − specificity)]. The predictive value "survivors" was calculated according to the following formula: (100 − prevalence) × specificity × 100/[(100 − prevalence) × specificity + prevalence × (100 − sensitivity)]. In this context, the postoperative in-hospital mortality was considered as prevalence.

A ROC curve was obtained by plotting the true-positive proportion (sensitivity) vs the false-positive proportion (1 − specificity) *(20)*. The area under those curves (*C*-statistic) was calculated by nonlinear regression.

By a stepwise multiple logistic regression, the prognostic significance (odds ratio) of the following characteristics was assessed: age, sex, body mass index, preoperative ejection fraction, smoking, diabetes mellitus, type of operation, emergency surgery, renal deficiency, pulmonary hypertension, and endocarditis, as well as the serum concentrations of cholesterol, CRP, ALT, and triglycerides.

In general, $P < 0.05$ was considered statistically significant.

Results

Some of the basal clinical characteristics of both groups, including the kind of cardiothoracic surgery, are summarized in Table 1. These characteristics have already been demonstrated as critical factors for outcome. Eighty-seven patients (4.2%) died in hospital during the postoperative period. Age, sex, body mass index, ejection fraction, smoking, and diabetes mellitus were evenly distributed between deceased and survivors. On the other hand, significant differences were found between deceased and survivors concerning some types of operation, emergency surgery, renal deficiency, pulmonary hypertension, and endocarditis. Because of this partly uneven distribution, all of the listed characteristics together with some selected laboratory findings were primarily taken into consideration when odds ratios were calculated by means of a stepwise multiple logistic regression (see below).

Preoperative and postoperative serum cholesterol concentrations of the deceased and survivors are shown in Fig. 1. The mean (± SE) preoperative serum cholesterol concentration of the deceased [5.87 ± 0.23 mmol/L (227 ± 9 mg/dL); n = 53] was nearly identical with that of survivors [5.95 ± 0.03 mmol/L (230 ± 1 mg/dL); n = 1418]. During the first 2 days after surgery, the mean cholesterol concentration decreased in both groups, i.e., to 2.87 ± 0.16 mmol/L (111 ± 6 mg/dL; n = 30) in the survivors and 2.53 ± 0.47 mmol/L (98 ± 18 mg/dL; n =

Table 1. Preoperative data (mean ± SE) of patients who either died in hospital after cardiothoracic surgery (deceased) or survived (survivors).

	Deceased (n = 87)	Survivors (n = 1987)	*P*
Age, years	65.6 ± 1.1	64.1 ± 0.2	NS[a]
Sex, M/F, %	71/29	70/30	NS
Body mass index, kg/m^2	26.1 ± 0.4	26.5 ± 0.1	NS
Ejection fraction, %	59.3 ± 2.1[b]	62.3 ± 0.4[c]	NS
Smoking, %	29.9	37.9	NS
Diabetes mellitus, %	24.1	25.2	NS
Operation, %			
CABG	57.5	75.9	<0.001
Valve surgery	14.9	13.4	NS
Valve surgery and CABG	13.8	6.9	<0.05
Aneurysm surgery	9.2	0.8	<0.001
Others	4.6	3.0	NS
Emergency surgery, %	26.4	4.0	<0.001
Renal deficiency, %	19.5	10.2	<0.01
Pulmonary hypertension, %	6.9	2.5	<0.05
Endocarditis, %	5.7	0.7	<0.001

[a] NS, not significant; CABG, coronary artery bypass grafting.
[b] n = 54.
[c] n = 1506.

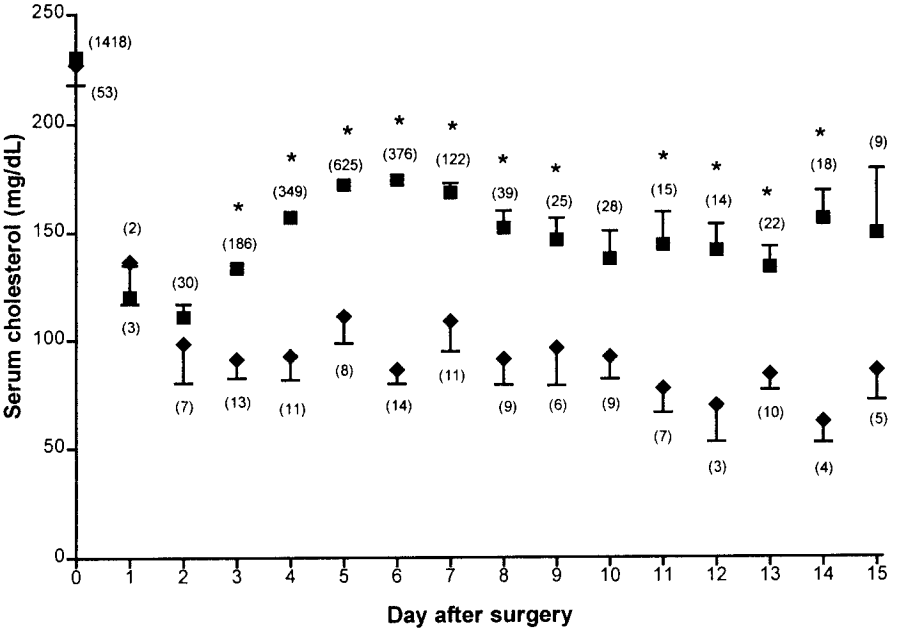

Fig. 1. Serum cholesterol of deceased (♦) and survivors (■) before and after cardiothoracic surgery using a heart-lung machine.

Preoperative concentrations of cholesterol are shown as day 0. The *bars* indicate SE. Values in *parentheses* indicate number of all values available. *, significance of univariate analysis ($P < 0.05$, Student *t*-test). Conversion formula for cholesterol: mg/dL × 0.02586 = mmol/L.

7) in the deceased. Thereafter, in the survivors, the mean cholesterol concentration increased, whereas it remained low in the deceased. For the cholesterol concentration, the most striking difference between groups was observed between days 4 and 7. In this period of time, the mean cholesterol concentration of the survivors (n = 1440) and deceased (n = 38) was 4.37 ± 0.03 mmol/L (169 ± 1 mg/dL) and 2.46 ± 0.16 mmol/L (95 ± 6 mg/dL), respectively, the difference being significant ($P < 0.001$). The difference in the mean cholesterol concentration between survivors [3.70 ± 0.13 mmol/L (143 ± 5 mg/dL); n = 99] and deceased [2.20 ± 0.16 mmol/L (85 ± 6 mg/dL); n = 26] was also significant between days 8 and 11 ($P < 0.001$). Moreover, between days 4 and 7, none of the deceased (n = 38) showed a serum cholesterol concentration >5.17 mmol/L (>200 mg/dL), whereas in that period of time at least 20% of the available cholesterol concentrations of the survivors were again >5.17 mmol/L (>200 mg/dL). Finally, between days 8 and 11, the cholesterol concentration of the deceased did not exceed 3.59 mmol/L (139 mg/dL; n = 26). On the other hand, at this time 47.5% of the available cholesterol concentrations of the survivors were >3.62 mmol/L (>140 mg/dL; data not shown). Moreover, because of the variable timing of the values that we used within the two selected time periods for the deceased, we also calculated the mean postoperative time for the cholesterol values. Between days 4 and 7 and days 8 and 11, the mean time was 5.6 and 9.5 days, respectively, matching the theoretical mean almost ideally. Therefore, the values selected were distributed evenly throughout the time period and are not biased toward values closer to the time of death.

The survival curve of the deceased is shown in Fig. 2; day 0 indicates the postoperative day on which the serum cholesterol was <3.10 mmol/L (<120 mg/dL) for the first time. On average, such a serum cholesterol appeared 12 ± 2 days (median, 8 days; n = 41) before death.

Because no significant odds ratio was found for diabetes mellitus, smoking, endocarditis, and pulmonary hypertension, these characteristics were not taken into consideration for final calculation of the odds ratios presented in Table 2. Between days 4 and 7 after surgery, a cholesterol concentration <1.55 mmol/L (<60 mg/dL) in the deceased group had a positive predictive value of 66.6% and an odds ratio of 8.5 (Table 2). If the cutoff value for cholesterol was increased to 3.1 mmol/L (120 mg/dL), the (positive) predictive value decreased in an inverse relationship, whereas the odds ratio increased up to 15.5. Finally, in this period of time, a cholesterol cutoff of 3.1 mmol/L (120 mg/dL) gave a relatively high sensitivity and specificity, underscoring its practical usefulness.

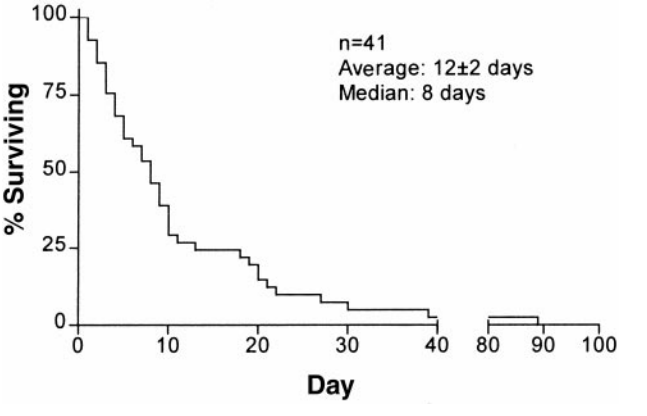

Fig. 2. Life spans of deceased who had undergone cardiothoracic surgery using a heart-lung machine.

Postoperative day 0 indicates the day on which the serum cholesterol was <3.10 mmol/L (<120 mg/dL) for the first time.

Table 2. Statistical results regarding the prognostic power of cholesterol and CRP in view of deceased vs survivors after cardiothoracic surgery.

	Predictive value				Odds ratio[a]			Area under curve (*C*-statistic)
	Deceased	Survivors	Sensitivity	Specificity	Estimate	Confidence interval	*P*	
Cholesterol, days 4–7								0.90
Cutoff								
1.55 mmol/L (60 mg/dL)	66.6	96.4	15.8	99.7	8.5	1.4–50.6	<0.05	
2.07 mmol/L (80 mg/dL)	50.7	97.2	34.2	98.5	6.3	2.2–18.1	<0.001	
2.59 mmol/L (100 mg/dL)	38.1	98.2	60.5	95.7	12.6	5.1–30.8	<0.001	
3.10 mmol/L (120 mg/dL)	25.4	99.0	78.9	89.9	15.5	6.2–38.8	<0.001	
Cholesterol, days 8–11								0.84
Cutoff								
1.55 mmol/L (60 mg/dL)	21.7	96.5	19.2	97.0	5.0	0.7–34.8	NS[b]	
2.07 mmol/L (80 mg/dL)	21.3	97.7	50.0	91.9	3.9	0.9–16.0	NS	
2.59 mmol/L (100 mg/dL)	13.6	98.4	69.2	80.8	5.9	1.5–22.5	<0.01	
3.10 mmol/L (120 mg/dL)	9.5	99.0	84.6	64.7	5.1	1.2–21.8	<0.05	
CRP, days 4–7								0.77
Cutoff, 120 mg/L	10.5	98.8	80.5	70.0	7.4	2.9–19.1	<0.001	
CRP, days 8–11								0.76
Cutoff, 120 mg/L	7.9	98.4	78.6	59.6	11.8	3.5–39.4	<0.001	

[a] Calculated by logistic regression with consideration for age, sex, body mass index, preoperative ejection fraction, emergency surgery, type of operation, renal deficiency, serum cholesterol, triglycerides, CRP, and ALT.
[b] NS, not significant.

When the cholesterol values between days 4 and 7 were compared with those between days 8 and 11 after surgery, overall the later postoperative period of time had a lower prognostic power. Furthermore, compared with cholesterol for both time periods, all other factors in question, including the laboratory indicators (CRP, ALT, triglycerides), showed a lower prognostic power. Therefore, for clarity, in Table 2 only data for the second-best indicator (CRP) were included. The highest odds ratio (11.8) of this acute phase marker in terms of in-hospital mortality was found postoperatively between days 8 and 11 at a cutoff of 3.1 mmol/L (120 mg/dL). However, even at such a relatively moderately increased cutoff concentration, the odds ratio was still distinctly lower than the odds ratio of 15.5 for cholesterol values <3.1 mmol/L (<120 mg/dL) between days 4 and 7 after surgery. Finally, the overall superior prognostic power of serum cholesterol is documented by the area under the curve (*C*-statistic). As shown in Table 2, the highest value was found for cholesterol in the postoperative time period between days 4 and 7.

Fig. 3 shows that none of the causes of death was associated with a significantly lower cholesterol concentration than the others; 85% of all deceased had lowest cholesterol concentrations <2.59 mmol/L (<100 mg/dL).

Discussion

To our knowledge, this is the first retrospective case-control study in which postoperative serum cholesterol concentrations were analyzed with regard to their prognostic significance in terms of in-hospital mortality of patients who had undergone cardiothoracic surgery. For comparison, several clinical markers already demonstrated as prognostic indicators for patients undergoing cardiothoracic surgery were also considered. In addition to cholesterol, we included in the present study well-established laboratory indicators of inflammation (CRP), liver damage (ALT), and lipid metabolism (triglycerides). Several reasons have led us to this selection: (*a*) Patho-

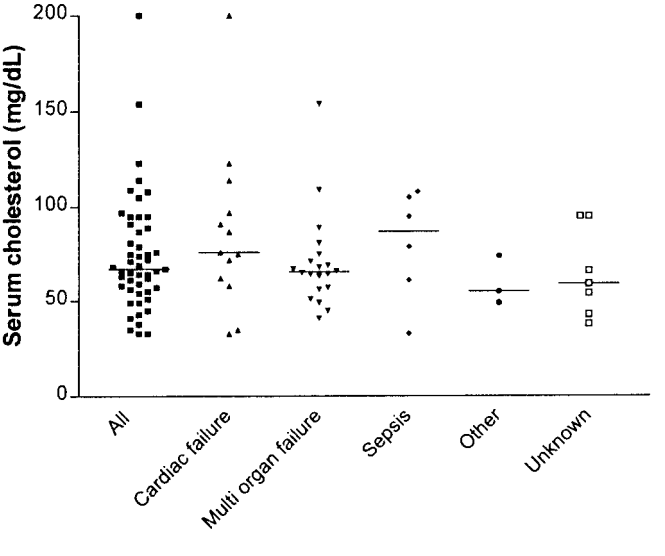

Fig. 3. Lowest serum cholesterol concentrations of those patients who had died from various causes after cardiothoracic surgery.

Medians are indicated by *horizontal bars*. Conversion formula for cholesterol: mg/dL × 0.02586 = mmol/L.

physiological links between those indicators and cholesterol are conceivable. (*b*) The impact of the standardized therapeutic measures during the postoperative course on the selected laboratory indicators is of minor significance. (*c*) The stepwise logistic regression forced us to reduce our final database to a meaningful number of ~15 variables.

Our study clearly demonstrates that in the long run, postoperative cholesterol concentrations were significantly lower in the deceased than in the survivors. This difference between both groups was largest in the postoperative time period between days 4 and 7. At that time, a cholesterol concentration <3.1 mmol/L (<120 mg/dL) was associated with an odds ratio of 15.5, which indicates a relatively high risk of in-hospital mortality. Therefore, it seems attractive in future studies to ascertain whether the meaning of vital scores such as the APACHE II *(8)* can be improved significantly by including the postoperative cholesterol concentration as an independent variable in those scores.

Interestingly, the time course reveals that during the first 2 postoperative days both the deceased and survivors showed a sharp decline of serum cholesterol. Several other studies found a similar decline within a few hours after abdominal surgery *(8, 21, 22)* or severe trauma *(22–24)*. Obviously, such a decline of serum cholesterol seems to be a more common phenomenon in situations in which patients are physically unusually burdened. However, the underlying pathophysiology is not fully understood. In this context, several authors have claimed that the regular decline of the cholesterol concentration after surgery and trauma might be attributed to a temporary liver malfunction *(12, 17, 19)*. In our study, liver damage as a possible underlying mechanism for the decline of cholesterol was indicated by a significant inverse correlation between ALT activity and cholesterol concentration ($r = -0.187$). However, an even stronger inverse correlation was found between the CRP concentration and the cholesterol concentration ($r = -0.317$), suggesting a possible connection between inflammatory processes and cholesterol metabolism. Indeed, the acute phase reaction, which is known to always start immediately after major surgery, seems to have an impact on cholesterol homeostasis. Inflammatory cytokines are able to up-regulate LDL receptor activity, thus leading to an increased peripheral uptake of cholesterol *(17)*, the consequence of which might be a decreased serum cholesterol concentration. On the other hand, recent findings have suggested that cholesterol synthesis is also up-regulated by acute phase events *(25)*.

In addition, it must be considered that all patients in this study underwent heparinization during surgery and several days thereafter. Heparin activates lipoprotein lipase *(26)*, which in turn could lead to an increased internalization of VLDL and LDL *(27)*, followed by a decrease in serum cholesterol.

Finally, because of replacement therapy, it must be recognized that our findings are probably not free of biases. Particularly during an operation and shortly thereafter a rather standardized replacement therapy takes place, leading to an unavoidable dilution of the circulating blood volume. Because of limited availability of data, the intravenous replacement and diuretic therapies of the 2074 patients in the present study were not taken into consideration. The discussion of possible pathophysiological events in context with the presented postoperative time course of cholesterol therefore remains speculative until the actual impact of such intravenous replacement and diuretic therapy on the various laboratory values has been determined. On the other hand, recent studies by others *(28, 29)* have also shown that cardiothoracic surgery leads to an rapid and significant fall in cholesterol. When those authors corrected their results for hemodilution, the response pattern remained unchanged. Therefore, the postoperative time course of cholesterol cannot be attributed solely to dilution effects. All in all, additional studies are needed to explain exhaustively the mechanism that gives rise to the significant decline in cholesterol concentrations immediately after cardiothoracic surgery.

It is remarkable that the cholesterol concentration remained relatively low between days 3 and 6 after surgery in the deceased, whereas in the survivors, cholesterol increased steadily. Obviously, in the deceased soon after surgery the balance between cholesterol synthesis and peripheral uptake and degradation seemed to favor the latter. Again, the impact of inflammation on the cholesterol concentration, which has been discussed above, could give rise to such constantly low cholesterol concentrations in the deceased because of ongoing relatively high cytokine secretion. However, rather low cholesterol concentrations were found in all of the deceased, not just those suffering from severe inflammation caused by infection. Therefore, factors other than inflammatory processes caused by infection might play a pathophysiological role *(4, 6, 15, 25, 30, 31)*.

Our study revealed that cholesterol concentrations that remain relatively low after surgery possess a rather high odds ratio in terms of in-hospital mortality. Earlier studies documented the poor prognosis of rather low cholesterol concentrations after surgery *(8, 9, 21, 22)*. However, to date no information is available regarding the postoperative time period during which the cholesterol possesses its highest prognostic significance. According to our study, a cholesterol determination seems to be prognostically most valuable between days 4 and 7. By day 8 after surgery, the prognostic power of a measured cholesterol concentration is significantly lower.

However, the lower prognostic power of cholesterol values measured 8 days and longer after surgery may in part result from patients with the highest cholesterol concentrations in the surviving population being excluded from later time points by virtue of optimal recovery and discharge from the hospital. This possible negative bias is underscored by the fact that, on average, the length of stay in hospital was 2.7 days shorter in the

surviving population (9.2 days) compared with the deceased (11.8 days), although this difference in length of stay was not statistically significant.

Furthermore, compared with cholesterol, neither CRP as an indicator of inflammation nor ALT as an indicator of liver damage has as high a diagnostic meaning with regard to the risk assessment of mortal outcome. However, if CRP (cutoff, 120 mg/L) is used in combination with cholesterol [cutoff, 3.1 mmol/L (120 mg/dL)] to predict mortality, for the postoperative time period between days 4 and 7 the odds ratio was 19.5 (confidence interval, 8.3–46.0), which is even better than the highest odds ratio of 15.5 found in this study for cholesterol alone.

Finally, the high diagnostic meaning of serum cholesterol with regard to the risk assessment of mortal outcome is underscored by the *C*-statistic, which revealed a value for cholesterol of 0.90. This number is extraordinarily high. For diagnostic purposes, acceptable *C*-statistic values are 0.70–0.85 *(20)*, as found in our study for CRP. In septic patients, CRP showed a *C*-statistic value in terms of outcome prediction *(32)* that is similar to our CRP data.

Postoperative triglyceride concentrations had no prognostic significance in terms of in-hospital mortality (data not shown). In patients with hematologic malignant diseases, it has also been reported that the cholesterol concentration better reflects the seriousness of the illness than triglycerides *(1)*. It is known that cytokines such as interleukin-2 and other factors of the immune system produce a down-regulation of cholesterol concentrations without lowering triglycerides *(17, 33)*.

The analysis of the postoperative life span of the deceased indicated that critically low cholesterol concentrations were found not just immediately before death. Rather, 50% of the deceased were still alive more than 8 days after the cholesterol concentration was for the first time <3.1 mmol/L (<120 mg/dL). Therefore, critically low cholesterol concentrations may help at a relatively early time to identify patients with an increased risk of mortality. In future prospective studies, it must be shown whether intensifying the treatment of patients with critically low cholesterol concentrations can reduce their postoperative mortality rate.

In conclusion, our study indicates that critically low cholesterol concentrations in patients after cardiothoracic surgery are associated with a significantly increased risk for mortal outcome. The postoperative time period at which the cholesterol concentration possesses the highest prognostic significance is between days 4 and 7. Additional studies are needed to clarify whether the cholesterol concentration is itself a risk factor or whether it is just an indicator of increased risk.

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