ONLINE FIRST

Complications of Elective Liver Resections in a Center With Low Mortality

A Simple Score to Predict Morbidity

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Objective: To develop a score predicting the morbidity of liver resections in a center with low mortality.

Design, Setting, and Patients: The study was based on a prospective database of all liver resections performed at the Geneva University Hospitals between January 1, 1991, and October 30, 2009 (a total of 726 elective liver resections in 689 patients). Perioperative complications and their severity were graded according to the original classification by Clavien et al. Variables independently associated with the occurrence of complications were identified using a linear regression analysis model. A score was computed with all independent variables in an assessment population including two-thirds of the liver resections and was further validated in a population including one-third of the liver resections.

Results: Overall mortality was 0.7% (5 of 726 liver resections). We recorded 375 different complications in 259 hepatic resections (36% of resections had ≥1 complication). In the assessment group, resection of 3 or more segments, an American Society of Anesthesiologists score of 3 or higher, and resection for a malignant neoplasm independently predicted the risk of complications. A score integrating these 3 factors significantly predicted the risk of postoperative complications. The score also correlated with the occurrence of major complications.

Conclusion: The score allows for identification of patients most susceptible to complications, in whom efforts against specific postoperative morbidities can be concentrated.

Arch Surg. Published online July 18, 2011. doi:10.1001/archsurg.2011.175

Hepatic resection, the treatment of choice for most patients with focal liver tumors, has changed markedly during the last 2 decades. Although liver resections have become common, particularly in dedicated units with liver transplant facilities where mortality rates are lower than 2%,[1-3] more invasive procedures are being performed on sicker patients with the aid of portal embolization,[4-6] precise preoperative computed tomographic volumetry,[7,8] improved perioperative management,[9,10] and, in patients with colorectal metastases, effective neoadjuvant chemotherapies and innovative multidisciplinary strategies.[11-14] Hence, despite decidedly lower mortality rates, liver resections remain complex procedures with important risks of perioperative morbidity and mortality.[15]

A number of studies have looked at factors predicting adverse events after liver resection. Some have analyzed the association between preoperative variables and general complications,[15-21] and others have developed predictive scores for specific adverse events such as postoperative renal failure and the need for blood transfusion.[22,23] However, to our knowledge, no study to date has developed a score integrating preoperative variables to predict general complications. Such a score, if applicable to all liver resections, would help to tailor the operation to the needs of the patient and would identify subjects requiring more specialized postoperative management. The aims of our study were to investigate the morbidity in our center—a tertiary care facility with a multidisciplinary team for hepatobiliary diseases and transplantation where the mortality of liver resection is below 1%—and to develop a simple score predicting the risks of complication.

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METHODS

This study was based on a prospective database of all surgical hepatic interventions performed at Geneva University Hospitals. The investigation complied with the rules of our institutional ethical board and the Declaration of Helsinki ethical guidelines.

All patients undergoing elective liver resection between January 1, 1991, and October 30,

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Table 1. American Society of Anesthesiologists Physical Status Classification[a]

ASA Score	Definition
1	A normal healthy patient
2	A patient with mild systemic disease
3	A patient with severe systemic disease
4	A patient with severe systemic disease that is a constant threat to life
5	A moribund patient who is not expected to survive without the operation
6	A declared brain-dead patient whose organs are being removed for donor organ purposes

Abbreviation: ASA, American Society of Anesthesiologists.
[a]Based on the ASA Physical Status Classification System, July 2010, with permission of the ASA. A copy of the full text can be obtained from ASA, 520 N Northwest Hwy, Park Ridge, IL 60068-2573.

Table 2. Modified Classification of Complications[a]

Complication Grade	Definition
I	Not life threatening, not requiring drugs other than analgesic, antipyretic, antiemetic, antidiarrheal, or drugs required for urinary retention or low urinary tract infection; requiring only interventions that can be performed at bedside; never associated with hospital stay greater than twice the median stay for the procedure
IIa	Requiring only use of drug therapy, total parenteral nutrition, or blood transfusion
IIb	Requiring therapeutic imaging procedures, therapeutic endoscopy
IIc	Requiring reoperation
III	Any complication with residual and lasting disability and the presence of persistent and objective signs of life-threatening diseases or organ resection
IV	Death as a result of a complication

[a]Adapted with permission from the article by Clavien et al.[27]

2009, were included. Patients undergoing liver surgery but not resection, such as cyst unroofing, and patients undergoing emergency surgery were excluded. All procedures were performed or supervised by a senior hepatobiliary surgeon.

Since 1991, the management of liver resections has been standardized to minimize perioperative and postoperative complications. Once a surgical indication was established, patients were counseled to stop smoking and to increase their physical activity. Since 1996, patients undergoing extensive liver resection exceeding 70% of the functional liver mass (or 60% if aged >80 years or after extensive neoadjuvant chemotherapy) had portal vein embolization prior to surgery. Most patients had a subcostal transversal laparotomy; however, 7% of patients who required associated surgery (eg, colectomy) had a midline incision. Intraoperatively, patients received an average of 300 mL of fluid per hour. Since 2008, systematic monitoring of the central venous pressure, aiming to remain between 4 and 8 mm Hg, was replaced by transesophageal aortic Doppler monitoring.[24,25] During surgery, special attention was given to minimize blood loss and to avoid transfusion. The Pringle maneuver was used only on demand (for bleeding or to increase visibility when dissecting hilar structures), and total vascular exclusion was used only for tumors that invaded at least 2 hepatic veins.[26] Liver resection was performed using an ultrasonic scalpel (cavitational ultrasonic surgical aspiration) and bipolar and argon-beam coagulation. Doppler ultrasonography was frequently used to guide the resection when margins were macroscopically unclear or when tumors had to be dissected near venous or portal pedicles. Metallic clips and Vicryl ties were applied liberally on vascular and biliary vessels. After removal of the tumor, diluted methylene blue was injected through the cystic duct to identify bile leaks. Fibrin glue and regenerated cellulose mesh sealing were applied on the raw liver surface.

Since 2007, except for rare contraindications, all patients received epidural anesthesia for 4 days to decrease postoperative pain and to improve respiratory function and overall mobility. Patients were trained to perform respiratory and leg mobilization exercises from the day before the operation to prevent postoperative atelectasis and deep vein thrombosis. In the immediate postoperative period, patients spent 1 night in the recovery room and were thereafter admitted to a general surgical ward. Only patients with severe cardiac or pulmonary comorbidities were admitted to the intensive care unit. Compression stockings were applied as soon as the patient was in the recovery room. Standard intravenous heparin prophylaxis was started when the activated partial thromboplastin time was below 37 seconds, usually within 2 hours after the end of surgery, aiming to keep the activated partial thromboplastin time between 37 and 42 seconds. After 72 hours, anticoagulation was changed to prophylactic low-molecular-weight heparin until discharge.

All postoperative complications were recorded. When indicated, ultrasonography or computed tomography was performed to investigate any adverse event that could not be explained by physical examination and routine blood analysis or that did not resolve quickly and spontaneously.

The variables recorded in the database included age, sex, American Society of Anesthesiology (ASA) score (**Table 1**), presence of cirrhosis, preoperative hemoglobin level and prothrombin time, indication for liver resection, extent of surgery (number of liver segments resected), additional surgical procedures during the liver resection and their relationship with the hepatectomy (eg, unrelated to liver resection [colectomy for cancer or simultaneous hernia repair] or related to liver resection [diaphragmatic resection in the case of local invasion or biliary reconstruction for disease involving the main bile duct]), number of red blood cell units transfused during surgery, use and duration of the Pringle maneuver or vascular exclusion maneuver, and use of a surgical abdominal drain. The ASA score was categorized as low (ASA score 1-2) or high (ASA score ≥3).

Perioperative complications were defined as complications within 30 days after surgery, and their severity was graded according to the original classification by Clavien et al.[27] We defined grade IV complications as all deaths occurring within 30 days after surgery or directly related to surgery (eg, complication involving a hospital stay >30 days and leading to death). We modified the classification by adding a grade IIc for patients who needed a new operation (**Table 2**). Minor complications were defined as grade I and IIa, and major complications were defined as grade IIb or higher. When more than 1 complication was present, the complication with the highest grade was recorded. Postoperative liver insufficiency was defined as a factor V level below 30% and by the 50-50 criteria[28] (prothrombin index <50% and serum bilirubin level >50 μmol/L [to convert to milligrams per deciliter, divide by 17.104] at day 5) since 2005 (data before 2005 were categorized retrospectively according to this definition). Patients not reaching the 50-50 criteria who had a prothrombin ratio lower than 70% and/or transient ascites and/or transient hyperbilirubinemia (with

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Table 3. Patients' Demographic Characteristics

Characteristic	Value
Liver resections, No. (%)	726 (100)
Age, mean (SD), y	55.3 (14.8)
Sex, No.	
Male	343
Female	383
ASA score, No. (%)	
1	159 (25)
2	384 (60)
3	96 (15)
4	3 (1)
Preoperative prothrombin time, mean (SD), s	95 (9.5)
Preoperative hemoglobin, mean (SD), g/dL	13.29 (1.66)
Type of indication for surgery, No. (%)	
Benign	210 (29)
Malignant	516 (71)
Type of liver resection, No. (%)	
Minor, <3 segments	393 (54)
Major, ≥3 segments	333 (46)
Perioperative transfusion, units of RBCs, No. (%)	
0	521 (77)
1	21 (3)
2	63 (9)
>2	70 (10)
Associated procedures, No. (%)	
None	378 (55)
Linked to liver surgery	182 (26)
Independent from liver surgery	134 (19)
Pringle maneuver, No. (%)	
Yes	223 (53)
No	195 (47)
Abdominal fluid drainage, No. (%)	
Yes	372 (62)
No	229 (38)

Abbreviations: ASA, American Society of Anesthesiologists; RBCs, red blood cells.

SI conversion factor: To convert hemoglobin to grams per liter, multiply by 10.0.

a serum bilirubin level <50 μmol/L) on day 5 were considered patients with slow liver recovery. A pleural effusion was considered a complication when it was symptomatic or required invasive treatment.

Variables independently associated with the occurrence of perioperative complications were identified using a linear regession analysis model. A score was computed with all independent variables, predicting the occurrence of perioperative complications. To validate the score, we further divided the study population into an analysis group, including patients from 1991 to 2004 (approximately two-thirds of the initial population), and a validation group, with patients from 2005 to 2009 (one-third of the initial population). These groups were defined after ensuring that their baseline characteristics and the incidence of complications were similar.

After validation, we correlated the score to the severity of complications for the overall period (assessment and validation groups together). Liver resections for which no complications were present were excluded.

Binomial data were analyzed with the χ^2 test. Multiple categorical variables were assessed with analysis of variance with Bonferroni post hoc test. Statistical analyses were performed with SPSS version 17.0 statistical software (SPSS Inc, Chicago, Illinois) and Excel for Mac version 12.2.3 software (Microsoft Corp, Redmond, Washington). $P < .05$ was considered statistically significant.

RESULTS

In the study period, 726 elective liver resections were performed in 689 patients. Fifty-eight patients had 2 liver resections, and 3 patients had 3 liver resections. Patients' demographic characteristics are shown in **Table 3**.

A majority of patients underwent surgery for malignant disease. The most common malignant neoplasms were colorectal cancer metastases (n=272), hepatocellular carcinoma (n=88), cholangiocarcinoma (n=40), gallbladder carcinoma (n=23), and breast cancer metastases (n=21). The most benign diseases were focal nodular hyperplasia (n=48), hydatid cysts (n=44), living-donor graft harvesting (n=27), hemangiomas (n=25), and adenomas (n=19).

Overall mortality was 0.7% (5 of 726 liver resections). One patient died on postoperative day 19 of intra-abdominal bleeding and refractory ascites after major resection for polycystic hepatorenal disease and extensive liver fibrosis. Two patients died after a second resection for colorectal metastases: one of septic shock from inhalation pneumonia on day 6 and one of hepatocellular failure 13 days after massive perioperative bleeding. One patient died on day 4 of cardiac arrhythmia after resection for hepatocellular carcinoma, and one patient died on day 25 after resection of metastases from gastric cancer because of a rapid progression of previously subclinical lung metastases.

Of the 726 hepatic resections performed, 375 different complications were recorded in 259 hepatic resections (36% of resections had ≥1 complication). For 4 liver resections, the presence or absence of complications was not recorded but there was no mortality. Many complications were noninfectious pulmonary events such as atelectasis or symptomatic pleural effusion, which were transient and often resolved with routine postoperative management (**Table 4**). Most complications were minor (grades I and IIa, 60% of overall complications) (**Table 5**).

To identify variables independently predicting the occurrence of complications and to design and validate a score, all liver resections between January 1, 1991, and December 31, 2004, were allocated to the assessment group (n=487), and liver resections between January 1, 2005, and October 30, 2009, were allocated to the validation group (n=239). The complication prevalence between the 2 periods was similar ($P=.11$, analysis of variance).

A univariate analysis of the correlation between recorded variables and complication occurrence in the assessment period was performed (**Table 6**). All of these variables were further analyzed in a linear regression test.

In the assessment group, red blood cell transfusion, extent of surgery (major or minor), ASA score (1-2 or 3-4), and benign or malignant indication for liver resection independently predicted the risk of complication (**Table 7**). To develop a score that could be used before surgery (ie, when planning the operation), red blood cell transfusion was excluded from this analysis (the other 3 variables were retained). One point was attributed to each variable and the score was calculated by adding the points (**Table 8**).

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Table 4. List of Complications

Complication	No. (%) (n=375)
Infectious[a]	54 (14)
Symptomatic pleural effusion	41 (11)
Slow liver recovery	40 (11)
Sterile abdominal fluid collection	36 (10)
Biliary leakage[b]	30 (8)
Other	30 (8)
Bleeding	21 (6)
Symptomatic atelectasis	15 (4)
Fever of unknown origin	13 (3)
Deep vein thrombosis or pulmonary embolism	12 (3)
Pneumothorax	11 (3)
Urinary retention	10 (3)
Cardiac[c]	9 (2)
Prolonged ileus	9 (2)
Peripheral palsy	9 (2)
Central nervous system impairment	8 (2)
Respiratory failure	6 (2)
Liver failure	6 (2)
Hematologic	5 (1)
Renal failure	4 (1)
Biliary stenosis	2 (0.5)
Pancreatitis	2 (0.5)
Gastroduodenal ulcer	1 (0.3)

[a] All bacterial-mediated complications regardless of the organ (eg, pneumonia, cholangitis, bacterial colitis, abdominal abscesses).
[b] Includes detection of bile in the abdominal drainage requiring imaging and prolonged abdominal drainage.
[c] Ischemic events, rhythmic events, and cardiac failure.

Table 5. Perioperative Morbidity and Mortality[a]

Stage	No. (%)
None	463 (64)
I	78 (11)
IIa	79 (11)
IIb	72 (10)
IIc	19 (3)
III	6 (1)
IV (Mortality)	5 (1)

[a] Classified according to a modified classification described by Clavien et al.[27]

Table 6. Univariate Analysis of Cases Between 1991 and 2004

Variable	Complication, %	Test	*P* Value
Age		*t* test	.30
Sex		χ^2	<.001
Male	43		
Female	26		
ASA score		χ^2	.002
1-2	31		
3-4	51		
Preoperative prothrombin time		*t* test	.02
Preoperative hemoglobin level		*t* test	.29
Type of indication for surgery		χ^2	<.001
Benign	24		
Malignant	39		
Type of liver resection		χ^2	<.001
Minor	25		
Major	45		
Perioperative transfusion of RBCs		*t* test	<.001
Associated procedures independent from liver surgery		χ^2	.51
No	33		
Yes	37		
Pringle maneuver		χ^2	.66
No	33		
Yes	37		
Abdominal fluid drainage		χ^2	<.001
No	23		
Yes	43		

Abbreviations: ASA, American Society of Anesthesiologists; RBCs, red blood cells.

Table 7. Multivariate Analysis of Cases Between 1991 and 2004

Factor	Standardized Beta (95% CI)	*P* Value
Type of liver resection	0.170 (0.075-0.245)	<.001
Type of indication	0.118 (0.028-0.204)	.01
ASA score group	0.114 (0.035-0.274)	.01
Perioperative transfusion of RBCs	0.217 (0.021-0.050)	<.001

Abbreviations: ASA, American Society of Anesthesiologists; CI, confidence interval; RBCs, red blood cells.

Our score correlated with the rate of complications in both the assessment and validation groups. In the assessment group, complications occurred in 15%, 32%, 43%, and 65% for scores of 0, 1, 2, and 3, respectively ($P < .001$). In the validation group, complications occurred in 22%, 33%, 41%, and 58%, respectively ($P < .001$). In addition to correlating with the rate of complications, the score also predicted their severity, as major complications were present in 32%, 36%, 44%, and 46% for scores of 0, 1, 2, and 3, respectively ($P < .001$) (**Figure**).

COMMENT

The aims of the present study were the following: (1) to assess the rate of complications after liver resection using a standardized reporting system in a specialized, low-mortality center where a dedicated team of senior surgeons and anesthetists performed all liver resections and liver transplants; (2) to determine factors associated with the occurrence of complications; and (3) to design a score predicting morbidity.

In the literature, the rate of postoperative complications after liver resections has been reported to be between 20% and 50%.[29-31] One of the difficulties when comparing morbidity is the difference between the definitions of adverse events. In many studies, complications are presented as a list excluding a large number of items[32] or taking only major complications into account. Since 2001, we applied the classification of complications described by Clavien et al[27] in 1992 because of its simplicity and its ability to exhaustively include all adverse events. Minor complications such as pulmonary atelectasis, while

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Table 8. Scoring System[a]

Variable	Point
ASA score	
1-2	0
3-5	1
Type of liver resection	
Minor, <3 segments	0
Major, ≥3 segments	1
Type of indication	
Benign	0
Malignant	1

Abbreviation: ASA, American Society of Anesthesiologists.
[a]The sum of points indicates the patient's score.

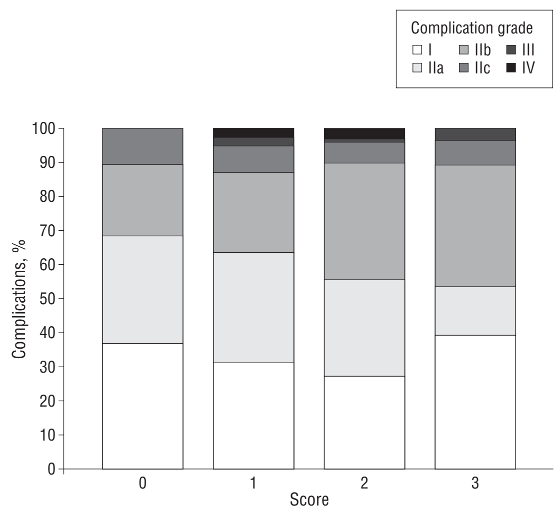

Figure. Severity of complications by score group. When complications were grouped as minor (grades I and IIa) vs major (grades >IIa), the score significantly correlated with the risk of major complications, as major complications were present in 32%, 36%, 44%, and 46% for scores 0, 1, 2, and 3, respectively ($P<.001$).

often not reported in previous works, have their own cost, can increase hospital stay, and can lead to major complications.[33] We therefore took all postoperative adverse events into account. As a matter of fact, the 1992 classification by Clavien et al perfectly fit our objectives and we chose not to update the reporting system to the new 2004 Dindo-Clavien classification.[34] In total, 36% of the procedures were associated with almost 1 complication. Approximately 60% of them were considered minor and could be treated noninvasively.

The mortality rate in the present series was 0.7%, which is lower than the 1% considered standard for resection on normal liver parenchyma in a high-volume center[15] and can be considered low given that 44 patients (6%) had cirrhosis. However, debriefing of these cases showed that even these deaths could have been prevented by more careful operative or postoperative management.

Postoperative liver failure was rare in our series and has become an infrequent event in the era of portal embolization and 2-stage hepatectomy.[13,35] Other factors that may have contributed to the low incidence of liver failure are the systematic discussion—in particular for patients with malignant disease—of the operative strategy in a multidisciplinary team with radiologists, oncologists, and surgeons and the liberal use of liver biopsy and transjugular pressure studies. Only 6 patients had postoperative liver failure in our series (0.8% of all liver resections), of whom 1 patient died.

A large number of studies assessing the risks related to liver resections have been published. Many have included intraoperative parameters such as blood transfusion or blood loss that are associated with postoperative complications.[16,19,20,22,36] While blood transfusion was also associated with postoperative complications in our study, we did not enter this factor in the final calculation of the risk score as the score was intended to predict complications preoperatively. Abdominal drains after the procedure and associated nonhepatic surgery are 2 intraoperative variables that can be predicted in the preoperative period, but they were not significantly associated with postoperative complications. Although the presence of an abdominal drain was strongly associated with the occurrence of complications in the univariate analysis, this association disappeared in the multivariate analysis, probably owing to a bias related to the extent of resection. Our policy is to more liberally drain major hepatic resection, and the correlation between the use of drains and major resections was very high ($P<.001$, χ^2 test).

Of the variables analyzed, we did not include biochemical parameters except for preoperative hemoglobin level and prothrombin time. Increased preoperative levels of bilirubin, albumin, alanine aminotransferase, and creatinine have already been shown to be associated with postoperative complications.[2,22,23] In our study, biochemical parameters were taken into account in the Child-Pugh score (eg, prothrombin time and bilirubin level, which were normal because only Child A patients were considered for hepatectomy) or integrated into the ASA score as a reflection of nutritional status (eg, albumin level).[2] Along the same line, individual comorbidities such as diabetes or cardiovascular disease were taken into account by the ASA score.

Age is no longer considered a contraindication to liver resection[37,38] and was not associated with higher complication rates in our study. A recent multicenter study demonstrated the feasibility of liver resections for colorectal liver metastases in elderly patients, although significantly higher complication rates are observed in older subjects.[39]

Although non–liver-associated surgical procedures significantly correlated with higher morbidity and with a higher need for blood transfusion in other studies,[15,17,22] their presence did not predict complications in our study. Nevertheless, the recommendation in our unit is to avoid a technically demanding hepatectomy associated with moderate- or high-risk surgery such as rectal resection.

Cirrhosis was not associated with complications in our study, but patients were highly selected (only 2 patients were Child B) and the extent of surgery was carefully adapted to the functional reserve. Similar results were found in other series with a similar patient selection, where again cirrhosis was not associated with higher morbidity.[20]

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We reported 3 preoperative variables independently associated with perioperative complications, each reflecting a different preoperative parameter: (1) the ASA score reflected the status of the patient's comorbidities; (2) the indication reflected the type of disease requiring surgery; and (3) the type of liver resection reflected the extent of surgery. All 3 variables are general preoperative parameters, are always available in the preoperative period, and do not need specific measurements. We chose to integrate them in a simple and intuitive score that can be determined at the bedside or in the preoperative outpatient clinic. The result of the score was associated with the occurrence of postoperative complications and their severity. More than one-third of the patients with a score higher than 1 had a postoperative complication requiring an invasive procedure in more than one-third of cases. Patients receiving a major resection for a malignant neoplasm already have at least a score of 2, and even a low ASA score. Patients with a high score are likely to benefit from preoperative conditioning (optimization of nutrition, cessation of smoking, physical exercise, biliary drainage in the case of jaundice, right portal vein embolization if appropriate) and active postoperative management (respiratory physiotherapy and mobilization). Moreover, even if the type of operation and the comorbidities cannot be modified in a given patient, our score may help to estimate the incidence of complications in the discussion for informed consent.

In conclusion, with a dedicated and experienced multidisciplinary unit, mortality rates after liver resection lower than 1% can be obtained; nevertheless, morbidity rates are still high (>30%). The easy identification of patients who are more vulnerable to complications allows for appropriate modifications to improve patients' preoperative clinical conditions before surgery (nutrition, smoking, and physical activity) and, after the safest procedure is performed, to direct efforts against specific morbidities after surgery (pulmonary embolism, atelectasis, etc) by focused protective protocols.

Accepted for Publication: May 9, 2011.
Published Online: July 18, 2011. doi:10.1001/archsurg.2011.175
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Financial Disclosure: None reported.
Funding/Support: Dr Toso was supported by SCORE grant 3232230-126233 from the Swiss National Science Foundation.
Additional Contributions: Seema Toso, MD, corrected the manuscript and Stéphanie Hauss-Meyer helped in data collection.

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