Chapter 2

The Comprehensive Complication Index (CCI)
A Novel Continuous Scale to Measure Surgical Morbidity

Ksenija Slankamenac, Rolf Graf, Jeffrey Barkun, Milo A. Puhan,
Pierre-Alain Clavien

References


ABSTRACT

OBJECTIVE: To develop and validate a comprehensive complication index (CCI) that integrates all events with their respective severity.

BACKGROUND: Reporting of surgical complications is inconsistent and often incomplete. Most studies fail to provide information about the severity of complications, or only inform on the most severe event, ignoring events of lesser severity.

METHODS: We used an established classification of complications, adopting methods from operation-risk-index analysis in marketing research to develop a formula that considers all complications that may occur in a patient. The weights of each grade of complication, defined as median reference values (MRV), were obtained from 472 participants, who rated 30 different complications. Validation to assess sensitivity to treatment effects and validity of the CCI was performed through four different approaches based on 1299 patients.

RESULTS: The CCI is calculated as the sum of all complications that are weighted for their severity (multiplication of the MRVs from patients and physicians). The final formula yields a continuous scale to rank the severity of any combination of complications from 0 to 100 in a single patient. The CCI was highly sensitive in detecting treatment effect differences in the context of a randomized trial (effect size detected by CCI vs. conventional standardized morbidity outcomes). It also showed a negative correlation with postoperative health status ($r = -0.24$, $p = 0.002$), and high correlation with the results of patient-rated single and multiple complications on conjoint analysis ($r = 0.94$, $p < 0.001$).

CONCLUSIONS: The CCI summarizes all postoperative complications and is more sensitive than existing morbidity endpoints. It may serve as a standardized and widely applicable primary endpoint in surgical trials and other interventional fields of medicine. The CCI can be readily computed on the basis of tabulated complications according to the Clavien-Dindo classification (available at www.assessurgery.com).
INTRODUCTION

For many years, mortality has been the sole measure to assess the risk of most surgical procedures. With the dramatic decrease of mortality following major interventions, the focus has shifted towards other endpoints, such as morbidity, quality of life, and cost. Morbidity, as a consequence of complications following a procedure, has emerged as the key parameter to measure harmful outcome for most studies evaluating invasive interventions, especially when efficacy is similar. Unfortunately, the various and unstandardized definitions used to describe complications have led to much confusion in the literature. About 80% of studies describing complications fail to provide any information about their severity. Most authors selectively report only complications judged to be relevant, e.g. those requiring surgical re-exploration, while ignoring any event of lesser magnitude. This “tower of Babel” syndrome has led to a heterogeneous and obvious under-reporting of complications throughout the surgical literature, and has globally hindered surgical research due to a lack of standardized methodology.

In 1992, a categorization of adverse events after a surgical procedure was proposed to differentiate “complications” from “failure to cure” and “sequelae”. Failure to cure referred to the inability to achieve the goal of the operation, such as residual cancer after an attempt at curative resection of a tumor or the recurrence of disease, and sequelae to events inherent to a procedure, such as diabetes after total pancreatectomy. All other negative events were covered under the umbrella “complications”, and their severity was defined according to the degree of invasiveness of the therapy needed to correct the complication. This system was modified after 10 years of routine use in several centers leading to the Clavien-Dindo classification, which describes five grades of severity for most known complications. This system has seen extensive use and been validated in hundreds of studies across many fields of surgery.

For ease of handling, usually only the single most severe complication occurring in a patient during a given episode of care is reported, although a description of all postoperative complications is possible in a tabulated form. It thus “ignores” events of lesser severity, failing to represent the true overall morbidity burden of a procedure. To better report and summarize the overall morbidity following surgery, we conducted a series of studies to develop and validate a novel comprehensive scoring scheme, based on the widely-established Clavien-Dindo classification.

MATERIAL AND METHODS

The study addresses two aims: first, to develop a comprehensive complication index (CCI) taking into account all complications following a procedure and their respective severity and second, to validate this index from four different perspectives. The development of the CCI was based on the adapted Clavien-Dindo classification system (Table 1). The studies were all approved by the local IRB and internationally registered at clinicaltrials.gov (NCT00782704, NCT00516711).
Development of the CCI

Estimation of the relative importance of single complications of the CCI–Development cohort

We obtained data on 30 common post-operative complications, as scored by patients and physicians, which have been reported elsewhere\textsuperscript{22}. The physicians were enrolled from multiple institutions: the Zurich University Hospital and community hospitals in the German speaking part of Switzerland, Germany and Austria\textsuperscript{22}. These included surgeons as well as physicians from closely related disciplines, such as anesthesiology and intensive care units. Patients scheduled for any elective abdominal surgery were enrolled from the Department of Surgery of the Zurich University Hospital, and were tested on the day prior to surgery\textsuperscript{22}. Candidates for organ transplantation and outpatients were excluded.

In brief, 227 patients and 245 physicians rated the severity of 30 individual complications using a numerical analogue scale from 0 (best) to 100 (worst). They received a questionnaire, with appropriate and slightly different phrasing for each population of evaluators, describing the typical manifestation and therapeutic consequences for each of these events\textsuperscript{22}. The 30 scenarios presented the five most frequent and relevant complications within each grade of the Clavien-Dindo score (grade I-IVb), excluding death (grade V)\textsuperscript{22} (see Questionnaire example for patients, Supplemental Digital Content 1, see Questionnaire example for physicians, Supplemental Digital Content 2).

Development of a mathematical formula for the CCI

Whereas the Clavien-Dindo classification is based on an ordinal scale and selects the single most severe complication following a procedure, we postulated that the CCI must incorporate all post-operative complications, while including their relative severity, as reflected by both the perspectives of patients and physicians. We recognized that simply summing up complications by their ascending severity, as described in the Clavien-Dindo classification would give too much weight to the complications with moderate severity (e.g. grade II). This is particularly true with concurrent complications, where adding up moderately severe complications would give an inappropriately high score. To weigh complications with different severities more appropriately, we thus adopted the “operation risk index” approach, which is widely used in economic sciences, and which synthesizes perspectives from different stakeholders\textsuperscript{23-25}. The operation risk index was first developed to predict the general business climate by a number of predictive criteria, such as political stability, corruption, and inflation rate. Briefly, stakeholders ($st$) representing different professional groups in economy were asked for their opinion on different items by appointing a value ($v$) of 0 (bad) to 4 (excellent). The risk index is then calculated stepwise by first multiplying these values for a given item as perceived by each stakeholder $V_{\text{item}(i)} = (V_{st1} \times V_{st2} \ldots \times V_{stn})$. By taking products of these values rather than single values more important items receive more weight than less important values in the summary index that includes the sum of these products ($\sum V_{\text{item}(i)}$)\textsuperscript{23-25}.
As a first step, we used physicians and patients, as different expert populations. The median (ratings are not normally distributed) reference value from physicians (MRVphys) and patients (MRVpat) for each grade of complication were then (see Table, Supplemental Digital Content 3) multiplied (MRVphys*MRVpat) and compared: for example, a grade I complication such as wound infection drained at the bedside (e.g. MRVphys = 15 and MRVpat =20, i.e. 15x20=300) had a much lower weight than a grade IIIb complication such as a reoperation due to a complication (MRVphys = 65 and MRVpat =70, i.e.65x70=4550). In a next step, these figures were summed (∑(MRVphys*MRVpat)) to incorporate all postoperative complications of different severities occurring in an individual patient, giving a “raw” CCI which reflects the totality of the postoperative morbidity experience.

Theoretically, there is no limit for the “raw” CCI, due to the possibility of an “unlimited” number of complications per patient. However, in a cohort of over 1200 patients operated from 2005 to 2008, who underwent major abdominal surgery such as Roux-en-Y gastric bypass surgery, liver, pancreas, small bowel and colon resections, >99% had a “raw” CCI below 40,000. To ease the clinical applicability of the CCI, we tested different transformations (logarithmic, square and third roots) to find a distribution of CCI scores close to a normal distribution and to set the lower CCI limit at 0 and the upper at 100.

Validation of the CCI

The newly developed CCI was validated through four different approaches.

Briefly, in the first validation, we used histograms and interquartile ranges to assess how well the CCI discriminated in 764 patients from Zurich experiencing at least one postoperative complication. This first validation population was composed of patients out of a cost analysis study, a trial examining pharmacological preconditioning in the context of liver resection, and the current CCI development population.

In the second validation study, we focused on the ability of the CCI to detect treatment effects, referred to as “responsiveness”. We re-analyzed data collected from a previously published randomized clinical trial (RCT) in which patients undergoing liver surgery were randomly pre-treated with or without protective volatile anesthetic (sevoflurane). We postulated a priori greater responsiveness for the CCI compared to the endpoints used in the RCT (proportion of patients with a major complication and with any complication according the Clavien-Dindo) because the CCI includes substantially more information (i.e. all complications vs. only single most serious complication). This responsiveness is reflected by the effect size expressing the magnitude of coded complications.

In a third validation we assessed the post-operative health status according to the EuroQol-5D at the day of discharge in 172 patients who had undergone any elective abdominal surgery. We
hypothesized that there would be a statistically significant negative correlation \((p-values \leq 0.05)\) between the CCI and the postoperative health status.

For the fourth validation, we conducted a “conjoint analysis”, another method adopted from economic sciences and increasingly applied in the medical field\(^{31}\). The most frequent use of conjoint analysis is in the market research. A conjoint analysis is testing different attributes (e.g. color or tire dimension of a new car) of a specific product by rating each attribute of a product on a score. Finally, the conjoint analysis is used to determine how people value and favor different attributes.

We assumed that the estimations of post-operative scenarios with multiple complications will positively and highly correlate with the CCI that only considered single complications. We tested whether combining the relative weights, obtained for single complications in our development cohort adequately represent scenarios where multiple complications occurred. Therefore we created another questionnaire where we asked patients undergoing any elective abdominal surgery in Zurich between February and April 2011 about the severity of several different combinations of complications on a numerical analogue scale from 0 to 100. Inclusion criteria were equal to those in the development population. We excluded patients for any transplantation, living donors and one-day-surgery patients. The questionnaire contained 15 self-administered question cards including four scenarios (generalized edema (grade I), intestinal ileus (grade II), anastomotic insufficiency (grade IIIb) and acute renal failure (grade IVa), which describe each of these four complications in isolation, and eleven different scenarios with a combination of up to four simultaneous complications. We calculated the CCI for each of these fifteen scenarios and compared the CCI to the ratings obtained in the conjoint analysis. We postulated that the CCI could adequately combine multiple combinations, if the correlation with the ratings from the conjoint analysis exceeded 0.8 (Pearson correlation coefficient).

**Sample size calculation and statistics**

The sample size calculation for the development cohort was based on a pilot study\(^{12}\). To detect a difference of 5 on the 0-100 scale we calculated that we would need 219 patients and 219 physicians, assuming a standard deviation of 12.5, a power of 80% at a significance level of 0.05, and expected a drop-out rate of 15%.

For the second as well as the third validations we used data collected in previously published studies\(^{22,27}\). Therefore, we did not perform a separate sample size calculation. Sample size calculations for a conjoint analysis (fourth validation) are a topic of controversy\(^{32,33}\). With four attributes (grades of complications), 15 tasks (scenarios) and a 20% drop-out rate we estimated to need a minimum of 72 respondents would be required\(^{33}\). We used means (standard deviation [SD]) to describe CCI data and the Pearson correlation coefficient for correlations. For the re-analysis of the randomized trial we used multivariable linear regression with the CCI as dependent and group allocation as independent variables, with adjustment for potential confounders as reported earlier\(^{27}\). In order to assess the relative responsiveness of the CCI, major complications and any complications to detect a change, we
calculated effect sizes for the effect of preconditioning (Cohen’s effect size for the continuous CCI and logarithm of the odds ratio multiplied by $\sqrt{3/\pi}$ for the dichotomous variables any [yes/no] or major complication [$\leq$ IIIa / $>$IIIa])$^{29}$.

We conducted all analyses using STATA (version 10, Stata Corp., College Station, Texas).

RESULTS

Development of the CCI

Two hundred and forty-five physicians and 227 patients participated in the development cohort, for which detailed characteristics were reported elsewhere$^{22}$. As only one patient of the development cohort had a value of over 40,000 (0.4%, 41,050) (see Figure, Supplemental Digital Content 4a), we further looked at an independent cohort of 1,255 patients undergoing major elective abdominal surgery from 2005-2008. In the latter, again a single patient exhibited a value $>$40,000 (0.08%) (see Figure, Supplemental Digital Content 4b), therefore we arbitrarily set the maximum to 40,000 for the sum of complications, representing $>$99.5% of all patients. Applying the square root of the sum of complications came closest to converting results to a normal distribution. Finally, dividing by two, the scale of the “raw” CCI of 0-40,000 could be transformed in almost all cases to a number between 0 (no complication) and 100 (see Figure, Supplemental Digital Content 5a-c). The final formula for the CCI is therefore: $\text{CCI} = \sqrt{\left( \sum \text{MRV}_{\text{phys}} \times \text{MRV}_{\text{pat.}} \right) / 2}$.

Examples of the CCI

Six patients, who developed a single complication, and five patients, who developed several post-operative complications, are presented to illustrate the clinical application of the CCI (Table 2a&b). For single complications, the CCI ranged from 8.7 to 46.2 (Table 2a, Figure 1a), while these figures ranged from 17.3 to 88.6 in the presence of multiple complications (Table 2b, Figure 1b). The examples show that the CCI weighs severe complications (patient#10: CCI of 56.1) more heavily than several complications of lesser degree (patient 8: CCI of 30.8), whereas multiple mild and severe complications lead to a much greater CCI (patient#11: 88.6) (Table 2b, Figure 1b).

To further demonstrate the consequences of this algorithm, the weight of a single grade I Clavien-Dindo complication is highlighted under different scenarios. If experienced alone, a grade I complication corresponds to a CCI of 8.7 points. However, as part of multiple complications, the relative contribution of a grade I complication decreases with an increasing CCI. For example, for a CCI of 12.2, the second grade I complication adds only 3.5 points. In more complex situations, the loss of contribution of a grade I complication to the CCI is even greater, i.e. for a CCI of 30.8 it is 1.2 and for a CCI of 94.1 it is 0.4 (Figure 2). Thus, a low-grade complication becomes less and less important, when experienced in combination with more severe complications.
Validation of the CCI

In the first validation, Figure 3a shows the distribution of the CCI in 764 patients who developed at least one post-operative complication (see Figure, Supplemental Digital Content 6) and were part of a larger cohort of 1,491 patients undergoing any elective abdominal surgery at the Department of Surgery of Zurich University Hospital from 2005-2008. Figure 3a shows that 205 patients (13.7%) had a CCI between 8.7 and 20, and 28% (418 out of 1491) had a CCI from 20 to 40, the range where most combinations of complications occurred. A CCI over 50 was less frequent (6.4%, 96 out of 1491). One hundred and thirty-two patients (17.3%) with severe complications (≥ grade IIIb) had many additional mild and moderate complications (grade I-IIIa), but their contribution to the CCI is relatively small. For comparison, Figure 3b shows the frequencies of only the highest-grade complication (grade I to IVb), currently the way to report complications in the Clavien-Dindo classification. Comparing these two figures, it is apparent that the CCI better discriminates among patients than the Clavien-Dindo classification.

In a second validation, we tested the responsiveness of the CCI in a recently published RCT, in which patients undergoing liver surgery were randomly pre-treated with protective volatile anesthetic (sevoflurane) (see Figure, Supplemental Digital Content 6). The mean CCI in the sevoflurane group was 10.4 (SD 18.9), vs. 30.5 (SD 25.3) in the control group. The between-group difference was statistically significant (adjusted difference of -22.8 (95% CI: -34.8 to -10.7, p<0.001). The original dichotomous use of “any complication” as primary outcome, an effect size of 0.19 had been recorded and with the Clavien-Dindo classification to measure “major complication alone”, the effect size was 0.33. The re-analysis of the trial using the CCI showed an effect size of 0.41 indicating the greater discriminatory power of the CCI compared to both other endpoints.

In a third validation, we observed that post-operative health status (median 65; IQR 50-75) negatively correlated with the CCI (median 8.7 (IQR 0–23.4); r = -0.24, p=0.002), further supporting the discriminatory value of the CCI (see Table, Supplemental Digital Content 7).

In a fourth validation, we asked patients to evaluate complication scenarios that included one or more different types of complications to assess their perception of a more complex situation. We observed a very high correlation (r=0.94, p<0.001) of the CCI with the ratings from conjoint analysis for the 15 scenarios with single and multiple complications (see Tables, Supplemental Digital Content 8 & 9, and see Figure, Supplemental Digital Content 10). This analysis also confirmed that minor complications would receive less weight, if additional and more severe complications were said to have occurred.

DISCUSSION

In this study, we propose a comprehensive complication index (CCI) that summarizes the entire postoperative experience of the patient with respect to complications. We combined all complications according to their severity in a single score ranging from 0 to 100. Validations from four different
perspectives showed that the CCI discriminates well between patients with a different number and severity of complications, and that the CCI is more responsive to the effects of a specific therapy than other endpoints.\textsuperscript{9, 12} In addition, the validity of the CCI is supported through comparisons with postoperative health status and the results from conjoint analysis that captured the relative and total severities of multiple complications.

The development of the CCI is the result of a lengthy, progressive, and rigorous iterative process. Over the last 20 years, the senior author developed and validated a simple scale of complications, based on the degree of invasiveness of the therapy applied to correct the complication leading to the Clavien-Dindo classification.\textsuperscript{1, 9, 12} The first effort to define and rank negative outcome after surgery goes back to 1992, when the senior author along with Steven Strasberg, at that time both at the University of Toronto, made an attempt to critically evaluate the recently introduced laparoscopic approach to treat gallstone disease.\textsuperscript{1, 34} They proposed new definitions of what constitutes a negative event after a surgical procedure, differentiating complications, from failure to cure and sequelae,\textsuperscript{1, 17} and focus on a simple system to rank complications by severity.\textsuperscript{1, 17} The basis of the score was to measure the degree of invasiveness of the therapy applied to correct the complication, as well as the length of stay. This system including four grades of severity, although used in a few studies, did not really enjoy wide acceptance.\textsuperscript{1, 17} This classification was re-evaluated in 2004 with the development of the Clavien-Dindo classification.\textsuperscript{9} While the degree of invasiveness of the therapy to treat the complication remained the basis of the new system, variables such as the length of stay were eliminated to give more weight to life threatening complications involving organ failure. The new proposal was tested in a large cohort of patients, who underwent a variety of general surgery procedures, and in ten centers around the world for inter-observer variation and applicability.\textsuperscript{9} Difficult scenarios were re-evaluated after five years among seven centers located on each continent to secure consistency in reporting.\textsuperscript{12}

Currently, this system is routinely used in many centers and the literature for quality assessment, included in national databases, and in high quality RCTs.\textsuperscript{18, 19, 35-37} Considering its simplicity and reproducibility,\textsuperscript{9, 12} a number of outcome studies have used this classification system, which focuses on the most severe complication. The various degrees of severity have been shown repeatedly to correlate with perceptions from patients, nurses and physicians,\textsuperscript{12, 22} overall cost of the procedure,\textsuperscript{26} hospital stay\textsuperscript{9} and other pertinent factors.\textsuperscript{9} One limitation, however, is that for ease of numerical analysis, the whole postoperative course is selectively described by the single most severe complication, ignoring others of lesser magnitude, which may still be very pertinent to the patient, health care provider and payer. For example, how can we compare the postoperative course of a patient experiencing four grade II complications vs. another presenting a single grade III event? It is conceivable that the four more benign complications are perceived as being “worse” than the single grade III complication.

In order to correct this drawback, and in the absence of an accepted approach in the medical literature to develop a score such as the CCI, we turned to the techniques of operation risk index and to
conjoint analysis. Those methods are used in economy and marketing\textsuperscript{23-25} to adjust for multiple evaluation factors. We also used two different perspectives, those of physicians and patients, to measure the severity of post-operative complications. In line with the economists, we then developed a mathematical formula that captures the multidimensional nature of postoperative complications with a single number ranging from 0 to 100. This approach, developed in synergy between clinicians and statisticians, leads to an easily interpretable measure of the postoperative course, as illustrated in Table 2 and Figure 1.

Such an index may also offer a more precise tool in clinical trials, databases or registries, and patient experience audits. Unlike the CCI, the Clavien-Dindo classification is based on an ordinal scale which belies underlying graded numerical assumptions and may overly summarize details related to the totality of the patient morbidity burden. On the other hand, in view of its simplicity and categorical nature, the Clavien-Dindo score remains a practical tool to allow clinicians to describe individual patients e.g. at morbidity/mortality (M&M) conferences, or in evaluating the impact of specific types of complications after a procedure\textsuperscript{38}, such as fistulas following pancreatic surgery\textsuperscript{21} or general surgical outcome after laparoscopic prostatectomy\textsuperscript{35}. Because both scoring systems are closely related, their simultaneous recording is recommended for clinical groups. Others have developed a morbidity index based on the National Surgical Quality Improvement Program (NSQIP) to assess specific procedures and their associated aggregate of postoperative complications, but did not focus on an index summarizing all post-operative complications in individual patients\textsuperscript{39,40}

The CCI also allows longitudinal assessment of the morbidity since the addition of a complication appearing at a later time point is now feasible, and may help assess the ‘evolution’ of morbidity over time. This is difficult with the current reporting tools, as either an additional complication has no impact, if it is less than the most severe, or it changes everything, if it is more severe than the complications experienced so far. This aspect is of special relevance considering the current reporting in the surgical literature, which typically focuses on “procedural” or “in-hospital” morbidity, ignoring any longer follow-up. The very nature of the CCI may also allow to better decipher relationships between simultaneously occurring complications because it measures clusters of complications, akin to syndromes rather than individual symptoms. This may be important in certain patient groups so that care may target the interplay of harms rather than a single severe index complication. The CCI, rather than individual morbidity reports, may thus be better suited to evaluate perioperative care in surgical institutions.

Our data suggest that the CCI is highly discriminatory and responsive to treatment effects. As a consequence, clinical trials may be able to more easily detect clinically relevant signals, which could reduce the large number of surgical trials that show “negative results”, some of which may in fact have been meaningful. As many prospective trials begin to use electronic data collection, a module calculating the CCI could easily be incorporated. The CCI may even be incorporated in clinical information systems to serve as a quality control and even benchmarking tool, although for this later
use, risk adjustment must be included for proper interpretation of any CCI values. For those purposes, we created a simple online program (www.assessurgery.com), which can be used to calculate the CCI in individual or various groups of patients. As attractive as the CCI appears, it is still important to report on specific complications and their severities. Thereby, intervention-specific complications can still be analyzed.

Our project is not without limitations. One criticism might be that the assessment of events by individual patients was not based on “actual” complications experienced by them. Our rationale to skip this approach relies on difficulties in interpreting and validating such data. The individual circumstances of a patient make standardizing and comparing postoperative ratings very difficult. Ratings are not only influenced by a patients’ specific postoperative course but by pre-existing health conditions. For example, a severely-ill patient developing organ failure (grade IV) after major surgery may be just happy that he/she is still alive and may, therefore, perceive his/her own complication to be less severe than a patient experiencing a wound infection successfully drained at the bedside (grade II) after a hernia repair. To assure a standardized procedure, a single investigator (KS) approached each patient on the day of admission, i.e. one day before surgery, and spent at least 30 min to explain the rationale of the study and to answer any questions. Patients were given appropriate time and rest for their evaluation.

Another limitation is the inclusion of participants living in German speaking countries only. We included, however, a broad sample of participants from 15 different nationalities, differing in professional background (for physicians), ethnic origin, age and gender (for patients). Nevertheless, another important step forward would be to obtain ratings from additional patients and physicians and procedures including those from other countries and health systems to explore whether the weights used for the CCI need to be calibrated, when moving from one population to another. Even though the CCI is developed on a broad spectrum of patients undergoing a variety of major and minor general surgical procedures, it might be worthwhile to test the CCI in other specialized fields such as cardiac surgery, gynecology and neurosurgery.

In conclusion, the availability of a CCI may bring major changes in both the manner and the accuracy, in which we assess surgical or other interventional procedures. In the future, CCI and mortality could be part of standardized outcome reports at hospital discharge and, for example, three months after surgery, along with the use of the Clavien-Dindo system at M&M conferences (www.assessurgery.com). The CCI may become the urgently needed outcome tool to longitudinally measure morbidity associated with invasive procedures and serve as an objective primary or secondary endpoint in more optimally and clinically significantly powered clinical trials.
Table 1: Clavien-Dindo classification adapted from^9

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I</td>
<td>Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions. Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside.</td>
</tr>
<tr>
<td>Grade II</td>
<td>Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.</td>
</tr>
<tr>
<td>Grade III</td>
<td>Requiring surgical, endoscopic or radiological intervention.</td>
</tr>
<tr>
<td>IIIa</td>
<td>Intervention not under general anesthesia.</td>
</tr>
<tr>
<td>IIIb</td>
<td>Intervention under general anesthesia.</td>
</tr>
<tr>
<td>Grade IV</td>
<td>Life-threatening complication (including CNS complications)* requiring IC/ICU management.</td>
</tr>
<tr>
<td>IVa</td>
<td>Single organ dysfunction (including dialysis).</td>
</tr>
<tr>
<td>IVb</td>
<td>Multiorgan dysfunction.</td>
</tr>
<tr>
<td>Grade V</td>
<td>Death of a patient.</td>
</tr>
</tbody>
</table>

*Brain hemorrhage, ischemic stroke, subarachnoid bleeding, but excluding transient ischemic attacks. CNS = central nervous system; IC = intermediate care; ICU = intensive care unit.
### Table 2a: Six examples of the CCI in case of single complications

<table>
<thead>
<tr>
<th>Patient</th>
<th>Complications</th>
<th>Grade of complication</th>
<th>Weights: (MRVphys x MRVpat)</th>
<th>Comprehensive complication index (CCI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>nausea &amp; vomiting</td>
<td>I</td>
<td>300 (15 x 20)</td>
<td>8.7</td>
</tr>
<tr>
<td>Patient 2</td>
<td>pneumonia</td>
<td>II</td>
<td>1750 (35 x 50)</td>
<td>20.9</td>
</tr>
<tr>
<td>Patient 3</td>
<td>pneumothorax</td>
<td>IIIa</td>
<td>2750 (50 x 55)</td>
<td>26.2</td>
</tr>
<tr>
<td>Patient 4</td>
<td>fascia dehiscence</td>
<td>IIIb</td>
<td>4550 (65 x 70)</td>
<td>33.7</td>
</tr>
<tr>
<td>Patient 5</td>
<td>acute renal failure</td>
<td>IVa</td>
<td>7200 (80 x 90)</td>
<td>42.4</td>
</tr>
<tr>
<td>Patient 6</td>
<td>anastomotic insufficiency</td>
<td>IVb</td>
<td>8550 (90 x 95)</td>
<td>46.2</td>
</tr>
</tbody>
</table>

**MRVphys** = median reference value of physicians; **MRVpat** = median reference value of patients

### Table 2b: Five examples of the CCI in case of multiple complications

<table>
<thead>
<tr>
<th>Patient</th>
<th>Complications</th>
<th>Grades of complications</th>
<th>Weights: (MRVphys x MRVpat)</th>
<th>Comprehensive complication index (CCI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 7</td>
<td>pain exacerbation</td>
<td>I</td>
<td>300</td>
<td>17.3</td>
</tr>
<tr>
<td></td>
<td>nausea &amp; vomiting</td>
<td>I</td>
<td>300</td>
<td></td>
</tr>
<tr>
<td></td>
<td>hematoma</td>
<td>I</td>
<td>300</td>
<td></td>
</tr>
<tr>
<td></td>
<td>generalized oedema</td>
<td>I</td>
<td>300</td>
<td></td>
</tr>
<tr>
<td>Patient 8</td>
<td>nausea &amp; vomiting</td>
<td>I</td>
<td>300</td>
<td>30.8</td>
</tr>
<tr>
<td></td>
<td>pneumonia</td>
<td>II</td>
<td>1750</td>
<td></td>
</tr>
<tr>
<td></td>
<td>urinary tract infection</td>
<td>II</td>
<td>1750</td>
<td></td>
</tr>
<tr>
<td>Patient 9</td>
<td>wound infection</td>
<td>I</td>
<td>300</td>
<td>40.5</td>
</tr>
<tr>
<td></td>
<td>urinary tract infection</td>
<td>II</td>
<td>1750</td>
<td></td>
</tr>
<tr>
<td></td>
<td>gastric ulcer</td>
<td>II</td>
<td>1750</td>
<td></td>
</tr>
<tr>
<td></td>
<td>pneumothorax</td>
<td>IIIa</td>
<td>2750</td>
<td></td>
</tr>
<tr>
<td>Patient 10</td>
<td>pneumonia</td>
<td>II</td>
<td>1750</td>
<td>56.1</td>
</tr>
<tr>
<td></td>
<td>arterial hypertension</td>
<td>II</td>
<td>1750</td>
<td></td>
</tr>
<tr>
<td></td>
<td>anastomotic insufficiency</td>
<td>IIIb</td>
<td>4550</td>
<td></td>
</tr>
<tr>
<td></td>
<td>gastric ulcer perforation</td>
<td>IIIb</td>
<td>4550</td>
<td></td>
</tr>
<tr>
<td>Patient 11</td>
<td>wound infection</td>
<td>I</td>
<td>300</td>
<td>88.6</td>
</tr>
<tr>
<td></td>
<td>urinary tract infection</td>
<td>II</td>
<td>1750</td>
<td></td>
</tr>
<tr>
<td></td>
<td>deep venous thrombosis</td>
<td>II</td>
<td>1750</td>
<td></td>
</tr>
<tr>
<td></td>
<td>gastric ulcer bleeding</td>
<td>IIIa</td>
<td>2750</td>
<td></td>
</tr>
<tr>
<td></td>
<td>pleura empyema</td>
<td>IIIb</td>
<td>4550</td>
<td></td>
</tr>
<tr>
<td></td>
<td>anastomotic insufficiency</td>
<td>IIIb</td>
<td>4550</td>
<td></td>
</tr>
<tr>
<td></td>
<td>stroke</td>
<td>IVa</td>
<td>7200</td>
<td></td>
</tr>
<tr>
<td></td>
<td>central line infection with septic</td>
<td>IVb</td>
<td>8550</td>
<td></td>
</tr>
<tr>
<td></td>
<td>shock</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**MRVphys** = median reference value of physicians; **MRVpat** = median reference value of patients; *Death is arbitrarily defined with a CCI of 100*

**Example of the CCI calculated for patient 9:** 
\[
\text{CCI} = \sqrt{\frac{300 + 1750 + 1750 + 2750}{2}} = 40.5
\]
Figure 1a: The CCI of a single complication. The first six patients developed one single complication from grade I to grade IVb according to the Clavien-Dindo classification (Table 2a). The CCI of these single complications increases from grade I (CCI=8.7) to grade IVb (CCI=46.2).

Figure 1b: These five patients (patient #7 to patient #11) developed multiple post-operative complications (Table 2b). The CCIs ranged from 17.3 to 88.6 in the presence of multiple complications. The CCI increases with the occurrence of an additional postoperative complication. The increase of the CCI depends on the severity of the additional complication. For example, patient #9 developed one grade I (wound infection), two grade II (urinary tract infection, gastric ulcer) and one grade IIIa (pneumothorax) complication and his CCI is still lower (CCI_{pat9}=40.5) than one grade IVa (CCI_{grade IVa}=42.4) or one grade IVb (CCI_{grade IVb}=46.2) complication (Table 2a & 2b). Whereas the CCI of patient #11 almost reaches the maximum (CCI_{pat11}=88.6) due to the development of mild as well as multiple severe complications (Table 2b).
Figure 2: Weight of a grade I complication in combination with more severe complications. If experienced in isolation a grade I complication corresponds to CCI of 8.7 points. When associated with multiple complications, the contribution of this grade I complication to the CCI decreases accordingly. For a CCI of 12.2 due to other complications, the second grade I complication weighs only 3.5 points. In more complex situations, the loss is even higher e.g. for a CCI of 30.8, it is 1.2, for a CCI 94.1 it is 0.4. Thus, a low-grade complication is less important, if experienced in combination with more severe complications.
Figure 3: Distribution of the CCI and the highest grade of complications in an independent patient population. 3a: frequency of patients relative to their CCI. Patients were grouped in increments of 3 points. 3b: frequency of patients with various complication grades. The highest grade for a given patient was used.