Complications in abdominal surgery: Assessment, prediction and prevention
Slankamenac, Ksenija

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
INTRODUCTION

This thesis describes the results of clinical research on the assessment, prediction and prevention of postoperative complications in abdominal surgery. It reports on a connected series of studies that aim at improving clinical practice through evidence-based instruments for evaluating postoperative complications and for identifying patients at high risk for complications, and through measures to reduce the risk of specific complications.

Almost 20 years ago, Richard Horton wrote about some deficiencies in most surgical studies, which could be attributed to poor methodology, including the lack of standardized outcome measures. These shortcomings were also identified by an interdisciplinary group of surgeons, epidemiologists, and statisticians, the so-called “Balliol group”, who disclosed a variety of issues related to the assessment of surgery in a series of three Lancet articles. This group indicated that the most significant shortcoming in surgical research was the lack of consensus about the preferred outcome measure and how to assess it. Reliable outcome reporting is important to assess and compare quality in surgery. Although there is a wide range of outcome measures used in medical published literature, there is currently no standardized definition which data should be collected for quality assessment.

The only endpoint consistently used in surgery is mortality. Mortality could probably be considered a reasonable marker a few decades ago, when there was still substantial risk of dying following many surgical procedures. Today, however, mortality is low even following most major procedures so that, the focus of outcome measurement has turned to postoperative complications and/or morbidity to assess surgical quality and outcome. But an unresolved issue is the absence of a standardized definition and assessment of postoperative complications. For example, a systematic review, published in 2001, found more than 40 different definitions of anastomotic leaks used in 107 studies. Terms such as major, severe or minor complications were used in an inconsistent manner, often even without any definition.

Concerned about these shortcomings, Clavien and Strasberg published a new definition for postoperative negative outcome in 1992. They proposed a grading system for complications based on the invasiveness and the resources associated with therapy needed to treat the complications. In 2004, a revised version of this system was put forward. This was based on the same principle, but eliminated a few more arbitrary criteria, such as length of stay. This so-called Clavien-Dindo classification classifies postoperative complications as grade I to grade V, according to the need for treatment (see Table 1). The applicability, simplicity and inter-observer variability of this revised classification system was concomitantly validated in a large cohort. The Clavien-Dindo classification is now widely adopted and used in the non-cardiac surgery, transplantation, urology and gynecology literature.
### Table 1: Clavien-Dindo classification

<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></td>
</tr>
<tr>
<td>IIIa</td>
<td>Requiring surgical, endoscopic or radiological intervention. Intervention not under general anesthesia.</td>
</tr>
<tr>
<td>IIIb</td>
<td>Intervention under general anesthesia.</td>
</tr>
<tr>
<td>Grade IV</td>
<td></td>
</tr>
<tr>
<td>IVa</td>
<td>Life-threatening complication (including CNS complications)* requiring IC/ICU management.</td>
</tr>
<tr>
<td>IVb</td>
<td>Single organ dysfunction (including dialysis).</td>
</tr>
<tr>
<td></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.

Complications following abdominal surgery are relatively frequent\(^{17}\). They are associated with mortality and costs\(^{18}\). The incidence of post-operative complications differs widely between subspecialties of abdominal surgery, whereas mortality is low and differs only slightly\(^{18}\). Furthermore, 47.5% of the patients develop more than one complication following a surgery\(^{18}\). Even though the Clavien-Dindo classification was presented as a possible reference standard by the Balliol group\(^{2-4}\), the system does not contain an overall evaluation of the outcome of a surgical procedure. Often, only the most severe complications are presented\(^{16}\).

To overcome these shortcomings, we performed a series of studies (Chapter one and two) to improve the assessment and reporting of postoperative complications and offer a standardized overall outcome for future surgical studies.

Chapter one of this thesis reports on a prospectively planned cross-sectional survey presenting the perceptions of surgical complications among patients, nurses and physicians\(^{19}\). In this study we investigated whether or not the widely established Clavien-Dindo classification system truly reflects the severity of postoperative complications by assessing the perception of complications by patients, practicing nurses and physicians\(^{19}\). We assumed that if the Clavien-Dindo classification system did not reflect the perceptions of complication neither of physicians, nurses nor patients, this grading system
would not be a useful system to assess the overall morbidity following any surgical intervention even if it is widely adopted.

Based on the results of this validation of the Clavien-Dindo classification system in chapter one, **Chapter two** describes the development and validation of a comprehensive complication index, one that aggregates all post-operative complications of an individual patient as well as their different severities into one single number\(^{20}\). Such a comprehensive complication index could become the urgently needed overall outcome measure for postoperative morbidity.

Not all patients have the same risk of post-operative complications. Identification of predictors and the development of prediction scores may help, with effective preventive measures, to reduce the risk for post-operative complications\(^{21, 22}\). A prediction score for multiple post-operative complications is probably too complex to build, and multiple predictions for specific post-operative complications could be considered. Therefore, we focused in this thesis on acute renal failure (ARF) as a potentially life-threatening outcome following liver resections and developed two prediction scores (Chapter three and four) to predict ARF.

The aim was to develop and validate simple and readily applicable prediction scores, based on pre- (Chapter three) as well as intra-operative parameters (Chapter four), in order to calculate the risk of postoperative ARF in patients undergoing a liver resection\(^{23, 24}\). The use of these two prediction scores may allow an early identification of patients at high risk of ARF, and support protective kidney treatments peri-operatively. Prediction scores can support the decision making process of patients and physicians. They may help to inform patients about different treatment strategies, avoiding undertreatment in some and over-treatment in others. By analyzing the clinical consequences of using prediction scores one can evaluate the clinical usefulness of such prediction scores\(^{25-28}\). Such an analysis of consequences goes beyond the traditional evaluation of the discrimination and calibration of a prediction model\(^{25}\).

Preventive measures need to be further developed. The design of a double-blinded randomized controlled trial is described in **Chapter five**, that will investigate for the first time if terlipressin improves the renal outcome in patients at moderate to high risk for ARF after liver surgery. Patients will be identified to be at moderate or high risk for ARF according to our prediction score developed in chapter three and randomized into the control or terlipressin arm. The hypothesis is that terlipressin reduces the incidence of ARF following liver resection in patients at moderate to high risk for ARF. We will restrict the trial to patients with a moderate or high risk for ARF because terlipressin, which is associated with potential harm, is unlikely to provide more benefit than harm in patients at low risk. We provide, as an innovative element of a clinical trial protocol, a quantitative benefit harm assessment in chapter five that shows above what threshold terlipressin may be more beneficial than harmful if a renal-protective effect exists at all.

In **Chapter six**, another potentially preventive treatment was investigated with the goal to improve the surgical outcome following liver surgery. This chapter presents a retrospective study that assessed
whether or not pharmacological conditioning with sevoflurane can protect the remnant liver from ischemia-reperfusion injury compared to intravenous anesthesia with propofol\textsuperscript{29}. It is known that pharmacological preconditioning with volatile anesthetics is an easily applicable non-invasive method to protect the remnant liver from ischemia-reperfusion injury\textsuperscript{30}. But the timing of the preconditioning procedure might be difficult and therefore an alternative could be the use of continuous volatile anesthetics throughout the surgical procedure.

We summarize our findings and present perspectives for future research and clinical practice in Chapter seven.

References