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Number of comorbidities and their impact on perioperative outcome and costs – a single centre cohort study

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Summary

AIMS OF THE STUDY: Multimorbidity is a growing global health problem, resulting in an increased perioperative risk for surgical patients. Data on both the prevalence of multimorbidity and its impact on perioperative outcome are limited. The American Society of Anesthesiologists (ASA) classification uses only the single most severe systemic disease to define the ASA class and ignores multimorbidity. This study aimed to assess the number and type of all anaesthesia-relevant comorbidities and to analyse their impact on outcome and hospital costs.

METHODS: This cohort study is nested in the ClassIntra® validation study and includes only patients enrolled at the University Hospital of Basel. Approximately 30 patients per surgical discipline undergoing any type of in-hospital surgery were followed up until hospital discharge to record all intra- and postoperative adverse events. In addition, the type and severity of all perioperatively relevant comorbidities were extracted from the electronic medical record according to a predefined list. The primary endpoint was the number of all anaesthesia-relevant comorbidities by ASA class. Using structural equation models, the direct and indirect effects of comorbidities on costs were estimated after adjustment for the ASA class and further relevant confounders and mediators.

RESULTS: Of 320 enrolled patients, 27 were ASA I (8%), 150 ASA II (47%), 116 ASA III (36%) and 27 ASA IV (8%). The median number of comorbidities per patient was 5 (range 0–18), this number significantly increasing with higher ASA class: 1 comorbidity (95% CI 0.0–2.0) in ASA I, 4 comorbidities (3.8–4.2) in ASA II, 9 (8.1–9.9) in ASA III and 12 (10–14) in ASA IV patients. Independent of ASA class, each additional comorbidity increased hospital costs by EUR 1,198 (95% CI 288–2108) with almost identical proportions of direct and indirect effects. The number of anaesthesia-relevant comorbidities also increased postoperative complications and postoperative length of hospital stay.

CONCLUSIONS: Multimorbidity in perioperative patients is highly prevalent and has a relevant impact on hospital costs, independent of the ASA class. Incorporating multimorbidity into the ASA classification might be warranted to improve its predictive ability and support adequate reimbursement.

The ClassIntra® validation study had been registered on ClinicalTrials.gov (NCT03009929).

Introduction

Multimorbidity is a global health problem in our aging society. It is magnified by lifestyle factors such as obesity, urbanisation, socioeconomic deprivation [1] and the resulting increase in non-communicable diseases. At the same time, the baseline risk status and the resulting complexity of patients undergoing surgical procedures has increased over recent decades [2]. According to a report from Canada [3], over one quarter of total inpatient acute care costs is associated with multimorbid patients, and healthcare costs are rising faster than the gross domestic product (GDP) [4]. This creates pressure to reduce healthcare costs as well as a need for efficient resource allocation.

Risk assessment and personalised management of multimorbid patients are becoming fundamental to assure optimal outcomes, thus lowering healthcare costs. One of these tools is the American Society of Anesthesiologists (ASA) classification [5], which was developed over 60 years ago. Despite several modifications, the ASA classification uses only the single most severe systemic disease to define the

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ASA class and ignores multimorbidity. The ASA classification has shown a strong association with perioperative mortality and morbidity [2, 6]. Furthermore, it is a strong predictor of surgical adverse events [7] and prolonged hospital intensive care unit (ICU) stay [8]. These perioperative outcomes are important drivers of higher costs [9, 10] and lower reimbursement [11]. Hence, the ASA classification plays a central role in perioperative risk assessment and is associated with healthcare costs of a surgical procedure. Given the far-reaching influence of the ASA classification [12], explicit consideration of multimorbidity may become essential.

Data on both the prevalence of multimorbidity and its impact on outcome and costs in the perioperative patient population are limited. This warrants an in-depth analysis of the costs and reimbursement in the perioperative patient population taking into account multimorbidity. Therefore, this study aimed to assess the number and severity of all anaesthesia-relevant comorbidities and analyse their direct and indirect effects on perioperative outcome and hospital costs in a predetermined perioperative patient population.

Methods

Ethics

The regional ethics committee Ethikkommission Nordwest- und Zentralschweiz (EKNZ, Basel, Switzerland) approved this study (reference No Req-2019-00753 and Req-2016-00469) and waived the requirement for a written informed consent.

Selection of participants

This investigator-initiated cohort study is nested in the prospective international multicentre study for the external validation of ClassIntra® [13] and includes only patients enrolled at the University Hospital of Basel. Details about the validation study of ClassIntra® , a newly developed classification of intraoperative adverse events, are described elsewhere [13]. In short, 2520 hospital inpatients undergoing any type of in-hospital surgery from any surgical discipline were included at 18 centres located in 12 countries. Patients with outpatient surgery, follow-up procedures or procedures without involvement of anaesthesia, and patients who refused to participate or had an ASA VI status (i.e., brain dead organ donor) were excluded. Patients were monitored intra- and postoperatively until hospital discharge for all perioperative adverse events. Afterwards, patients were followed up to assess 30-day mortality.

At the University Hospital of Basel, a consecutive sample of approximately 30 patients from each of the 13 surgical disciplines was enrolled in the ClassIntra® validation study between February 2017 and May 2018, to achieve a high generalisability. For the current research questions, all anaesthesia-relevant comorbidities as well as data on costs and reimbursement were retrieved from the electronic anaesthesia protocol and the electronic medical record, and entered into the online study database, making use of pseudonymisation to allow for reversal of the coded database using the unique patient-case identifiers.

Anaesthesia-relevant comorbidities

Initially, a list of all anaesthesia-relevant comorbidities was developed by a group of anaesthesiologists and anaesthesia trainees. This includes all comorbidities with an influence on intraoperative anaesthesia management and postoperative outcome. All of these comorbidities are routinely recorded by the anaesthesiologist before surgery. Each comorbidity was divided into five severity-classes and assigned to an appropriate ASA class (supplementary table 1 in the appendix). Whenever possible, this grading was based on official cut-offs, current definitions or on the examples detailed by the ASA [12]. If no such cut-offs were found, the extent of disease was graded according the generic definition of the ASA classification [5]. In cases of doubt, the grading was based on a consensus decision of a team of anaesthesiologists from the University Hospital of Basel with extensive expertise in perioperative care. Multimorbidity was defined as the presence of two or more comorbidities in a patient [1].

Missing data

ECG and laboratory testing were only performed according to preoperative guidelines. We assumed that the patient was healthy (ASA I) if no ECG or laboratory testing was available. We proceeded analogously with missing information on tobacco or other drug use.

Financial data

Costs were calculated based on a comprehensive accounting algorithm used by Swiss hospitals to internally compute provider costs associated with outpatient and inpatient visits (REKOLE®). Costs included imaging, laboratory tests, medical and treatment services, pharmaceutical products, nursing care, intensive care services, surgical procedures and operating room charges. Reimbursement was calculated before taxes as the difference between overall inpatient Diagnosis-Related Group revenues (Swiss DRG) and costs of the index hospitalisation. Swiss-DRG is a flat-fee based remuneration system for acute hospital care. Hospital cases grouped into the same DRG (based on ICD-10 diagnoses, procedures performed, age and some other criteria) receive identical remuneration as long as the length of stay falls in a typical range. Lengths of stay below or above this range lead to a lower or moderately higher remuneration. The remuneration for a given index hospitalisation also includes any hospitalisations during the immediate postoperative period (18 days) due to surgical complications. There are additional revenues for semi-privately and privately insured patients [14, 15].

Financial data were expressed in Euros using the average exchange rate of the recruitment period between February 2017 and May 2018 (1 Swiss franc = 0.8802 Euros).

Outcomes

The primary endpoint was the number of comorbidities relevant for the ASA (physical status) PS classification across all ASA classes. Secondary endpoints were the effect of ASA class and number of comorbidities on hospital costs and reimbursement.

Sample size

The sample size of the ClassIntra® validation study was 2520, allowing for robust estimation in the multivariable models, assuming at least one postoperative complication in 10% of the patients (i.e., at least 250 events) [13]. The sample of the current study consisted of all patients enrolled at the University Hospital of Basel, for whom we had access to all hospital charts and monetary data. About 30 consecutive patients from each surgical discipline were enrolled.

Statistical analysis

Baseline characteristics were summarised as mean and standard deviation (SD), median and interquartile range (IQR), or absolute (relative) frequencies as appropriate.

To investigate whether the number of comorbidities, our primary endpoint, increased with increasing ASA class, a median regression analysis with bootstrapped standard errors was used. The overall agreement between the preoperative ASA class assignment by the anaesthesiologist in charge (overall ASA PS class) and the retrospectively derived ASA class of the most severe comorbidity as assigned by the study team was calculated.

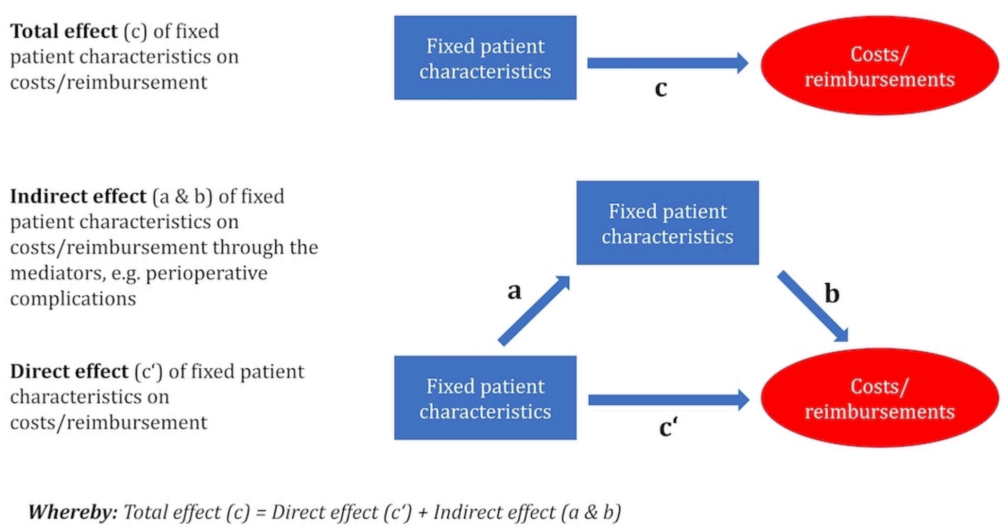
We further used structural equation models [16, 17] to estimate the effects of fixed patient characteristics and hospitalisation-related parameters on total hospital costs and reimbursements incurred by the hospital (fig. 1).

The perspective of cost assessment was, hence, that of the hospital, implying a restriction to the relevant subset of direct medical costs. These costs were not differentiated further (i.e., not separated into fixed and variable costs). However, the structural equation model allowed us to analyse complex relationships among multiple variables, where some variables are only predictors (exogenous variables) and others are only outcomes, and the remaining variables, referred to as intermediate variables, are both predictors and outcomes. These relationships may be direct or indirect (i.e., mediated by an intermediate variable; fig. 2), which we referred to as direct and indirect effects on costs. Structural equation modelling enables quantification of both the direct and mediated proportions of the total effect of a predictor variable on an outcome.

Patient characteristics were considered as exogenous variables and hospital costs or reimbursements as final outcomes, whereas hospitalisation-related parameters were considered as both: as potential mediators of causal effects and as sources of causal effects in their own right. Baseline characteristics included age, gender, ASA class, number of comorbidities, insurance class of the patients and complexity of the surgical procedure according to the British United Provident Association (BUPA) [18, 19]. This classification categorises all commonly performed surgical procedures into five complexity grades (minor, intermediate, major, major plus, and complex major operations) and has previously been used for scientific purposes [20]. When an undefined or missing complexity grade in the BUPA classification system (in n = 24, 7.5% of procedures) was found, a grade corresponding to a similar procedure was used, as defined by consensus of the core team and clinical experts in the field. There were no other missing values in any of the data. Hospitalisation-related parameters included intraoperative adverse events categorised according to ClassIntra® [13], the comprehensive complication index (CCI®) [21] as the weighted sum of all postoperative adverse events, length of ICU stay and length of hospital stay in days. For the latter, days on the ICU were excluded. All of these factors used in the structural equation model were prespecified and selected based on content and expert knowledge.

Analyses were conducted both for original and log-transformed monetary data. In the latter case, lengths of ICU and hospital stay were transformed using the function

Figure 1: Direct, indirect and total effects on monetary outcomes as calculated using structural equation models. The total effect (c) corresponds to the sum of the direct effects (c') and the indirect effects (a and b).



log(x+0.04). The choice of the constant c = 0.04 was a compromise between keeping as close as possible to the classical logarithmic transformation log(LOS_ICU), which would have led to the loss of patients without an ICU stay, and achieving a close to linear relationship between log(cost) and log(LOS_ICU+c). The variable ASA class was represented by indicator variables for each ASA class from I to IV, and complexity of the surgical procedure according to BUPA was replaced by a dichotomous variable with values 0 for complexity grades of "minor" to "major" and 1 for "major plus" and "complex major" operations. Final analyses were conducted without the variables gender, age and indirect effects of insurance class, as these variables did not improve goodness-of-fit. To adjust for potential heteroscedasticity of outcomes, robust standard errors were computed using the sandwich estimator. Although our analyses also provided estimates of direct, indirect and total effects on intermediate outcomes, we only report indirect, direct and total effects on the final outcomes. Complete model outputs are, however, provided in the supplementary tables 2 and 3 (appendix) for both costs and reimbursements. We conducted all analyses using Stata software, Version 16.

Sensitivity analyses

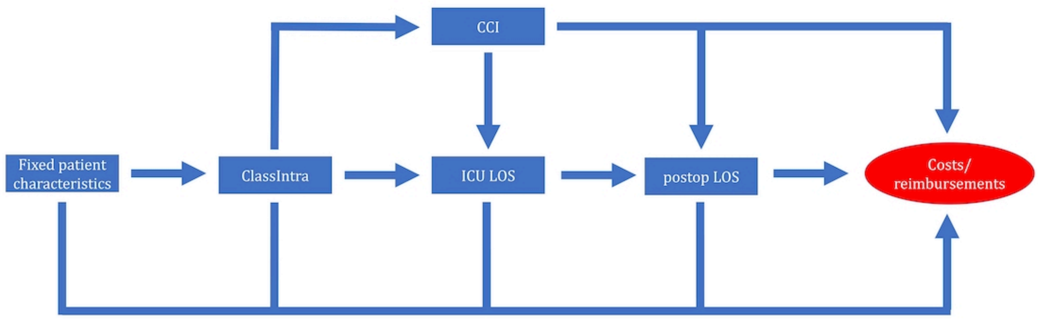
Five patients returned to the hospital within 18 days for the same diagnosis. In such cases, a single DRG was generated and was assigned to the readmission. These patients were excluded from the main analysis of monetary data and were only considered in a sensitivity analysis (supplementarytables 4 and 5). An additional five patients were outliers with a protracted postoperative length of hospital stay of over 40 days (n = 2) or an ICU stay of over 10 days (n = 3). These five patients were included in the models with log-transformed outcomes (supplementary tables 6 and 7) but were excluded in the linear regression models with untransformed monetary outcome variables (supplementary tables 8 and 9), as their inclusion would have introduced a non-linear pattern. Two patients died during the hospital stay and were excluded in the main analysis (see table 3) as reimbursement is different in this case, but they were included in a further sensitivity analysis (supplementary tables 10 and 11). An additional sensitivity analysis was performed excluding semi-privately and privately insured patients (supplementary tables 12 and 13).

Results

Baseline characteristics

At the University Hospital of Basel, 320 patients were enrolled in the ClassIntra® cohort study between February 2017 and May 2018 and were considered in the current study. There were approximately 30 patients for each of the 13 surgical disciplines. All patients could be followed up-until hospital discharge. Patients were on average 56 years old (SD 19), and 54% were women (n = 174). Patients were classified according to ASA PS as follows: 27 ASA I (8%), 150 ASA II (47%), 116 ASA III (36%) and 27 ASA IV (8%) patients (table 1). Overall agreement between preoperative assignment of ASA class by the anaesthesiologist in charge compared to the most severe ASA class, as derived from the assignment within the current data extraction, was 69% (n = 217). In cases of disagreement, the majority of patients were classified in a lower ASA class by the anaesthesiologist in charge (in 79/103 patients by one ASA class, in 1/103 patients by two ASA classes), whereas 22% (n = 23) were classified one ASA class higher. Patients had a median length of hospital stay of 4 days (IQR 2–6).

Figure 2: Path diagram for the relationship of cost-driving factors. This diagram reflects how potential cost-driving factors were included in the structural equation models. CCI: comprehensive complication index; LOS: length of stay



Number of comorbidities

On average, the patients had five comorbidities (range 0–18) with a significantly higher number of comorbidities with increasing ASA class. The median number of comorbidities was 1 in ASA I patients (95% CI 0.0–2.0; range 0–4), 4 in ASA II patients (95% CI 3.8–4.2; range 1–12), 9 in ASA III patients (95% CI 8.1–9.9; range 1-17), and 12 in ASA IV patients (95% CI 10–14; range 5–18) (fig. 3, table 2).

The most common comorbidities were risk of aspiration (n = 151), hypertension (n = 132), renal pathology (n = 125), neurological deficit (n = 113), smoking (n = 113), anaemia (n = 105) and allergies (n = 103). Among all ASA classes, the most commonly observed comorbidity clusters were cardiovascular (n = 177, 55%), neurological (n = 150, 47%) and liver or kidney (n = 150, 47%) disorders (table 2). The distribution of the severity of all comorbidities is shown in fig. 4.

Figure 3: Median number (95% confidence interval [CI]) of comorbidities in relation to the ASA class. Boxplots show average number (IQR and range) of all anaesthesia-relevant comorbidities in each patient (regardless of severity) across all ASA classes. The confidence intervals are estimated in a median regression model using bootstrapped standard errors.

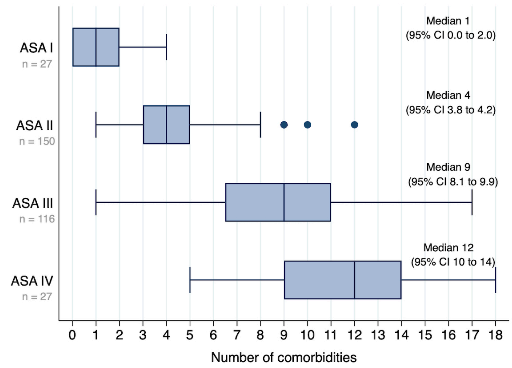


Table 1:
Patient and procedural characteristics for the total study population (n = 320) and for the different ASA PS classes
Quantitative variables are reported as mean (SD), quantitative as number (percentage).

		All patients (n = 320)	ASA I (n = 27, 8.4%)	ASA II (n = 150, 47%)	ASA III (n = 116, 36%)	ASA IV (n = 27, 8.4%)
Age		56 (19)	36 (15)	49 (17)	65 (15)	70 (13)
Sex	Female	174 (54%)	14 (52%)	90 (60%)	60 (52%)	10 (37%)
	Male	146 (46%)	13 (48%)	60 (40%)	56 (48%)	17 (63%)
Body mass index (kg/m ^{2})		26.9 (5.6)	25.4 (3.5)	26.4 (4.6)	27.9 (6.1)	26.6 (8.3)
Surgical discipline	Visceral surgery	30 (9.4%)	3 (11%)	11 (7.3%)	12 (10%)	4 (15%)
	Orthopaedic surgery and traumatology	24 (7.5%)	3 (11%)	13 (8.7%)	8 (6.9%)	–
	Vascular surgery	18 (5.6%)	--	1 (0.7%)	15 (13%)	2 (7.4%)
	Urology	28 (8.8%)	2 (7.4%)	13 (8.7%)	13 (11%)	–
	Ear, nose, throat and maxillofacial surgery	57 (18%)	14 (52%)	29 (19%)	13 (11%)	1 (3.7%)
	Neurosurgery and spine surgery	62 (19%)	–	32 (21%)	27 (23%)	3 (11%)
	Cardiac surgery	28 (8.8%)	–	–	13 (11%)	15 (56%)
	Gynaecology	30 (9.4%)	4 (15%)	19 (13%)	6 (5.2%)	1 (3.7%)
	Obstetrics	30 (9.4%)	--	26 (17%)	4 (3.5%)	–
	Reconstructive and hand surgery	13 (4.1%)	1 (3.7%)	6 (4.0%)	5 (4.3%)	1 (3.7%)
Urgency of the procedure	Planned	294 (92%)	24 (89%)	137 (91%)	109 (94%)	24 (89%)
	Unplanned	26 (8.1%)	3 (11%)	13 (8.7%)	7 (6.0%)	3 (11%)
Complexity of surgical procedure[1]	Minor	17 (5.3%)	1 (3.7%)	10 (6.7%)	5 (4.3%)	1 (3.7%)
	Intermediate	41 (13%)	4 (15%)	16 (11%)	18 (16%)	3 (11%)
	Major	102 (32%)	13 (48%)	62 (41%)	24 (21%)	3 (11%)
	Major plus	72 (23%)	6 (22%)	41 (27%)	22 (19%)	3 (11%)
	Complex major operation	88 (28%)	3 (11%)	21 (14%)	47 (41%)	17 (63%)
Anaesthesia technique	General anaesthesia	252 (79%)	24 (89%)	108 (72%)	94 (81%)	26 (96%)
	Regional anaesthesia	45 (14%)	1 (3.7%)	31 (21%)	13 (11%)	1 (3.7%)
	Combined techniques	14 (4.4%)	2 (7.4%)	5 (3.3%)	6 (5.2%)	–
	Monitored anaesthesia care	9 (2.8%)	–	6 (4.0%)	3 (2.6%)	–
Insurance class	Basic	235 (73%)	24 (89%)	110 (73%)	85 (73%)	16 (59%)
	Semi-private	49 (15%	3 (11%)	20 (13%)	18 (16%)	8 (30%)
	Private	36 (11%)	–	20 (13%)	13 (11%)	3 (11%)
Length of ICU stay [2] (days), median (IQR)		1 (1–2)	1 (1–1)	1 (1–1)	1 (1–2)	2 (1–3)
pLOS[3] (days), median (IQR)		4 (2–6)	2 (1–3)	3 (2–4)	5 (3–7)	7 (6–10)

[1] When an undefined or missing complexity grade in the BUPA classification system (n = 24, 7.5% of procedures) was found, a grade corresponding to a similar procedure was used, as defined through consensus by the core team and clinical experts in the field. There were no missing values in any of the other variables.

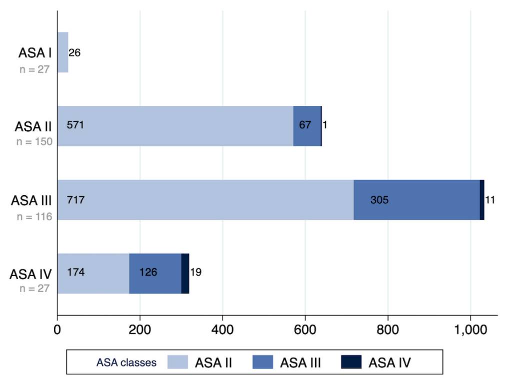
[2] In total, 74 (23%) required at least one day in the ICU.

‡ pLOS = Postoperative length of stay (excluding days on ICU).

Costs

On average, the indirect, direct and total effects on costs increased with rising ASA classification, as did the proportional contribution of the indirect effect to the total effect. However, only the cost difference between ASA IV and ASA I patients was statistically significant, with additional costs of EUR 30,631 (95% CI 15,205–46,057) for total costs, most of which were caused by an indirect effect (EUR 27,415, 95% CI 11,180–43,649). Independent of the ASA class, the total effect of the number of comorbidities on costs was statistically significant, with an average increase by EUR 1198 (95% CI 288–2108) for each additional comorbidity and with almost identical contributions of direct and indirect effects. The indirect path can be explained by each additional comorbidity significantly prolonging length of hospital stay, independent of the ASA class (output not shown), without a corresponding statistically significant effect on the length of ICU stay.

Figure 4: Number and severity of comorbidities according to ASA class. Number and severity of all anaesthesia-relevant comorbidities for all patients in the corresponding overall ASA class. The ASA class of each comorbidity has been assigned as if this comorbidity would have been the only one in this patient.



Moreover, increasing surgical complexity, as well as intra- and postoperative adverse events, also led to a significant, mainly indirect effect on increasing costs, whereas increasing insurance class, postoperative length of hospital and ICU stay led to a mainly direct effect on increasing costs (table 3). Whereas the cost-driving effect of intraoperative adverse events was mainly mediated by their positive association with postoperative adverse events and the length of ICU stay, the cost-driving effect of postoperative adverse events was mainly mediated through a prolonged ICU and hospital stay (supplementary table 2).

The sensitivity analyses of the log-transformed outcome enabling the additional inclusion of patients with protracted hospital and ICU stay (n = 5) and of those who died during hospital stay (n = 2) are shown in the appendix in supplementary tables 6 and 7. As a consequence of the log-transformation of the outcome, the magnitudes of the results of these analyses are not directly comparable to the results for the untransformed outcome. However, differences in the relative importance of the indirect effects become apparent. The number of comorbidities had a significant total indirect and direct effect on the costs, independent of the ASA classes. Furthermore, the total effect on costs when comparing ASA III with I also became significant. The sensitivity analysis in the subgroup of patients with basic insurance showed similar results to the main model, but with greater uncertainty reflected by wider confidence intervals (supplementary tables 12 and 13).

Reimbursement

The analysis of reimbursement only showed significant positive effects of increasing insurance class. On average, reimbursement increased by EUR 3097 (95% CI 1942–4251) per increase in insurance class (table 4).

In the sensitivity analysis using a log-transformed outcome, number of comorbidities, postoperative adverse

Table 2:
Comorbidities for the total study population (n = 320) and for the different ASA PS classes

This table gives an overview of the number and severity of anaesthesia-relevant comorbidities. An ASA class was assigned to each comorbidity by the study team. The columns correspond to the overall ASA PS classes as preoperatively assigned by the treating anaesthesiologists. Quantitative variables are reported as median (IQR), quantitative as number (percentages).

	All patients (n = 320)	ASA I (n = 27, 8.4%)	ASA II (n = 150, 47%)	ASA III (n = 116, 36%)	ASA IV (n = 27, 8.4%)
Number of comorbidities	5 (0–18)	1 (0–4)	4 (1–12)	9 (1–17)	12 (5–18)
ASA class of most severe anaesthesia-relevant comorbidity					
– ASA I	12 (3.8%)	12 (44%)	–	–	–
– ASA II	123 (38%)	15 (56%)	96 (64%)	12 (10%)	–
– ASA III	157 (49%)	–	53 (35%)	93 (80%)	11 (41%)
– ASA IV	28 (8.8%)	–	1 (0.7%)	11 (9.5%)	16 (59%)
Types of comorbidities					
– Cardiovascular	177 (55%)	1 (3.7%)	49 (33%)	100 (86%)	27 (100%)
– Pulmonary	139 (43%)	3 (11%)	60 (40%)	65 (56%)	11 (41%)
– Neurology	150 (47%)	–	67 (45%)	70 (60%)	13 (48%)
– Trauma/coagulation	128 (40%)	2 (7.4%)	40 (27%)	64 (55%)	22 (81%)
– Liver/kidney	150 (47%)	1 (3.7%)	55 (37%)	60 (60%)	24 (89%)
- Airway (incl. BMI and risk for aspiration)	179 (56%)	6 (22%)	93 (62%)	68 (59%)	12 (44%)
– Metabolic disorder (including diabetes etc.)	117 (37%)	6 (22%)	41 (21%)	59 (51%)	21 (78%
– Allergies	103 (32%)	5 (19%)	53 (35%)	35 (30%)	10 (37%)
– Pregnancy	30 (9.4%)	–	26 (17%)	4 (3.5%)	–
– Substance abuse (e.g., alcohol, drugs)	39 (12%)	--	11 (7.3%)	24 (21%)	4 (15%)
– Others	118 (37%)	–	42 (28%)	62 (53%)	14 (52%)

events and higher surgical complexity significantly decreased reimbursement in addition to the insurance class.

Discussion

Principal findings

In patients presenting for surgery from a broad range of surgical disciplines in a single tertiary centre, the prevalence of multimorbidity was high, especially in patients assigned to higher ASA classes. Independent of ASA class, each additional comorbidity increased the total effect on hospital costs with almost identical proportions of direct and indirect effects. The path analysis revealed that intra- and postoperative complications mainly had an indirect effect on costs, whereas the length of hospital and ICU stay mostly had a direct effect. Regarding the results on reimbursement, only the insurance class revealed a significant positive effect. In addition to a relevant effect of comorbidities on costs, we demonstrated that anaesthesia-relevant comorbidities impacted postoperative complications and postoperative length of stay.

Strengths and limitations of the study

A major strength of this study was that the results are based on baseline and outcome data with granular details prospectively recorded during a cohort study, covering a broad range of surgical disciplines. Additionally, our

Table 3:
Indirect, direct and total effects on costs (in Euros).

Coefficients are mean differences (mean diff.) in cost. Patients with protracted hospital or ICU stay and patients who died during hospital stay were excluded. R-squared 57.1% (n = 308).

	Indirect effect		**Direct effect**		**Total effect**		**Proportion of total effect mediated**
Factor	**Mean diff.**	**95% CI**	**Mean diff.**	**95% CI**	**Mean diff.**	**95% CI**	
ASA class II vs I	2177	–829; 5182	–3060	–5876; –244	–883	–4824; 3057	42%
ASA class III vs I	6220	902; 11,538	–2728	–7488; 2031	3491	–3580; 10,563	70%
ASA class IV vs I	27,415	11,180; 43,649	3216	–6515; 12,948	30,631	15,205; 46,057	89%
Comorbidities (per one additional comorbidity)	577	–136; 1290	621	–16; 1258	1198	288; 2108	48%
Complexity of surgery (BUPA Major Plus and CMO1 vs Minor to Major)	10,905	6322; 15,489	–1374	–5387; 2639	9531	5708; 13,354	89%
Insurance (per one class increase)[2]	–	–	4724	1919; 7529	4724	1919; 7529	–
ClassIntra® (per one grade increase)	2378	487; 4269	22	–1250; 1295	2400	579; 4222	99%
CCI® (per 10 units increase)[3]	5485	2089; 8880	455	–845; 1755	5940	2810; 9070	92%
Length of ICU stay (per one day increase)	–929	–2835; 978	11,759	6547; 16,970	10,830	4134; 17,526	7.3%
Length of postop stay (per one day increase)	–	–	2184	1403; 2965	2184	1403; 2965	–

[1] CMO: complex major operations; [2] insurance class has only been included as a direct effect. [3] CCI: comprehensive complication index

Table 4:
Indirect, direct and total effects on reimbursement (in Euros).

Coefficients are mean differences in reimbursement; patients with protracted hospital or ICU stay and patients who died during hospital stay were excluded. R-squared 56.5% (n = 308)

	Indirect effect		**Direct effect**		**Total effect**		**Proportion of total effect mediated**
Factor	**Mean difference**	**95% CI**	**Mean difference**	**95% CI**	**Mean difference**	**95% CI**	
ASA class II vs I	–255	–761; 312	447	–1269; 2162	222	–1415; 1859	33%
ASA class III vs I	–743	–1782; 296	3047	–420; 6515	2304	–961; 5569	20%
ASA class IV vs I	–3224	–9301; 2854	1647	–5307; 8601	–1577	–8147; 4993	66%
Comorbidities (per one additional comorbidity)	–89	–240; 62	–180	–488; 129	–269	–635; 97	33%
Complexity of surgery (BUPA Major Plus and CMO[1] vs Minor to Major)	–1186	–3530; 1157	946	–1532; 3424	–241	–1769; 1288	56%
Insurance (per one class increase)[2]	–	–	3097	1942; 4251	3097	1942; 4251	–
ClassIntra® (per one grade increase)	–327	–1025; 372	329	–507; 1166	3	–760; 765	50%
CCI® (per 10 units increase)[3]	–695	–2057; 667	–268	–1244; 708	–963	–2213; 287	72%
Length of ICU stay (per one day increase)	149	–125; 424	–1174	–4640; 2291	–1025	–4578; 2528	11%
Length of postop stay (per one day increase)	–	–	–351	–724; 22	–351	–724; 22	—

[1] CMO: complex major operations; [2] insurance class has only been included as a direct effect; [3] CCI: comprehensive complication index

analysis involved structural equation modelling, enabling not only an estimation of the total effects but also a quantification of direct and indirect effects taking into account the complex relationship of all variables. Our cost analysis is, however, limited by its restriction to total costs without distinction between fixed and variable costs. Whereas the cost data correspond to effective costs based on drug and material costs, infrastructure, salaries and overheads, the reimbursement data are based on negotiated base rates specific for each Swiss hospital. Generalisability of our results is limited because of greatly differing reimbursement systems in other countries.

The retrospective data collection about type and extent of comorbidities is a limitation of this study. However, misclassification bias is limited as the severity of all anaesthesia-relevant comorbidities was based on predefined definitions elaborated and revised by a team of experienced anaesthesiologists, frequently following official cut-offs. In order to ensure the best possible accuracy, every unclear comorbidity assignment was discussed and verified with a senior team member. This resulted in some discrepancies, particularly between the preoperative overall ASA class assignment by the anaesthesiologists in charge and the retrospective assignment of certain comorbidities in our study, strictly following the ASA guidelines. However, in the monetary analysis, only the number of comorbidities was considered, disregarding the severity and potential differences in prognostic relevance. The relevance of multimorbidity on perioperative clinical outcome will be evaluated in a multicentre study including additional national and international study centres from the multicentre validation study of ClassIntra® [13]. The larger sample size will allow for broader generalisability to different hospital settings and countries, and provide a basis for determining whether certain comorbidities are prognostically more relevant than others.

Findings in relation to other studies

Literature investigating the effect of multimorbidity on outcome and hospital costs in perioperative patients is sparse and typically based on administrative data. Usually, only a selection of postoperative adverse events and comorbidities is considered, whereby most studies have used classifications not routinely applied nor validated in perioperative medicine such as the Charlson comorbidity index. In addition, the prognostic value of these other classifications is not well established in perioperative medicine, whereas the ASA class has previously been shown to be strongly associated with length of hospital stay and hospital costs in general [22], orthopaedic [23] and spine surgery [24, 25]. Nevertheless, numerous studies [26–30] support the assumption that comorbidities lead to an increase in hospital costs mediated by a higher susceptibility of multimorbid patients to postoperative complications, although we could only show supporting evidence for this association in our sensitivity analysis using a log-transformed outcome excluding recurring patients. Extending the results of Whitmore and colleagues who found a significant association between increasing ASA class and costs only in patients undergoing spine surgery [31], we were able to show a linear association between the number of comorbidities and total costs independent of the corresponding ASA class.

A well-known surgical risk calculator developed by the American College of Surgeons National Surgery Quality Improvement Program (ACS NSQIP Surgical Risk Calculator) [32] allows calculation of the risk for a set of postoperative complications based on a selected number of preoperative patient and operative risk factors. Although the ACS-NSQIP risk calculator had been developed using data from all surgical subspecialities, a recent review showed unconvincing performance in predicting postoperative complications in a variety of surgical disciplines [33]. The lack of a strong and generalisable correlation between the predicted risk and postoperative complications renders high performance in predicting hospital costs unlikely. This has been confirmed by a single-centre retrospective study in neurosurgical patients, which found only a moderate correlation between the risk predicted using the ACS NSQIP risk calculator and hospital costs [34].

According to several other studies, postoperative complications lead to an increase in length of hospital stay [35] and costs [9, 10, 35, 36]. In our study, not only postoperative, but also intraoperative adverse events led to significantly increased costs. In the case of intraoperative adverse events, the effect was partly mediated by the number and severity of postoperative adverse events and a prolonged length of ICU stay. This is in line with a study in patients undergoing noncardiac surgery [37], where increased costs related to postoperative adverse events were mostly driven by a prolonged length of ICU and hospital stay.

Regarding hospital reimbursement, Dimick et al. [38] and Eappen et al. [35] found the contribution margin in patients experiencing postoperative complications to be dependent on the payer mix, whereas our main model did not show a significant increase or decrease in reimbursement in the case of a postoperative complication. In two different sensitivity analyses, we found that the inclusion of patients with protracted ICU or hospital stay led to a significant negative effect of postoperative complications on the reimbursement. This could be due to the Swiss DRG not adequately reimbursing for patients with poor outcome [39].

Implication for clinicians

Our study showed that, in addition to the ASA class, the number of comorbidities had a relevant direct effect on the risk of postoperative complications, and an indirect effect on length of postoperative stay and costs. This affects the decision between conservative and invasive treatment, bed planning on the ward, reimbursement negotiations with insurance providers and type of postoperative care.

The single disease framework of the ASA classification, by using only the single most severe systemic disease to define the ASA class, may be responsible for the cost increasing effect of each additional comorbidity in our study. Thus, integrating multimorbidity into the ASA classification could allow for an easier and more accurate reimbursement. In addition, integration could allow for better perioperative planning and management, since comorbidities also seem to increase length of hospital stay and the risk for postoperative complications. The number of comorbidities consists of information readily available after the anaesthesia consultation, hence their integration would be far easier as compared to the use of a separate risk calculator.

Implication for future research

Non-randomised outcome studies aim to adjust for patients' basic risk profiles. Up to now, the ASA classification has frequently been used to adjust for the complexity of a patient's physical health status as a single covariate in perioperative outcome research [40]. When the ASA classification system was devised in 1941, multimorbidity was less common than it is today. Given the increase of concomitant diseases over recent decades, the ASA classification has declined in value as a predictor of perioperative risk ignoring multimorbidity [2]. Our study provides evidence that – in addition to the adjustment according to ASA class – the number of comorbidities is an important co-factor for the occurrence of postoperative complications, and hence also for postoperative length of stay and hospital costs. Therefore, adjusting the classification to incorporate this relevant confounder for postoperative outcomes may be desirable.

Conclusion

In demonstrating that the number of anaesthesia-relevant comorbidities is large, increases with increasing ASA class and is responsible for higher hospital costs, this study shows the importance of assessing and explicitly considering multimorbidity in the perioperative risk assessment. Moreover, the number of comorbidities is a crucial additional covariate for investigating perioperative outcomes, since the most severe comorbidity, as reflected by the ASA class, is not sufficient for confounder adjustment.

In particular, we show that hospital costs grow with the number of comorbidities, independent of ASA class. In line with the sparse literature on this topic, the relationship between comorbidity and hospital costs was mainly mediated by a prolonged length of hospital stay related to intra- and postoperative adverse events. We suggest that the assessment of all anaesthesia-relevant comorbidities and possibly their integration into the current ASA classification may improve its predictive framework and would potentially allow for a more precise prediction of costs.

Data accessibility statement

De-identified patient-level data are available on request for investigators whose proposed use of the data has been approved by a review committee identified for this purpose.

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LC, LA, CS and SDK had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: LC, LA, CG, MK and SDK

Acquisition, analysis, or interpretation of data: LC, LA, CS, NO, CG, LAS, MS, SDK

Drafting of the manuscript: LC, LA and SDK

Critical revision of the manuscript for important intellectual content: CS, NO, CG, MK, LAS, MS

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Potential competing interests

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. No potential conflict of interest was disclosed

Presentation

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Appendix

Table of contents

Table 1: ASA physical status relevant comorbidities and corresponding ASA class grading

	The ASA physical status classification[1]	
ASA 1	A normal healthy patient	
ASA 2	A patient with mild systemic disease	
ASA 3	A patient with severe systemic disease	
ASA 4	A patient with severe systemic disease that is a constant threat to life	
ASA 5	A moribund patient who is not expected to survive without the operation	
ASA 6	A declared brain-dead patient whose organs are being removed for donor purposes	
Organ	**Classification**	**ASA**
General conditions	**BMI**[2]	
	BMI < 16	3
	16 < BMI < 18.5	2
	18.5 - 30	1
	30 < BMI < 40	2
	BMI > 40	3
	Pregnancy	
	Without complications[2]	2
	With complications	3
	Acute Trauma - Injury Severity Score ISS[*3,] *(Remarks see page 11)*	
	Minor or ISS 0 - 2	1
	Moderate or ISS 3 - 8	2
	Serious or ISS 9 - 49	3
	Severe or ISS 50 - 74	4
	Critical or ISS 50 - 74	4

	Maximum/massive trauma[2] or ISS = 75	5
	Haemorrhage and haemorrhagic shock[4]	
	Class I, i.e. loss up to 15% of blood volume	2
	Class II, i.e. loss 15 - 30% of blood volume, tachycardia, reduced pulse pressure	3
	Class III, i.e. loss 30 - 40% of blood volume, marked tachycardia, hypotension	4
	Class IV, i.e. loss more than 40% of blood volume, immediately life-threatening	5
Neurology	**GCS (Glasgow Coma Scale)**	
	15	1
	13 - 14	2
	9 - 12	3
	< 8	4
	Epilepsy	2-5
	Neurological deficit	2-5
	Neurodegenerative disease (e.g. Parkinson's disease, Alzheimer`s disease, Chorea Huntington, MMS < 24,[5 6] history of delirium)	3-5
	Depression	2-5
	Polyneuropathy	2-5
	Status post CVI/TIA[2]	
	History of CVI/TIA (> 3 months)	3
	Recent CVI/TIA (< 3 months)	4
	Intracranial bleeding	
	Subdural bleeding/haematoma	3
	Subarachnoid/epidural bleeding	4
	With mass effect[2]	5
Airway, pulmonary disease	**Smoker†**	

	Never smoker[2]	1
	Current smoker[2]	2-5
	According to pack years[7]	
	Pack years 1 - 10	2
	Pack years > 11	3
	Former smoker, i.e. > 4 weeks[8 9]	
	History of pack years 1 - 10	1
	History of pack years 10 - 40	2
	History of pack years > 40	3
	OSAS[10] or risk assessment by using STOP-Bang questionnaire‡[11 12,]	
	Mild (apnoea/hypopnoea index (AHI) 5-14/hr)	2
	Moderate risk (AHI 15 - 30/hr)	3
	Severe risk (AHI > 30/hr)	
	Low risk 0 - 2	1
	Intermediate risk 3-4	2
	High risk 5-8	3
	Obstructive lung disease[2]	
	Mild COPD/asthma	2
	COPD	3-4
	Poorly controlled COPD	3-4
	ARDS	4
	Restrictive lung disease[13] (if information available and if no obstructive lung disease is present, i.e. FEV1/FVC ≥ 0.7 and FVC < 80)	
	FVC/TLC ≥ 80	1
	Mild restriction: TLC 65 - 80	2
	Moderate restriction: TLC 50 - 60	2
	Severe restriction: TLC < 50	3

	Airway	
	Expected difficult airway (e.g. adipositas, Mallampati III-IV, thyromentale distance, etc)	2
	Known difficult airway	2
	Risk for aspiration	
	No risk	1
	Risk for aspiration	2
	Increased risk for aspiration (e.g. ileus, etc)	3
Cardiovascular	**MET§[14]**	
	> 4	1
	< 4	3
	Hypotension	2-5
	Hypertension	
	“Well-controlled”[2] (i.e. WHO Grade I and II or SBP < 160 or DBP < 110)	2
	Hypertensive crisis/emergency (i.e. WHO Grade III or SBP ≥ 160 or DBP ≥ 110)	3
	Coronary heart disease[2]	
	No history of myocardial infarction	2
	History of myocardial infarction (> 3 months)	3
	Recent myocardial infarction (< 3 months)	4
	Ongoing cardiac ischaemia	4
	Coronary stents[2]	
	No	1
	History of stent (> 3 months)	3
	Recent stent (< 3 months)	4
	Valve dysfunction	
	Minimal dysfunction	2
	Moderate dysfunction	3

	Severe dysfunction	4
	Heart failure	
	NYHA I[15]: No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath). NYHA II: Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea (shortness of breath) OR current EF grey zone, i.e. EF 40 - 49% NYHA III: Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnoea OR moderate reduction in current EF[2], i.e. EF 30 - 39% NYHA IV: Unable to perform any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases OR severe reduction in ejection fraction[2], i.e. EF < 30%	2 2 3 4
	Arrhythmias, pathological ECG	2-5
	Atrial fibrillation	3
	ECG not available	
	Pacemaker	3
	ICD	3
	ICD and pacemaker[2]	3
	Thrombosis	
	History of thrombosis/pulmonary embolism after treatment Current thrombosis/pulmonary embolism under treatment Current (central) pulmonary embolism	2 3 4
	PAD	2-5
	With stent in any arteries	3-5
	Aneurysm (abdominal/thoracic)	
	> 35 mm and < 55 mm ≥ 55 mm for men and 45 mm for women, abdominal ≥ 55 mm or rapid progression > 2 mm/year, thoracic	3 4 4

	Ruptured[2]	5
	Infection/sepsis and septic shock¶[16]	
	Infection	2
	Sepsis	3
	Septic shock[2]	4
	Coagulation disorder**	
	Clopidogrel, NOAC, OAC (Marcoumar), heparin	3
	Factor-5-Leiden mutation	2
	Intake of dual platelet inhibitors	3
	DIC[2]	4
	Acetylsalicylic acid alone	1
	Others, please specify and choose ASA class	2-5
	Thrombocytopenia[17]	
	Tc < 100,000/µL	2
	Tc < 50,000/µL	3
	Tc < 20,000/µL	4
Liver	**Hepatopathy**	
	status post HAV, HBV, HCV, HDV	2
	active hepatitis[2]	3
	Other hepatopathy	2-5
	Liver cirrhosis relating to Child-Pugh score	
	Class A	2
	Class B	3
	Class C	4
Kidney	**Renal insufficiency**	
	GFR 60 - 89	2

	GFR 30 - 59	3
	GFR < 29 with dialysis[2]	3
	GFR < 29 without dialysis[2]	4
Metabolism, endocrinological disease	**Diabetes mellitus (type 1 and 2)[2]**	
	Well controlled (i.e. HbA1c < 6.5%)	2
	Poorly controlled (i.e. HbA1c > 6.4%)	3
	Thyroid disorders	
	Well-controlled	2
	Symptomatic hypo-/hyperthyreoidism	3
	Myxoedema coma	4
	Thyreotoxic crisis	4
	Cushing syndrome, adrenal Insufficiency	2-5
	Dyslipidemia	2-5
Abnormal electrolyte concentrations	**Potassium**	
	Hypokalaemia < 3.5	2
	Potassium > 3.4 and < 5.5 mmol/L without clinical relevance	1
	Hyperkalaemia > 4.5 and < 5.5 but with a clinical relevance	2
	e.g. hyperkalaemia[18] > 5.5 and < 6.5 mmol/L	3
	Hyperkalaemia > 6.5 mmol/L	4
	Sodium[19]	
	Borderline hyponatremia (130 ≤ Na < 135 mmol/L)	1
	Mild hyponatremia (125 ≤ Na < 130 mmol/L) but with a clinical relevance	2
	Severe hyponatremia (Na < 125 mmol/L)	3
	Borderline hypernatremia (145 < Na ≤ 150 mmol/L)	1

	Mild hypernatremia (150 < Na ≤ 155 mmol/L)	2
	Severe hypernatraemia (Na > 155 mmol/L)	3
	Total Calcium[20]	
	Moderate hypocalcaemia (1.9 - 2.1 mmol/L)	2
	Severe hypocalcaemia (< 1.9 mmol/L)	3
	Normal calcium or mild hyper- or hypocalcaemia (2.11 - 2.88 mmol/L)	1
	Moderate hypercalcaemia (2.89 - 4.50 mmol/L)	2
	Severe hypercalcaemia (> 4.50 mmol/L)	3
	Anaemia[21 22]	
	Mild anaemia with haemoglobin >10 g/dL	2
	Haemoglobin 8 - 10 g/dL	2
	Haemoglobin 5 - 8 g/dL	3
	Haemoglobin < 5 g/dL	4
Drugs†	**Alcohol**[2]	
	None/minimal	1
	Social	2
	Dependency/abuse/iv/substitution	3
	Others	
	Single substance/socially integrated	2-5
	Polytoxicity	3-5
Others	**Allergy**	
	Pollinosis	2
	Drugs, relevant non-drug related allergies	2-5
	Latex allergy	3
	Neuromuscular disease, e.g. multiple sclerosis, mysthenia gravis, etc.	2-5
	History of malignant hyperthermia (MH)	2

	MH-associated muscular diseases, e.g. central core disease	2
	Autoimmune disease, e.g. rheumatism, Morbus Crohn, etc.	2-5
	Malignant tumour	
	M0	2
	M1	3
	Current progressive/metastatic/non-curable	4
	Transplantation with immunosuppression	
	Stable under immunosuppression	3
	Transplant failure	4
	Genetic/other disease relevant for anaesthesia/perioperative care (Please specify and choose corresponding ASA class)	
	Hopkins Frailty Score‡‡[23 24]	
	Robust (not frail: Hopkins Frailty Score 0)	1
	Mildly frail (Hopkins Frailty Score 1-2)	2
	Frail (Hopkins Frailty Score 3-5)	3

* Generic ASA physical health status classification and all anaesthesia-related comorbidities categorised according to their severity grade using the ASA-classification as if this comorbidity would have been the only one in this patient. Whenever possible, this grading was based on official cut-offs, current definitions (see references) or on the examples detailed by the ASA.[25] A further remark regarding trauma and STOP Bang can be found on the following page. If no such cut-offs were found, the extent of disease was graded according the generic definition of the ASA classification.[1] In case of doubt, the grading was based on a consensus decision of a team of anaesthesiologists from the University Hospital of Basel with extensive expertise in perioperative care.

Abbreviations used:

ASA = American Society of Anesthesiologists
ECG = Electrocardiography
BMI = Body Mass Index
ICD = Implantable Cardioverter Defibrillator
MMS = Mini Mental State
PAD = Peripheral Artery Disease
CVI = Cerebrovascular Infarction
NOAC = Novel Oral Anticoagulants
TIA = Transient Ischemic Attack
OAC = Oral Anticoagulants
OSAS = Obstructive Sleep Apnea Syndrome
DIC = Disseminated Intravascular Coagulation
AHI = Apnea Hypopnea Index
Tc = Thrombocytes
COPD = Chronic Obstructive Pulmonary Disease
HAV = Hepatitis A Virus
ARDS = Acute Respiratory Distress Syndrome
HBV = Hepatitis B Virus
FEV1 = Forced Expiratory Volume per second
HCV = Hepatitis C Virus
FVC = Forced Vital Capacity
HDV = Hepatitis D Virus
TLC = Total Lung Capacity
GFR = Glomerular Filtration Rate
MET = Metabolic Equivalent of Task
HbA1c = Hemoglobin A1c
SBP = Systolic Blood Pressure
DBP = Diastolic Blood Pressure
WHO = World Health Organization
NYHA = New York Heart Association

Remarks for Table 1

*** Acute Trauma - Injury Severity Score ISS[3]**

Acute Trauma - Injury Severity Score ISS[3] (take sum of squared score of three most severe injuries of the following areas:	Comment: if one region receives a score of 6, score is 75; otherwise use rule mentioned. Max 75; severe injury with score ≥ 50
Head and neck worst injury?	0=No; 1=minor; 2=moderate; 3=serious; 4=severe; 5=critical; 6=unsurvivable
Face worst injury?	0=No; 1=minor; 2=moderate; 3=serious; 4=severe; 5=critical; 6=unsurvivable
Chest worst injury?	0=No; 1=minor; 2=moderate; 3=serious; 4=severe; 5=critical; 6=unsurvivable
Abdomen worst injury?	0=No; 1=minor; 2=moderate; 3=serious; 4=severe; 5=critical; 6=unsurvivable
Extremity (including pelvis) worst injury?	0=No; 1=minor; 2=moderate; 3=serious; 4=severe; 5=critical; 6=unsurvivable
External worst injury?	0=No; 1=minor; 2=moderate; 3=serious; 4=severe; 5=critical; 6=unsurvivable
Examples	SHF
If not enough information available use Trauma - Overall Abbreviated Injury Scale AIS[26]	

STOP-Bang[27]

Snoring	Yes
Tired	Yes
Observed	Stops breathing during sleep
Pressure	(Un)treated hypertension
BMI	> 35
Age	> 50
Neck	Circumference > 43 for male and 41 for female
Gender	Male gender

† In case of lack of information, the patient is assumed to be abstinent.

‡ In case no OSAS or STOP-Bang information is available, these clinical signs are used.

§ In case of a trauma patient, the METs achieved before the trauma are used.

¶ According to consensus definitions for sepsis and septic shock.

** If anticoagulation was stopped early enough for normal coagulation, ASA class 1 is used.

‡‡ In case of a trauma patient, the frailty score achieved before the trauma is use.

Table 2: Complete cost model with full output (in Euros)

Structural equation model including all patients (n=320) showing total effects of fixed patient characteristics and hospitalisation-related parameters on total hospital costs. Patient characteristics were considered as exogenous variables while hospitalisation-related parameters were considered both as potential mediators of causal effects and as sources of causal effects in their own right.

Outcome	Covariate	Mean differences in costs	95% CI
ClassIntra®	ASA class II vs I	0.43	0.12; 0.74
	ASA class III vs I	0.68	0.23; 1.13
	ASA class IV vs I	1.41	0.75; 2.06
	Age (per each year increase)	-0.00	-0.01; 0.01
	Gender (male vs female)	-0.02	-0.22; 0.19
	Complexity of surgery (Major Plus/ CMO vs Minor to Major)	0.57	0.36; 0.77
	Comorbidities (per each additional one)	-0.00	-0.05; 0.04
	Insurance (per one class increase)	-0.08	-0.24; 0.08
	Intercept	0.16	-0.30; 0.63
CCI®	ClassIntra® (per one grade increase)	3.87	2.06; 5.68
	ASA class II vs I	-2.56	-6.42; 1.30
	ASA class III vs I	-1.94	-8.01; 4.13
	ASA class IV vs I	13.56	3.37; 23.75
	Age (per each year increase)	-0.08	-0.21; 0.05
	Gender (male vs female)	-1.23	-4.28; 1.81
	Complexity of surgery (Major Plus/ CMO vs Minor to Major)	1.26	-1.88; 4.41
	Comorbidities (per each additional one)	0.83	0.12; 1.53
	Insurance (per one class increase)	-0.30	-2.38; 1.78
	Intercept	5.58	0.43; 11.58

Length of postop stay	ClassIntra® (per one grade increase)	-0.06	-0.64; 0.51
	CCI® (per one unit increase)	0.15	0.06; 0.25
	Length of ICU stay (per one day increase)	-0.60	-1.42; 0.22
	ASA class II vs I	-1.32	-3.85; 1.20
	ASA class III vs I	-0.75	-3.67; 2.17
	ASA class IV vs I	-1.71	-6.67; 3.26
	Age (per each year increase)	0.03	-0.00; 0.06
	Sex (male vs female)	-0.63	-1.67; 0.42
	Complexity of surgery (Major Plus/ CMO vs Minor to Major)	1.92	0.88; 2.95
	Comorbidities (per each additional one)	0.13	-0.09; 0.35
	Insurance (per one class increase)	0.11	-0.66; 0.87
	Intercept	2.09	0.07; 4.11
Length of ICU stay	ClassIntra® (per one grade increase)	0.19	0.03; 0.35
	CCI® (per one unit increase)	0.04	0.02; 0.07
	ASA class II vs I	-0.05	0.31; 0.21
	ASA class III vs I	-0.07	-0.59; 0.44
	ASA class IV vs I	0.79	-0.46; 2.04
	Age (per each year increase)	0.00	-0.00; 0.01
	Sex (male vs female)	0.14	-0.12; 0.40
	Complexity of surgery (Major Plus/ CMO vs Minor to Major)	0.25	-0.01; 0.51
	Comorbidities (per each additional one)	-0.01	-0.06; 0.04
	Insurance (per one class increase)	-0.17	-0.34; 0.00
	Intercept	-0.40	-1.03; 0.24
Costs	ClassIntra® (per one grade increase)	-1266.28	-3390.15; 857.59

	CCI® (per one unit increase)	393.99	53.73; 734.25
	Length of postop stay (per one day increase)	1455.93	885.40; 2026.47
	Length of ICU stay (per one day increase)	5201.65	2546.81; 7856.49
	ASA class II vs I	-3512.44	-6587.81; -437.07
	ASA class III vs I	-3403.45	-9113.96; 2307.07
	ASA class IV vs I	13493.20	3278.67; 23707.73
	Age (per each year increase)	-101.96	-203.90; -0.02
	Sex (male vs female)	2702.33	-513.89; 5918.55
	Complexity of surgery (Major Plus/ CMO vs Minor to Major)	4541.74	799.59; 8283.89
	Comorbidities (per each additional one)	1138.35	357.02; 1919.69
	Insurance (per one class increase)	6381.15	2850.19; 9912.11
	Intercept	-3727.32	-0.00; 3091.33

Table 3: Complete reimbursement model with full output (in Euros)

Structural equation model including all patients (n=320) showing total effects of fixed patient characteristics and hospitalisation-related parameters on total hospital reimbursement. Patient characteristics were considered as exogenous variables while hospitalisation-related parameters were considered both as potential mediators of causal effects and as sources of causal effects in their own right.

Outcome	Covariate	Mean differences in costs	95% CI
ClassIntra®	Sex (male vs female)	-0.02	-0.22; 0.19
	Age (per each year increase)	-0.00	-0.01; 0.01
	ASA class II vs I	0.43	-0.01; 0.74
	ASA class III vs I	0.68	0.23; 1.13
	ASA class IV vs I	1.41	0.75; 2.06
	Complexity of surgery (Major Plus/ CMO vs Minor to Major)	0.57	0.36; 0.77
	Comorbidities (per each additional one)	-0.00	-0.05; 0.04
	Insurance (per one class increase)	-0.08	-0.24; 0.08
	Intercept	0.16	-0.30; 0.63
CCI®	ClassIntra® (per one grade increase)	3.87	2.06; 5.68
	Sex (male vs female)	-1.23	-4.28; 1.81
	Age (per each year increase)	-0.08	-0.21; 0.05
	ASA class II vs I	-2.56	-6.42; 1.30
	ASA class III vs I	-1.94	-8.01; 4.13
	ASA class IV vs I	13.56	3.37; 23.75
	Complexity of surgery (Major Plus/ CMO vs Minor to Major)	1.26	-1.88; 4.41
	Comorbidities (per each additional one)	0.83	0.12; 1.53
	Insurance (per one class increase)	-0.30	-2.38; 1.78

	Intercept	5.58	-0.43; 11.58
Length of postop stay	ClassIntra® (per one grade increase)	-0.06	-0.64; 0.51
	CCI® (per one unit increase)	0.15	0.06; 0.25
	Length of ICU stay (per one day increase)	-0.60	-1.42; 0.22
	Sex (male vs female)	-0.63	-1.67; 0.42
	Age (per each year increase)	0.03	-0.00; 0.06
	ASA class II vs I	-1.32	-3.85; 1.20
	ASA class III vs I	-0.75	-3.67; 2.17
	ASA class IV vs I	-1.71	-6.67; 3.26
	Complexity of surgery (Major Plus/ CMO vs Minor to Major)	1.92	0.88; 2.95
	Comorbidities (per each additional one)	0.13	-0.09; 0.35
	Insurance (per one class increase)	0.11	-0.66; 0.87
	Intercept	2.09	0.07; 4.11
Length of ICU stay	ClassIntra® (per one grade increase)	0.19	0.03; 0.35
	CCI® (per one unit increase)	0.04	0.02; 0.07
	Sex (male vs female)	0.14	-0.12; 0.40
	Age (per each year increase)	0.00	-0.00; 0.01
	ASA class II vs I	-0.05	-0.31; 0.21
	ASA class III vs I	-0.07	-0.59; 0.44
	ASA class IV vs I	0.79	-0.46; 2.04
	Complexity of surgery (Major Plus/ CMO vs Minor to Major)	0.25	-0.01; 0.51
	Comorbidities (per each additional one)	-0.01	-0.06; 0.04
	Insurance (per one class increase)	-0.17	-0.34; 0.00
	Intercept	-0.40	-1.03; 0.24

Reimbursement	ClassIntra® (per one grade increase)	18.33	-1641.26; 1677.91
	CCI® (per one unit increase)	16.07	-184.28; 216.41
	Length of postop stay (per one day increase)	-456.38	-754.52; -158.24
	Length of ICU stay (per one day increase)	73.30	-984.15; 1130.74
	Sex (male vs female)	215.66	-3224.15; 3655.47
	Age (per each year increase)	48.32	-57.84; 154.47
	ASA class II vs I	7344.02	-4237.75; 18925.80
	ASA class III vs I	10,476.18	-1457.75; 22410.11
	ASA class IV vs I	1558.13	-0.00; 19031.04
	Complexity of surgery (Major Plus/ CMO vs Minor to Major)	1403.86	-2091.51; 4899.24
	Comorbidities (per each additional one)	-650.91	-1250.20; -51.62
	Insurance (per one class increase)	4268.41	2637.59; 5899.22
	Intercept	-11000.00	-0.00; 1308.39

Table 4: Cost model including all patients (in Euros)

Indirect, direct and total effects on costs. Coefficients are mean differences in cost; all patients were included(n=320), and age and sex were considered as additional covariates. R-squared 56.9%

	Indirect effect		**Direct effect**		**Total effect**		**Proportion of total effect mediated**
Factor	**Mean diff.**	**95% CI**	**Mean diff.**	**95% CI**	**Mean diff.**	**95% CI**	
ASA class II vs I	-3314	-10361; 3733	-3512	-6588; -437	-6826	-15,362; 1710	**49%**
ASA class III vs I	-947	-9841; 7946	-3403	-9114; 2307	-4351	-15,715; 7013	**22%**
ASA class IV vs I	19,378	2162; 36,593	13493	3278; 23,708	32,871	14,277; 51,465	**59%**
Age (per decade increase)	-155	-1310; 1000	-1020	-2039; 0	-1174	-2690; 341	**13%**
Sex (male vs female)	-1612	-5205; 1981	2702	-514; 5919	1090	-4057; 6238	**37%**
Comorbidities (per one additional comorbidity)	974	167; 1781	1138	357; 1920	2113	915; 3310	**46%**
Complexity of surgery (BUPA Major Plus and CMO vs Minor to Major)	7719	3374; 12,065	4542	800; 8284	12,261	7388; 17,134	**63%**
Insurance (per one class increase)	-1221	-3691; 1248	6381	2850; 9912	5160	684; 9635	**16%**
ClassIntra® (per one grade increase)	4563	2166; 6960	-1266	-3390; 858	3297	489; 6104	**78%**
CCI® (per 10 units increase)	4608	2144; 7071	3940	537; 7343	8548	6009; 11,086	**54%**
Length of ICU stay (per one day increase)	-995	-2283; 293	5202	2547; 7852	4207	1953; 6460	**16%**
Length of postop stay (per one day increase)	--	--	1456	885; 2026	1456	885; 2026	**--**

Table 5: Reimbursement model including all patients (in Euros)

Indirect, direct and total effects on reimbursement. Coefficients are mean differences in reimbursement; all patients were included(n=320), and age and sex were considered as additional covariates. R-squared 48.7%

	Indirect effect		**Direct effect**		**Total effect**		**Proportion of total effect mediated**
Factor	**Mean diff.**	**95% CI**	**Mean diff.**	**95% CI**	**Mean diff.**	**95% CI**	
ASA class II vs I	763	-814; 2339	7344	-4238; 18,926	8107	-3568; 19,782	**9.4%**
ASA class III vs I	407	-1504; 2317	10,476	-1458; 22,410	10,883	-1262; 23,028	**3.7%**
ASA class IV vs I	464	-3857; 4785	1558	-15915; 19,031	2022	-13,795; 17,839	**23%**
Age (per decade increase)	-83	-348; 181	483	-578; 1545	400	-767; 1567	**15%**
Sex (male vs female)	449	-243; 1141	216	-3224; 3656	664	-2846; 4175	**68%**
Comorbidities (per one additional comorbidity)	-112	-299; 76	-651	-1250; 52	-763	-1372; -153	**15%**
Complexity of surgery (BUPA Major Plus and CMO vs Minor to Major)	-983	-2469; 503	1404	-2092; 4899	421	-2316; 3157	**41%**
Insurance (per one class increase)	-109	-580; 363	4268	2638; 5899	4160	2528; 5792	**2.5%**
ClassIntra® (per one grade increase)	-77	-921; 767	18	-1641; 1678	-59	-1539; 1422	**81%**
CCI® (per 10 units increase)	-597	-1443; 249	161	-1843; 2164	-436	-2141; 1269	**79%**
Length of ICU stay (per one day increase)	312	-153; 776	73	-984; 1131	385	-739; 1510	**81%**
Length of postop stay (per one day increase)	--	--	-456	-755; -158	-456	-755; -158	**--**

Table 6: Log-cost model excluding recurrent patients

Indirect, direct and total effects on log-cost. Coefficients are exponentiated to report the ratio in geometric means associated with a one-unit increase in the corresponding predictor variable. From these ratios, the percentage increase in geometric mean can be derived using the formula 100*(effect-1), e.g. 1.08 corresponds to an 8% increase in geometric mean among ASA II as compared to ASA I patients); R-squared 67.3% (n=315)

	Indirect effect		**Direct effect**		**Total effect**		**Proportion of total effect mediated**
Factor	**Effect**	**95% CI**	**Effect**	**95% CI**	**Effect**	**95% CI**	
ASA class II vs I	1.08	0.91; 1.28	0.95	0.82; 1.11	1.03	0.80; 1.33	**61%**
ASA class III vs I	1.22	0.98; 1.53	1.10	0.91; 1.34	1.35	0.99; 1.83	**68%**
ASA class IV vs I	2.22	1.59; 3.08	1.22	0.90; 1.65	2.69	1.72; 4.22	**80%**
Comorbidities (per one additional comorbidity)	1.02	1.00; 1.04	1.02	1.00;1.05	1.05	1.02; 1.07	**48%**
Complexity of surgery (BUPA Major Plus and CMO vs Minor to Major)	1.51	1.33; 1.70	1.25	1.10; 1.43	1.88	1.63; 2.18	**65%**
Insurance (per one class increase)	*		1.25	1.16; 1.35	1.25	1.16; 1.35	**--**
ClassIntra® (per one grade increase)	1.11	1.05; 1.16	1.00	0.96; 1.05	1.11	1.04; 1.18	**96%**
CCI® (per 10 units increase)	1.08	1.03; 1.14	1.09	1.04; 1.15	1.18	1.13; 1.23	**46%**
Length of ICU stay (per a 2.7183-fold increase)	1.00	0.98; 1.02	1.13	1.10; 1.16	1.12	1.09; 1.17	**0.03%**
Length of postop stay (per a 2.7183-fold increase)	--	**--**	1.25	1.12; 1.40	1.25	1.12; 1.40	**--**

*Insurance class has only been included as a direct effect.

Table 7: Log-reimbursement model excluding recurrent patients

Indirect, direct and total effects on log-reimbursement. Coefficients are exponentiated to report the ratio in geometric means associated with a one-unit increase in the corresponding predictor variable. From these ratios, the percentage increase in geometric mean can be derived using the formula 100*(effect-1), e.g. 0.96 corresponds to a 4% decrease in geometric mean as compared to ASA I patients). R-squared 61.0% (n=315)

	Indirect effect		**Direct effect**		**Total effect**		**Proportion of total effect mediated**
Factor	**Effect**	**95% CI**	**Effect**	**95% CI**	**Effect**	**95% CI**	
ASA class II vs I	1.00	0.98; 1.03	0.97	0.87; 1.08	0.97	0.87; 1.08	**5.5%**
ASA class III vs I	1.00	0.96; 1.03	1.02	0.88; 1.19	1.02	0.88; 1.18	**10%**
ASA class IV vs I	0.95	0.88; 1.03	1.02	0.82; 1.25	0.96	0.80; 1.16	**78%**
Comorbidities (per one additional comorbidity)	1.00	0.99; 1.00	0.99	0.98;1.01	0.99	0.98; 1.00	**35%**
Complexity of surgery (Major Plus and CMO vs Minor to Major)	0.99	0.95; 1.02	0.93	0.87; 1.01	0.92	0.87; 0.98	**15%**
Insurance (per one class increase)	*		1.12	1.08; 1.16	1.12	1.08; 1.16	**--**
ClassIntra® (per one grade increase)	0.99	0.98; 1.00	1.01	0.97; 1.04	1.00	0.97; 1.02	**63%**
CCI® (per 10 units increase)	1.00	0.99; 1.01	0.97	0.95; 1.00	0.97	0.95; 0.99	**5.4%**
Length of ICU stay (per a 2.7183-fold increase)	1.00	1.00; 1.00	1.00	0.98;1.02	1.00	0.98;1.02	**0.0%**
Length of postop stay (per a 2.7183-fold increase)	--	**--**	0.98	0.96; 1.01	0.98	0.96; 1.01	**--**

*Insurance class has only been included as a direct effect.

Table 8: Cost model excluding recurrent patients and patients with a protracted hospital or ICU stay (in Euros)

Indirect, direct and total effects on costs. Coefficients are mean differences in cost; patients with protracted hospital or ICU stay were excluded in order to meet the linearity assumption. R-squared 60.4% (n=310)

	Indirect effect		**Direct effect**		**Total effect**		**Proportion of total effect mediated**
Factor	**Mean diff.**	**95% CI**	**Mean diff.**	**95% CI**	**Mean diff.**	**95% CI**	
ASA class II vs I	1528	-1565; 4621	-4332	-7597; -1067	-2804	-7502; 1894	**26%**
ASA class III vs I	4835	-947; 10,618	-5451	-11466; 564	-616	-9460; 8228	**47%**
ASA class IV vs I	28,302	12,980; 43,623	4917	-6133; 15,966	33,218	17,168; 49,269	**85%**
Comorbidities (per one additional comorbidity)	711	15; 1407	955	178; 1732	1666	588; 2743	**43%**
Complexity of surgery (BUPA Major Plus and CMO vs Minor to Major)	9236	3995; 14,477	805	-4370; 5980	10,041	6032; 14,051	**92%**
Insurance (per one class increase)	*	*	5900	2682; 9117	5900	2682; 9117	**--**
ClassIntra® (per one grade increase)	2947	986; 4908	-1223	-3476; 1031	1724	-708; 4156	**71%**
CCI® (per 10 units increase)	4046	958; 7133	3205	-748; 7157	7251	4286; 10,215	**56%**
Length of ICU stay (per one day increase)	-794	-2490; 902	9512	3349; 15675	8718	1585; 15,850	**7.7%**
Length of postop stay (per one day increase)	--	--	1926	1124; 2728	1926	1124; 2728	**--**

*Insurance class has only been included as a direct effect.

Table 9: Reimbursement model excluding recurrent patients and patients with a protracted hospital or ICU stay (in Euros)

Indirect, direct and total effects on reimbursement. Coefficients are mean differences in reimbursement; patients with protracted hospital or ICU stay were excluded in order to meet the linearity assumption. R-squared 58.6% (n=310)

	Indirect effect		**Direct effect**		**Total effect**		**Proportion of total effect mediated**
Factor	**Mean diff.**	**95% CI**	**Mean diff.**	**95% CI**	**Mean diff.**	**95% CI**	
ASA class II vs I	-212	-772; 349	341	-1360; 2042	-129	-1469; 1728	**38%**
ASA class III vs I	-700	-1790; 390	2824	-560; 6209	2124	-1014; 5262	**20%**
ASA class IV vs I	-3417	-9290; 2456	1845	-5036; 8726	-1572	-7947; 4803	**65%**
Comorbidities (per one additional comorbidity)	-98	-243; 48	-152	-458; 155	-249	-597; 98	**39%**
Complexity of surgery (BUPA Major Plus and CMO vs Minor to Major)	-1393	-3725; 939	1160	-1348; 3668	-233	-1768; 1302	**55%**
Insurance (per one class increase)	*	*	3199	2030; 4369	3199	2030; 4369	**--**
ClassIntra® (per one grade increase)	-292	-966; 382	208	-633; 1049	-84	-855; 687	**58%**
CCI® (per 10 units increase)	-680	-1896; 535	-32	-1035; 971	-713	-1784; 358	**95%**
Length of ICU stay (per one day increase)	150	-132; 433	-1434	-4824; 1956	-1284	-4797; 2229	**9.5%**
Length of postop stay (per one day increase)	--	--	-365	-750; 20	-365	-750; 20	**--**

* Insurance class has only been included as a direct effect.

Table 10: Cost model excluding recurrent patients (in Euros)

Indirect, direct and total effects on costs. Coefficients are mean differences in cost; patients with protracted hospital or ICU stay were NOT excluded. R-squared 55.2% (n=315)

	Indirect effect		**Direct effect**		**Total effect**		**Proportion of total effect mediated**
Factor	**Mean diff.**	**95% CI**	**Mean diff.**	**95% CI**	**Mean diff.**	**95% CI**	
ASA class II vs I	-3496	-10,748; 3756	-4381	-7794; -967	-7877	-16,960; 1207	**44%**
ASA class III vs I	-1319	-10,255; 7617	-4578	-10,544; 1397	-5897	-17,778; 5983	**22%**
ASA class IV vs I	21,085	3187; 38,983	11,149	384; 21,914	32,234	12,235; 52,233	**65%**
Comorbidities (per one additional comorbidity)	981	185; 1777	951	190; 1712	1932	793; 3071	**51%**
Complexity of surgery (BUPA Major Plus and CMO vs Minor to Major)	7464	3171; 11756	4033	60; 8006	11497	6724; 16,270	**65%**
Insurance (per one class increase)	*	*	6067	2719; 9416	6067	2719; 9416	**--**
ClassIntra® (per one grade increase)	4531	2032; 7031	-1362	-3564; 840	3242	354; 6130	**77%**
CCI® (per 10 units increase)	5160	2303; 8018	4195	766; 7625	8727	6170; 11,283	**52%**
Length of ICU stay (per one day increase)	-941	-2170; 288	5231	2575; 7886	4290	2051; 6528	**15%**
Length of postop stay (per one day increase)	--	--	1394	812; 1976	1394	812; 1976	**--**

* Insurance class has only been included as a direct effect.

Table 11: Reimbursement model excluding recurrent patients (in Euros)

Indirect, direct and total effects on reimbursement. Coefficients are mean differences in reimbursement; patients with protracted hospital or ICU stay were NOT excluded. R-squared 50.3% (n=315)

	Indirect effect		Direct effect		Total effect		Proportion of total effect mediated
Factor	**Mean diff.**	**95% CI**	**Mean diff.**	**95% CI**	**Mean diff.**	**95% CI**	
ASA class II vs I	788	-965; 2541	506	-1082; 2094	1294	-1037; 3625	**61%**
ASA class III vs I	352	-1563; 2266	3031	19; 6043	3383	-196; 6961	**10%**
ASA class IV vs I	-1415	-4990; 2160	1562	-4298; 7422	147	-6144; 6437	**48%**
Comorbidities (per one additional comorbidity)	-173	-350; 3	-160	-474; 154	-333	-700; 34	**52%**
Complexity of surgery (BUPA Major Plus and CMO vs Minor to Major)	-1464	-2565; -362	792	-907; 2492	-671	-2275; 933	**65%**
Insurance (per one class increase)	*	*	3311	2188; 4435	3311	2188; 4435	**--**
ClassIntra® (per one grade increase)	-424	-1030; 181	123	-660; 905	-302	-1090; 487	**78%**
CCI® (per 10 units increase)	-888	-1561; -215	-125	-1006; 756	-1013	-1969; -56	**88%**
Length of ICU stay (per one day increase)	299	-141; 738	-518	-1274; 237	-220	-1064; 624	**37%**
Length of postop stay (per one day increase)	--	--	-442	-598; -287	-442	-598; -287	**--**

* Insurance class has only been included as a direct effect.

Table 12: Main cost model excluding semi-privately and privately insured patients (in Euros)

Coefficients are mean differences in cost; patients with a protracted hospital or ICU stay, recurrent, semi-privately and privately insured patients and patients who died during hospital stay were excluded. R-squared 53.7% (n=225).

	Indirect effect		**Direct effect**		**Total effect**		**Proportion of total effect mediated**
Factor	**Mean diff.**	**95% CI**	**Mean diff.**	**95% CI**	**Mean diff.**	**95% CI**	
ASA class II vs I	2719	-978; 6416	-2109	-4775; 557	610	-3580; 4799	**56%**
ASA class III vs I	5635	-776; 12,047	-2294	-7670; 3083	3341	-5098; 11,780	**71%**
ASA class IV vs I	26245	3534; 48,956	9677	410; 18,944	35,922	13,400; 58,443	**73%**
Comorbidities (per one additional comorbidity)	711	-218; 1640	325	-226; 877	1037	22; 2052	**69%**
Complexity of surgery (Major Plus and CMO vs Minor to Major)	11101	5637; 16,564	-1981	-5816; 1855	9120	5602; 12,639	**85%**
ClassIntra® (per one grade increase)	2184	87; 4281	453	-789; 1694	2637	793; 4481	**83%**
CCI® (per 10 units increase)	5060	659; 9461	148	-985; 1280	5208	855; 9561	**97%**
Length of ICU stay (per one day increase)	696	-1484; 2876	10,707	4706; 16,708	11,403	3465; 19,341	**6.1%**
Length of postop stay (per one day increase)	--	--	2613	1712; 3514	2613	1712; 3514	**--**

Table 13: Main reimbursement model excluding semi-privately and privately insured patients (in Euros)

Coefficients are mean differences in reimbursement; patients with a protracted hospital or ICU stay, recurrent, semi-privately and privately insured patients and patients who died during hospital stay were excluded. R-squared 53.7% (n=225).

	Indirect effect		**Direct effect**		**Total effect**		**Proportion of total effect mediated**
Factor	**Mean diff.**	**95% CI**	**Mean diff.**	**95% CI**	**Mean diff.**	**95% CI**	
ASA class II vs I	-386	-1145; 373	815	-1160; 2790	429	-1468; 2327	**32%**
ASA class III vs I	-836	-2122; 451	3795	-278; 7868	2959	-1083; 7001	**18%**
ASA class IV vs I	-4218	-11,466; 3031	-459	-9870; 8952	-4677	-15,073; 5719	**90%**
Comorbidities (per one additional comorbidity)	-131	-362; 101	-197	-568; 175	-327	-778; 123	**40%**
Complexity of surgery (BUPA Major Plus and CMO vs Minor to Major)	-1524	-3952; 903	853	-1920; 3627	-671	-2514; 1171	**64%**
ClassIntra® (per one grade increase)	-526	-1343; 290	359	-676; 1393	-168	-1065; 729	**59%**
CCI® (per 10 units increase)	-753	-2218; 712	-571	-1695; 552	-1324	-2916; 268	**57%**
Length of ICU stay (per one day increase)	-112	-525; 301	-1502	-4803; 1798	-1614	-5185; 1957	**6.9%**
Length of postop stay (per one day increase)	--	--	-421	-911; 69	-421	-911; 69	--

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