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RESEARCH ARTICLE

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The number of comorbidities as an important cofactor to ASA class in predicting postoperative outcome: An international multicentre cohort study

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Abstract

Background: Multimorbidity is a growing burden in our ageing society and is associated with perioperative morbidity and mortality. Despite several modifications to the ASA physical status classification, multimorbidity as such is still not considered. Thus, the aim of this study was to quantify the burden of comorbidities in perioperative patients and to assess, independent of ASA class, its potential influence on perioperative outcome.

Methods: In a subpopulation of the prospective ClassIntra® validation study from eight international centres, type and severity of anaesthesia-relevant comorbidities

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were additionally extracted from electronic medical records for the current study. Patients from the validation study were of all ages, undergoing any type of in-hospital surgery and were followed up until 30 days postoperatively to assess perioperative outcomes. Primary endpoint was the number of comorbidities across ASA classes. The associated postoperative length of hospital stay (pLOS) and Comprehensive Complication Index (CCI®) were secondary endpoints. On a scale from 0 (no complication) to 100 (death) the CCI® measures the severity of postoperative morbidity as a weighted sum of all postoperative complications.

Results: Of 1421 enrolled patients, the mean number of comorbidities significantly increased from 1.5 in ASA I (95% CI, 1.1–1.9) to 10.5 in ASA IV (95% CI, 8.3–12.7) patients. Furthermore, independent of ASA class, postoperative complications measured by the CCI® increased per each comorbidity by 0.81 (95% CI, 0.40–1.23) and so did pLOS (geometric mean ratio, 1.03; 95% CI, 1.01–1.06).

Conclusions: These data quantify the high prevalence of multimorbidity in the surgical population and show that the number of comorbidities is predictive of negative postoperative outcomes, independent of ASA class.

Editorial Comment

The ASA score does not consider multimorbidity, and this may impact the ability to predict postoperative outcomes. This international observational study assessed comorbidities in 1421 patients undergoing surgery and found the number of comorbidities significantly increased with ASA score up to mean of 8.2 in ASA III and 10.5 in ASA IV. Interestingly, each comorbidity increased the Comprehensive Complication Index independently of ASA score, suggesting multimorbidity as an important addition to ASA classification.

1 | INTRODUCTION

Multimorbidity has become the most common chronic condition in our ageing society.[1] As the number of chronic diseases increases with age, multimorbidity is already present in >60% of those aged ≥65 years among the general population.[2,3] In paediatric patients, the comorbidity burden is generally low but is increasing due to advances in medicine leading to increased survival of complex medical conditions.[4]

Multimorbidity may be defined as "the complex interactions of several co-existing diseases."[5] Most studies use the definition of two or more co-existing medical conditions.[6,7] In general, multimorbidity is associated with functional impairment, poor quality of life,[8] polypharmacy,[9] increased healthcare costs[10] and mortality.[11] With the rising complexity of patients, preoperative risk assessment is of growing importance to guide perioperative management and improve patient outcomes.[12] Many risk assessment tools are available,[12–14] and most require comprehensive knowledge of comorbidities and laboratory results.[14] Yet, a retrospective multicentre study found documentation of individualised preoperative risk assessment to be low[15] but showed an excellent adherence in the documentation of the American Society of Anesthesiologists Physical Status (ASA PS) Classification System by anaesthesiologists. This simple but effective grading system was first introduced in 1941 as a tool for collecting data in scientific analyses.[16] It is widely used for recommendation of preoperative testing,[17] to guide perioperative management[13] and for healthcare billing.[18] Multiple studies have shown that an increase in ASA PS is associated with surgical adverse events,[19] prolonged hospital or intensive care unit stay,[20] and perioperative morbidity and mortality.[21–23] The ASA PS is, therefore, a crucial component for calculating individualised surgical risk in various scores.[18,24] Despite several modifications to the classification,[18,24–26] the single-most severe systemic disease remains decisive in defining a patient's ASA class irrespective of the number and the nature of all other comorbidities. We hypothesised that the single-most severe systemic disease is no longer sufficient to estimate a patient's physical status and that the number of existing comorbidities should also be considered. Therefore, the aim of this international multicentre study was to quantify the number and type of all anaesthesia-relevant comorbidities and to assess how they might influence perioperative outcome independent of the overall ASA class in patients undergoing a broad spectrum of surgical procedures.

2 | METHODS

2.1 | Study design and oversight

All relevant Swiss regional ethics committees approved this secondary research project (lead ethics committee: Ethikkommission Nordwest- und Zentralschweiz, EKNZ Req-2019-00753) and waived written informed consent. Ethical approval was not required for retrospectively collected data from the international centres involved in this study.

This investigator-initiated, international, multicentre, cohort study was conducted in a subset of five Swiss and three international centres from the Netherlands, England and New Zealand. All of these secondary and tertiary care centres had already participated in the prospective study for external validation of ClassIntra®. Suitable for convenience sampling, we focused on a representative subset of ClassIntra® study centres due to the difficulties of the burdensome retrospective assessment of the number and severity of all anaesthesia-relevant comorbidities. Details about the validation study are described elsewhere.[27] To summarise, the objective was to assess the validity of the newly developed classification for assessing intraoperative adverse events (ClassIntra® version 1.0). A total of 2520 in-hospital patients at 18 centres in 12 countries undergoing any type of surgery in the operating room were included in the validation study of Classintra®, were monitored intra- and postoperatively for adverse events until hospital discharge and were followed up to assess 30-day mortality. Patients with ambulatory surgery, patients who declined participation, ASA VI patients (brain-dead organ donor) and patients with follow-up procedures already included in the study or procedures without anaesthesia-involvement were excluded. For assessing intraoperative adverse events in a standardised way, ClassIntra® is the first prospectively validated classification, which is aligned with the Clavien-Dindo classification for recording postoperative complications. To investigate the new research question of the current study, we retrospectively collected information on the number and severity of all anaesthesia-relevant comorbidities within the recruited patients in addition to the already available patient and procedural characteristics. We extracted this information from medical records according to a predefined list (Table S1), and data were entered into an online study database.

2.2 | Anaesthesia-relevant comorbidities

A group of specialists in anaesthesia, internal- and intensive care medicine from the University Hospital of Basel elaborated a list consisting of all anaesthesia-relevant comorbidities (Table S1). Every comorbidity was weighted and assigned to an appropriate ASA class in line with official cut-offs, current definitions or examples detailed by the ASA[26] as if it were the only comorbidity in the corresponding patient. The sources of grading are listed accordingly. Comorbidities without a declared source were graded based on consensus decision of the team.

To assure consistency in data collection, we established rules for several common comorbidities. Any patient with type 1 or 2 diabetes with accurate treatment and compliance was considered a well-controlled ASA II patient. However, if diabetic patients presented with haemoglobin A1c (HbA1c) values >6.4%, they were classified as ASA III. When scoring ASA grade based on metabolic equivalents (MET) in trauma patients, we used their MET score achieved prior to their trauma. If anticoagulatory treatment was stopped early enough, coagulation was considered as normal. Supposing that an anaesthesia-relevant comorbidity was not included in our list, it was described under the term “others” and weighted according to its severity.

2.3 | Missing data, data collection and measurements

Our local research team at the different centres guaranteed a high quality of retrospective data extraction from electronic medical records as well as anaesthesia protocols based on questionnaires, patient self-reports and dialogue from the pre-anaesthetic assessment. In case of doubt or contradictory weighting of the extracted comorbidities compared to initial ASA class in the pre-anaesthesia protocol, the patient was reviewed and a decision was made after discussion within the team. If information regarding smoking behaviour or drug abuse was lacking, we assumed the patient to be abstinent. Likewise, in the absence of other information (e.g., electrocardiograph [ECG] or laboratory results), we classified the patient under the corresponding comorbidity as healthy (i.e., ASA I for the corresponding comorbidity).

2.4 | Study outcomes

The number and severity of anaesthesia-relevant comorbidities across the ASA classes of the patients were defined as the primary endpoint. Secondary endpoints were the associated perioperative outcomes intraoperative adverse events (iAE), postoperative length of hospital stay (pLOS) and the weighted sum of all postoperative complications according to the Comprehensive Complication Index (CCI®).[28] The CCI® is a validated index, which quantifies postoperative morbidity as a weighted sum of all postoperative complications according to Clavien Dindo[29] on a scale from 0 (no complication) to 100 (death).

2.5 | Statistical analysis

Baseline characteristics were summarised using mean (SD), median (IQR) or absolute (relative) frequencies as appropriate.

A mixed Poisson regression model with robust variance estimates, including overall ASA class as a fixed factor along with random intercepts and random slopes of ASA class (as a numerical variable) at the level of centres was used to determine whether the number of comorbidities increased with increasing overall ASA class (primary endpoint).

TABLE 1 Patient and procedural characteristics for the total study population ($n = 1421$) and for subgroups across all ASA PS classes.

	All patients ($n = 1421$, 100%)	ASA I patients ($n = 239$, 16.8%)	ASA II patients ($n = 676$, 47.6%)	ASA III patients ($n = 448$, 31.5%)	ASA IV patients ($n = 58$, 4.1%)
Age, median (IQR)					
Overall	57 (36–70)	24 (12–43)	54 (37–68)	68 (57–75)	71 (66–81)
Age < 16 year	7 (4–12)	8 (5–12)	6 (3–10)	9 (3–13)	–
Age ≥ 16 year	59 (45–71)	35 (24–49)	56 (42–69)	68 (58–75)	70.5 (66–81)
Sex, *n* (%)					
Female	672 (47%)	108 (45%)	348 (51%)	192 (43%)	24 (41%)
Male	749 (53%)	131 (55%)	328 (49%)	256 (57%)	34 (59%)
Body mass index (kg/m^2), mean (SD)[a]					
Overall	26.6 (6.5)	23.1 (5.2)	26.3 (5.9)	28.7 (7.2)	26.8 (6.7)
Age < 16 year	18.2 (5.0)	18.5 (5.9)	18.0 (3.8)	15.5 (1.7)	–
Age ≥ 16 year	27.3 (6.2)	24.7 (3.7)	26.9 (5.5)	28.8 (7.2)	26.8 (6.7)
Surgical discipline, *n* (%)					
Gastrointestinal surgery	519 (37%)	54 (23%)	274 (41%)	181 (40%)	10 (17%)
Orthopaedic surgery and traumatology	283 (20%)	84 (35%)	147 (22%)	51 (11%)	1 (1.7%)
Vascular surgery	135 (10%)	3 (1.3%)	29 (4.3%)	90 (20%)	13 (22%)
Ear, nose, throat and maxillofacial surgery	110 (7.7%)	38 (16%)	54 (8.0%)	17 (3.8%)	1 (1.7%)
Neurosurgery and spine surgery	73 (5.1%)	2 (0.8%)	39 (5.8%)	29 (6.5%)	3 (5.2%)
Cardiac surgery	69 (4.9%)	–	15 (2.2%)	29 (6.5%)	25 (43%)
Urological surgery	60 (4.2%)	11 (4.6%)	27 (4.0%)	20 (4.5%)	2 (3.5%)
Paediatric surgery	54 (3.8%)	33 (14%)	20 (3.0%)	1 (0.2%)	–
Gynaecology	44 (3.1%)	4 (1.7%)	26 (3.9%)	13 (2.9%)	1 (1.7%)
Obstetrics	44 (3.1%)	8 (3.4%)	32 (4.7%)	4 (0.9%)	–
Reconstructive and hand surgery	19 (1.3%)	2 (0.8%)	8 (1.2%)	8 (1.8%)	1 (1.7%)
Thoracic surgery	11 (0.8%)	–	5 (0.7%)	5 (1.1%)	1 (1.7%)
Urgency of the procedure, *n* (%)					
Planned	1248 (88%)	196 (82%)	596 (88%)	407 (91%)	49 (84%)
Unplanned	173 (12%)	43 (18%)	80 (12%)	41 (9.2%)	9 (16%)
Complexity of surgical procedure (original), *n* (%)[b]					
Minor	56 (3.9%)	11 (4.6%)	30 (4.4%)	13 (2.9%)	2 (3.5%)
Intermediate	229 (16%)	67 (28%)	100 (15%)	56 (13%)	6 (10%)
Major	433 (30%)	101 (42%)	225 (33%)	99 (22%)	8 (14%)
Major +	266 (19%)	33 (14%)	151 (22%)	76 (17%)	6 (10%)
Complex major	437 (31%)	27 (11%)	170 (25%)	204 (46%)	36 (62%)
Anaesthesia technique, *n* (%)					
General anaesthesia	1057 (74%)	180 (75%)	498 (74%)	330 (74%)	49 (84%)
Regional anaesthesia	122 (8.6%)	22 (9.2%)	62 (9.2%)	35 (7.8%)	3 (5.2%)
Combined techniques	225 (16%)	37 (15%)	110 (16%)	76 (17%)	2 (3.5%)
Monitored anaesthesia care	17 (1.2%)	–	6 (0.9%)	7 (1.6%)	4 (6.9%)

[a] 46 missing values overall; 3 missing values in patients aged ≥16 year; 43 missing values in patients aged <16 year; due to missing height.
[b] $n = 44$ undefined according to BUPA. Replaced with a grade corresponding to a similar procedure as defined through consensus by the core team and clinical experts in the field.

Multivariable mixed linear, log-linear, and logistic regression models, including random intercepts for the study centres, were used to investigate the association with secondary endpoints. Due to the low comorbidity burden in children, we excluded patients aged <16 years from multivariable analysis of the secondary endpoints. For each of the secondary endpoints, three different models were compared using the Akaike information criterion (AIC) and the Bayesian information criterion (BIC): (i) a model only considering overall ASA class, (ii) a model considering overall ASA class and the number of comorbidities added as a simple count, and (iii) a model considering overall ASA class and a weighted comorbidity count in which the severity grades of each comorbidity (i.e., the ASA classes of each comorbidity) were added. The analyses of all secondary endpoints were additionally adjusted for predefined factors such as age, sex, complexity and urgency of the surgical procedure, wound class and experience of the involved surgical team. Surgical experience was quantified based on the present team members (for details see supplementary file of the validation study of Classintra®).[27] The complexity of the surgical procedure was categorised into five grades according to the British United Provident Association (BUPA).[30] Groups of intermediate/major and major plus/complex major were compared to minor complexity surgical procedures as the reference group. When an undefined or missing complexity grade in the BUPA classification system was found, the grade of a similar procedure was used based on a consensus of the core team and clinical experts in the field. iAEs were categorised according to ClassIntra®,[27] and all postoperative adverse events according to Clavien-Dindo[29] and were afterwards summarised in the CCI®.[28] All analyses and graphs were made using Stata® IC version 16.1 for Mac (StataCorp, College Station, TX, USA).

3 | RESULTS

3.1 | Baseline characteristics

A total of 1421 patients were enrolled in our analysis from eight included study centres. The median age of included patients was 57 years (IQR, 36–70); 47% ($n = 672$) were female (Table 1). The median age for patients <16 years ($n = 148$) was 7 years (IQR, 4–12); whereas for patients ≥16 years ($n = 1273$), the median age was 59 years (IQR, 45–71). The patients were treated in 12 surgical disciplines, with numbers of surgeries ranging from 11 (1%) in thoracic surgery to 519 (37%) in gastrointestinal surgery. Most procedures were planned (88%, $n = 128$), were of major, major plus or complex major complexity (80%, $n = 1136$) and were performed under general anaesthesia (74%, $n = 1057$) (Table 1). Patients were classified as ASA I in 17% ($n = 239$), ASA II in 48% ($n = 676$), ASA III in 32% ($n = 448$) and ASA IV in 4% ($n = 58$) of the cases. No patients were classified as ASA V.

3.2 | Primary endpoint

Multimorbidity, defined as ≥2 anaesthesia-relevant comorbidities, was present in 84% of patients (Table S2). Overall, patients had a median number of five comorbidities (IQR, 5.5–17.5; range, 0–23). This number significantly increased with higher overall ASA class, prospectively assigned by the anaesthesiologist in charge, with a geometric mean of 1.5 comorbidities in ASA I (95% CI, 1.1–1.9), of 4.3 (95% CI, 3.4–5.2) in ASA II, of 8.2 (95% CI, 6.6–9.9) in ASA III and of 10.5 comorbidities in ASA IV patients (95% CI, 8.3–12.7; Figure 1 and Table S3). There was also an increase in the severity of the comorbidities in patients with higher overall ASA classes (Figure 2). In 33% of ASA III and in 45% of ASA IV patients, comorbidities were graded ASA III or higher (Table 2). The most common retrospectively assessed comorbidities were any degree of renal insufficiency ($n = 522$), hypertension ($n = 520$), smoking ($n = 440$), allergies ($n = 408$), the risk for aspiration ($n = 378$), body mass index (BMI) ($n = 372$) and malignant tumours ($n = 359$).

3.3 | Secondary endpoints

Multivariable regression analysis revealed consistent results for CCI® and pLOS. Both endpoints generally increased with rising ASA class, but this association strongly decreased when the number of comorbidities was included in the model (Tables 3 and 4), while the association of these endpoints with the number of comorbidities was clinically relevant. On average, each additional comorbidity, considered as a simple count, led to an increase in mean CCI® by 0.81 (95% CI, 0.40–1.23) and an increase in geometric mean ratio of pLOS by 3% (GMR, 1.03; 95% CI, 1.01–1.06), independent of the ASA class. The models for both endpoints performed best when comorbidities were included as a simple count, with no relevant improvement by including a weighted comorbidity count. The association of the number of comorbidities with CCI® estimated using the regression model is illustrated in Figure 3. The mean value of CCI® increases on average with the number of comorbidities, independent of the ASA class. In the final model including the number of comorbidities as a simple count, longer duration of surgery, emergency procedure and contaminated wounds prior to surgery all increased CCI® and pLOS (Tables 3 and 4). In addition, complex and major procedures were associated with increased pLOS, and males had shorter hospital stays than females (Table 3).

Similarly, the risk for any iAE increased with a higher ASA class. This association was also attenuated as soon as the number of comorbidities was included. However, none of these associations concerning iAE was clinically relevant. Here, the model without considering comorbidities as an independent co-factor performed marginally better than the other models. Only emergency procedures showed a clinically relevant increase in risk for any iAE (Table 5).

4 | DISCUSSION

This international multicentre study confirms a high prevalence of multimorbidity and quantifies its burden in a large surgical population undergoing in-hospital procedures from all surgical disciplines in different-sized hospital settings. The results further demonstrate that

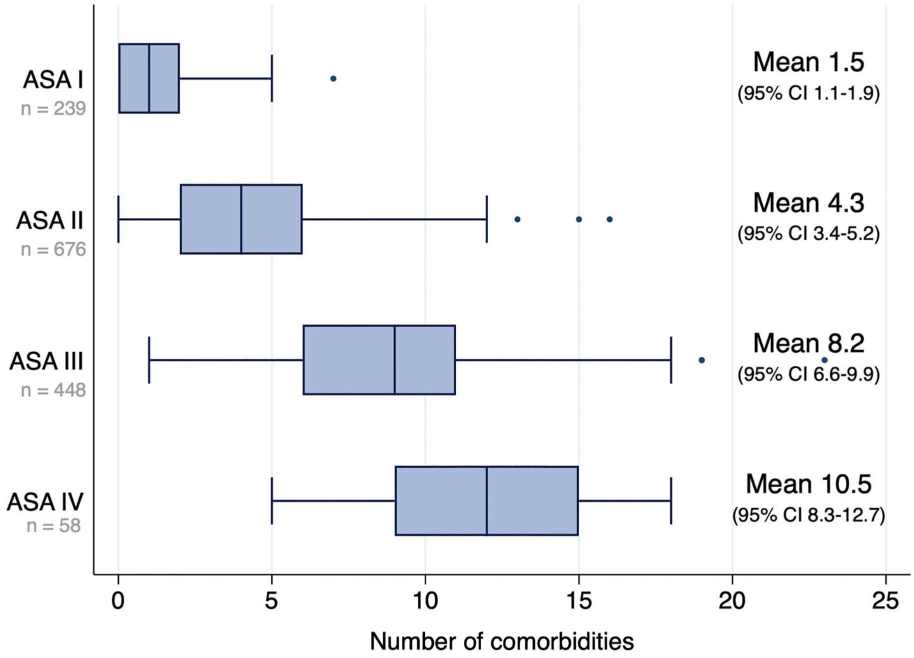

FIGURE 1 Number of comorbidities retrospectively assigned by the study team across the overall ASA class of the patients, preoperatively assigned by the anaesthesiologist in charge ($n = 1421$). Boxplots show the median number (quartiles and range) of all anaesthesia-relevant comorbidities of each patient (regardless of severity) across all ASA classes. The geometric mean numbers and 95% CIs have been estimated using a mixed Poisson regression model with random intercepts for the study centres and robust variance estimates.

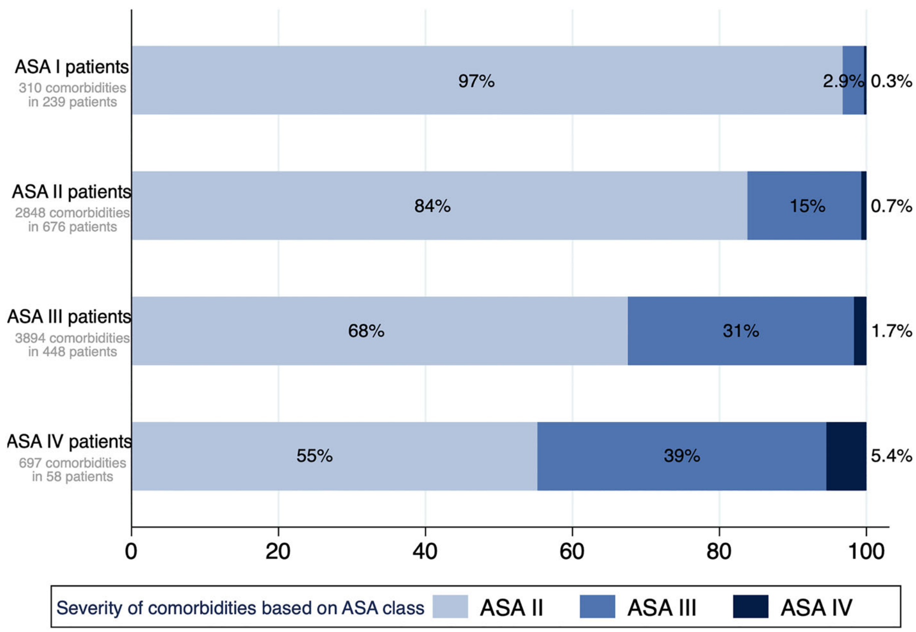

FIGURE 2 Number and severity of comorbidities according to ASA class ($n = 1421$). The patient's overall ASA class, preoperatively assigned by the anaesthesiologist in charge, is shown on the y-axis. ASA classes for all anaesthesia-relevant comorbidities were retrospectively assigned by the study team for the purpose of this study as if it were the only one in this patient (shown in percent on the x-axis). All anaesthesia-relevant comorbidities are plotted according to their number and severity across all patients, subdivided by the patient's overall ASA class. In 239 patients preoperatively assigned to ASA I, 97% of the 310 retrospectively identified comorbidities are assigned to ASA class II. As the comorbidities were not evenly distributed among the patients, there were patients with several comorbidities (mean value 1.5, see Figure 1) as well as those without comorbidities.

independent from the overall ASA class, the number of comorbidities is a strong predictor of the weighted sum score of all postoperative complications (CCI®) and of pLOS. The models using the simple count of comorbidities outperformed the models that only included ASA PS. On the other hand, ASA PS and simple as well as weighted comorbidity counts were not associated with iAEs.

Our results are in line with studies based on administrative data regarding outcome. Wu et al. showed that the number of

TABLE 2 Comorbidities for the total study population ($n = 1421$) and for subgroups across all ASA PS classes.

	All patients ($n = 1421$, 100%)	ASA I patients ($n = 239$, 16.8%)	ASA II patients ($n = 676$, 47.6%)	ASA III patients ($n = 448$, 31.5%)	ASA IV patients ($n = 58$, 4.1%)
Number of comorbidities, median (range)	5 (0–23)	1 (0–7)	4 (0–16)	9 (1–23)	12 (5–18)
Highest severity grade according to comorbidity grades, *n* (%)					
ASA I	81 (5.7%)	76 (32%)	5 (0.7%)	–	–
ASA II	572 (40%)	153 (64%)	374 (55%)	45 (10%)	–
ASA III	655 (46%)	9 (3.8%)	277 (41%)	343 (77%)	26 (45%)
ASA IV	113 (8.0%)	1 (0.4%)	20 (3.0%)	60 (13%)	32 (55%)
ASA class of comorbidities (several per patient possible), *n* (%)					
ASA II	5703 (74%)	300 (97%)	2388 (84%)	2630 (68%)	385 (55%)
ASA III	1923 (25%)	9 (2.9%)	441 (15%)	1199 (31%)	274 (39%)
ASA IV	125 (1.6%)	1 (0.3%)	20 (0.7%)	66 (1.7%)	38 (5.4%)
Groups of comorbidities, *n* (%)					
Cardiovascular/coagulation	729 (51%)	8 (3.4%)	286 (42%)	379 (85%)	56 (97%)
Others[a]	696 (49%)	61 (26%)	332 (49%)	271 (60%)	32 (55%)
Airway (incl. BMI and risk for aspiration)	679 (48%)	63 (26%)	331 (49%)	259 (58%)	26 (45%)
Liver/kidney	622 (44%)	15 (6.3%)	250 (37%)	303 (68%)	54 (93%)
Pulmonary	590 (42%)	43 (18%)	252 (37%)	264 (59%)	31 (53%)
Metabolic disorder (including diabetes, etc.)	451 (32%)	7 (2.9%)	161 (24%)	245 (55%)	38 (66%)
Neurology	438 (31%)	8 (3.4%)	192 (28%)	208 (46%)	30 (52%)
Trauma	409 (29%)	29 (21%)	141 (21%)	200 (45%)	39 (67%)
Allergies	408 (29%)	39 (16%)	203 (30%)	147 (33%)	19 (33%)
Substance abuse (e.g., alcohol, drugs)	268 (19%)	19 (8.0%)	118 (17%)	116 (26%)	15 (26%)
Pregnancy	41 (2.9%)	5 (2.1%)	32 (4.7%)	4 (0.9%)	–

[a]Incl. malignant hyperthermia, MH-associated muscular disease, neuromuscular disorders, rheumatism, malignant tumour, infection, transplantation.

comorbidities is equally associated with postoperative complications.[31] Fowler et al. found that the risk of death within 90 days after surgery increased 10-fold and 20-fold in patients with one and more than one chronic disease, respectively.[32] The results in both studies were not adjusted for ASA class. However, the prevalence of multimorbidity in the two studies was lower than the documented 84% in our data. This prevalence varies widely in the literature, ranging from 3.5% to 98.5% and is affected by the definition of multimorbidity, the sources for data collection and the number of comorbidities allowed for assessment.[6] Accordingly, the high prevalence in our study could be explained by our high-quality data and the large number of selected acute and chronic comorbidities. As part of the National Audit Project (NAP) in the United Kingdom, the Royal College of Anaesthetists has identified an increase in the comorbidity burden over the last decade. Surgical, non-obstetric patients are older, more obese and have higher ASA PS scores.[33]

In addition to quantifying the comorbidity burden, this study corroborates and supplements existing literature in showing its strong association with postoperative adverse outcomes.[31,32,34] In a single-centre analysis, we were already able to show its association with increased hospital costs, independent of the ASA class.[35] In the present multicentre cohort, we were able to better predict negative postoperative outcomes by including the number of all anaesthesia-relevant comorbidities than by using the single-disease ASA-PS framework. To the best of our knowledge, this has never been quantified and demonstrated in high-quality data of a large international population-based cohort.

One of the main strengths of this study is the international multicentre design including a large number and broad spectrum of surgical patients, hospitals and surgical disciplines, allowing for high generalisability. However, the sample size was inadequate for the analysis of a hard single endpoint like mortality. Instead, we used the CCI® (i.e., the

TABLE 3 Mixed linear regression models for CCI®.

Factor	Without comorbidity count Mean difference (95% CI)	Simple comorbidity count Mean difference (95% CI)	Weighted comorbidity count Mean difference (95% CI)
ASA class			
ASA II versus I	1.34 (−0.97–3.65)	−0.42 (−3.25–2.41)	−0.22 (−2.90–2.45)
ASA III versus I	5.76 (0.82–10.69)	1.00 (−5.83–7.83)	0.85 (−5.75–7.46)
ASA IV versus I	19.66 (6.74–32.59)	12.72 (0.98–24.46)	11.43 (1.44–21.41)
Comorbidities (per increase by one)	–	0.81 (0.40–1.23)	0.59 (0.24–0.94)
Age, year (per decade increase)	0.06 (−0.74–0.87)	−0.36 (−1.17–0.44)	−0.35 (−1.18–0.48)
Sex, male versus female	−0.56 (−2.16–1.05)	−0.88 (−2.33–0.56)	−0.96 (−2.44–0.51)
Length of surgery (per 10-min increase)	0.56 (0.31–0.80)	0.56 (0.33–0.78)	0.56 (0.33–0.79)
Wound class; non-clean versus clean	3.46 (0.59–6.33)	3.76 (1.14–6.37)	3.82 (1.18–6.46)
Complexity of surgical procedure (BUPA)			
Intermediate/major versus minor	−3.64 (−7.28–0.01)	−3.37 (−6.72–0.03)	−3.33 (−6.53–0.13)
Major+/complex major versus minor	−0.47 (−3.82–2.88)	−0.25 (−3.43–2.92)	−0.23 (−3.23–2.77)
Urgency of procedure; emergency versus planned	5.39 (1.07–9.71)	5.16 (0.79–9.53)	5.19 (0.79–9.59)
Experience of surgical team			
Low versus excellent	3.08 (−1.58–7.74)	2.67 (−2.12–7.45)	2.49 (−2.24–7.22)
Intermediate versus excellent	1.49 (−3.07–6.05)	1.36 (−3.40–6.11)	1.25 (−3.56–6.06)
Good versus excellent	−0.43 (−5.06–4.20)	−0.80 (−5.36–3.75)	−1.04 (−5.55–3.48)
Very good versus excellent	1.22 (−5.02–7.45)	0.47 (−5.40–6.34)	0.29 (−5.58–6.15)
AIC/BIC	10,890.63/10,978.16	10,872.99/10,965.67	10,871.32/10,964.01

Note: Random intercepts for the study centres and robust variance estimates were used with and without taking the number (simple comorbidity count) and severity (weighted comorbidity count) of comorbidities into account. Preoperative overall ASA class assignment by the anaesthesiologist in charge is considered ($n = 1273$, excluding patients aged <16 years).

weighted sum of all postoperative complications) including in-hospital mortality. Another strength is the high-quality data based on detailed outcomes prospectively collected in the validation study of ClassIntra® to which the current meticulously collected data about all comorbidities was correlated. One limitation is the retrospective collection of the number and type of all anaesthesia-relevant comorbidities. We increased accuracy by using multiple sources of data collection such as perioperative anaesthetic documentation, discharge letters, laboratory results and ECGs. This has been advocated to provide more reliable estimates and to minimise the risk of underreporting disease burden.[6] Compared to administrative data, our information of various detailed electronic health records allowed a better assessment of the overall comorbidity burden and a classification of the severity of each comorbidity. The source of data has a huge impact on its quality. Information about multimorbidity is largely extracted from patient self-reports or medical records and administrative databases.[7] Data from detailed sources assessing multimorbidity in a broad surgical population using simple and weighted counts of comorbidities was lacking so far.

In addition to the inconsistency of sources and measured outcomes, the absence of a standardised definition of multimorbidity further impedes comparability of the existing data. The authors of a review referring to the subject found that multimorbidity is generally measured by a simple count of conditions.[7] Weighted indices, mostly derived versions of the Charlson Comorbidity Index, are used less often but predominantly in hospital settings. The Charlson Comorbidity Index consists of initially 19 comorbidities with different fixed weights based on the adjusted risk of one-year mortality.[36]

The less frequently used Cumulative Illness Rating Scale (CIRS) measures the comorbidity burden based on the individually graded impairment of 14 organ systems.[37] Bo et al. demonstrated its association with mortality and prolonged hospitalisation in older surgical patients.[34] Compared to the CIRS, we increased the number of selected conditions allowing for several conditions in each organ system. To our knowledge, little is known about how the severity of comorbidities influences perioperative outcomes, and the need for such research has been stated.[38] We hypothesised a better prediction of adverse events when the severity is taken into account. Surprisingly, our weighted count showed limited added value especially when compared to the effort put into its assessment. Therefore, in line with the literature, our finding suggests a simple count of comorbidities to be sufficient for predicting clinical outcomes.[7] The connection

TABLE 4 Mixed log-linear regression models for length of postoperative stay.

Factor	Without comorbidity count Geometric mean ratio (95% CI)	Simple comorbidity count Geometric mean ratio (95% CI)	Weighted comorbidity count Geometric mean ratio (95% CI)
ASA class			
ASA II versus I	1.17 (1.01–1.36)	1.09 (0.95–1.24)	1.10 (0.96–1.25)
ASA III versus I	1.53 (1.22–1.92)	1.26 (1.05–1.52)	1.26 (1.07–1.49)
ASA IV versus I	2.43 (1.72–3.42)	1.84 (1.45–2.33)	1.76 (1.47–2.11)
Comorbidities (per increase by one)	–	1.03 (1.01–1.06)	1.02 (1.00–1.05)
Age, year (per decade increase)	1.02 (1.01–1.04)	1.01 (0.99–1.03)	1.01 (0.99–1.03)
Sex, male versus female	0.89 (0.82–0.98)	0.88 (0.80–0.96)	0.88 (0.80–0.96)
Length of surgery (per 10-min increase)	1.03 (1.03–1.04)	1.04 (1.03–1.04)	1.04 (1.03–1.04)
Wound class; non-clean versus clean	1.20 (1.00–1.45)	1.21 (1.01–1.46)	1.21 (1.01–1.46)
Complexity of surgical procedure (BUPA)			
Intermediate/major versus minor	0.87 (0.71–1.07)	0.88 (0.72–1.07)	0.88 (0.73–1.07)
Major+/complex major versus minor	1.32 (1.10–1.60)	1.33 (1.11–1.60)	1.33 (1.12–1.60)
Urgency of procedure, emergency versus planned	1.28 (1.09–1.49)	1.26 (1.07–1.48)	1.26 (1.07–1.49)
Experience of surgical team			
Low versus excellent	1.01 (0.74–1.36)	0.99 (0.72–1.36)	0.98 (0.71–1.36)
Intermediate versus excellent	0.94 (0.75–1.19)	0.94 (0.74–1.20)	0.93 (0.73–1.20)
Good versus excellent	0.92 (0.75–1.12)	0.91 (0.74–1.10)	0.90 (0.74–1.09)
Very good versus excellent	0.79 (0.54–1.14)	0.77 (0.52–1.13)	0.76 (0.51–1.14)
AIC/BIC	2765.41/2852.95	2748.34/2841.02	2748.06/2840.74

Note: Random intercepts for the study centres and robust variance estimates were used with and without taking the number (simple comorbidity count) and severity (weighted comorbidity count) of comorbidities into account. Preoperative overall ASA class assignment by the anaesthesiologist in charge is considered ($n = 1273$, excluding patients aged <16 years).

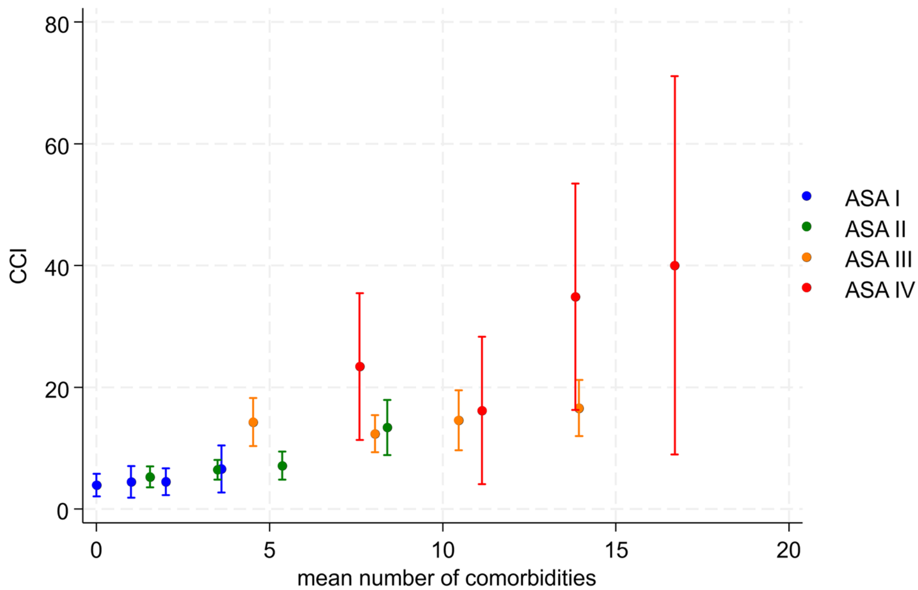

FIGURE 3 Mean CCI® in relation to the number of comorbidities and the patient's overall ASA class, preoperatively assigned by the anaesthesiologist in charge ($n = 1421$). The figure shows the mean values of CCI® with 95% CIs in the quartile classes of the number of comorbidities for ASA I (blue), ASA II (green), ASA III (orange) and ASA IV (red) patients. The x-coordinates of the dots are the mean values of the number of comorbidities in the respective quartile classes.

between ASA PS, functional capacity and frailty as well as their association with adverse surgical outcomes is of growing interest.[18,24] George et al. found frailty to be associated with postoperative mortality in a noncardiac patient cohort.[39] We aimed to include different frailty scores in our analysis, but a retrospective grading of frailty was not feasible.

In addition to quantifying a patient's physical status, surgical risk calculators use a selected number of patient- and surgery-related

TABLE 5 Mixed logistic regression models for any or no intraoperative adverse event according to ClassIntra® classification.

Factor	Without comorbidity count Odds ratio (95% CI)	Simple comorbidity count Odds ratio (95% CI)	Weighted comorbidity count Odds ratio (95% CI)
ASA class			
ASA II versus I	1.31 (0.78–2.19)	1.27 (0.75–2.16)	1.25 (0.74–2.12)
ASA III versus I	1.90 (1.09–3.30)	1.76 (0.94–3.30)	1.67 (0.89–3.11)
ASA IV versus I	1.89 (0.85–4.17)	1.69 (0.68–4.19)	1.51 (0.59–3.85)
Comorbidities (per increase by one)	–	1.01 (0.96–1.07)	1.02 (0.98–1.05)
Age, year (per decade increase)	1.06 (0.97–1.16)	1.05 (0.96–1.16)	1.05 (0.95–1.15)
Sex, male versus female	1.00 (0.76–1.31)	0.99 (0.75–1.31)	0.98 (0.75–1.30)
Wound class, non-clean versus clean	1.01 (0.72–1.42)	1.02 (0.73–1.42)	1.02 (0.73–1.43)
Complexity of surgical procedure (BUPA)			
Intermediate/major versus minor	1.82 (0.76–4.34)	1.82 (0.76–4.35)	1.83 (0.76–4.36)
Major+/complex major versus minor	2.91 (1.21–6.98)	2.92 (1.22–7.00)	2.94 (1.23–7.04)
Urgency of procedure, emergency versus planned	1.88 (1.18–3.00)	1.88 (1.18–2.99)	1.87 (1.18–2.98)
Experience of surgical team			
Low versus excellent	0.93 (0.58–1.50)	0.93 (0.58–1.49)	0.92 (0.57–1.48)
Intermediate versus excellent	0.84 (0.54–1.32)	0.84 (0.53–1.32)	0.83 (0.53–1.31)
Good versus excellent	0.47 (0.28–0.80)	0.47 (0.27–0.79)	0.46 (0.27–0.79)
Very good versus excellent	0.53 (0.25–1.12)	0.52 (0.25–1.11)	0.51 (0.24–1.09)
AIC/BIC	1338.21/1415.44	1339.97/1422.36	1339.43/1421.82

Note: Random intercepts for the study centres and robust variance estimates were used with and without taking the number (simple comorbidity count) and severity (weighted comorbidity count) of comorbidities into account. Preoperative overall ASA class assignment by the anaesthesiologist in charge is considered ($n = 1273$, excluding patients aged <16 years).

conditions to estimate the risk for postoperative complications. They often include the ASA PS for assessing a patient's physical reserve. The American College of Surgeons National Surgery Quality Improvement Program (ACS-NSQIP) Surgical Risk Calculator is widely used and includes data from all surgical subspecialities.[40] However, a recent review showed unconvincing performance in predicting postoperative complications in a variety of surgical disciplines.[41] Including the comorbidity burden into the ASA PS could possibly improve the risk calculator's prediction of adverse postoperative outcomes.

Multimorbidity reduces physical and cognitive function through various mechanisms such as complex disease and drug interactions.[42] Its integration into the ASA PS might follow up on the idea of Horvath et al. to refine the classification.[18] Multimorbidity could be integrated by counting comorbidities with the number referring to an appropriate ASA class defined by cut-offs. More detailed analyses with a comparison of the performance of different scores and our simple solution of integrating the (unweighted) number of all comorbidities were beyond the scope of this study. The additional assessment of frailty as much as an inclusion of both in- and outpatients would be desirable for future studies, although the comorbidity burden is expected to be clearly lower in an outpatient population.

Prospective research is needed concerning the type as well as the number of conditions that define multimorbidity in the perioperative setting, how it could be integrated into the ASA PS and whether its integration would improve prediction of adverse events.

4.1 | Conclusions

The ASA PS Classification System was introduced over 80 years ago when multimorbidity was the exception and not the rule. The complexity of surgical patients has increased over time, and multimorbidity has become the most common chronic condition in our ageing society. This study has enabled us to quantify the epidemiology of anaesthesia-relevant comorbidities in a broad surgical cohort. Accurate perioperative risk stratification is of growing importance to optimise surgical outcomes. The ASA PS, an important variable in multiple surgical risk calculators, and its focus on the most severe comorbidity could be optimised to fully characterise a patient's physical status. Correspondingly, our study shows that the number of comorbidities is associated with negative postoperative outcomes, independent of ASA class.

AUTHOR CONTRIBUTIONS

Conceptualisation: Salome Dell-Kuster, Christian A. Grob, Luzius W. Angehrn, Luzius A. Steiner. Methodology: Salome Dell-Kuster, Christian Schindler, Luzius W. Angehrn, Christian A. Grob, Mark Kaufmann. Formal and Statistical Analysis: Salome Dell-Kuster, Christian Schindler, Luzius W. Angehrn, Christian A. Grob. Investigation: Christian A. Grob, Luzius W. Angehrn, Sonja Joller, Larsa Gawria, Kim Albers, Jonathon Murtagh, Sonja Meier, Heinz R. Bruppacher. Resources: Dieter Hahnloser, Michael Winiker, Thomas O. Erb, Philippe Schumacher,

Gregory O'Grady, Luzius A. Steiner. Writing–Original Draft: Christian A. Grob, Luzius W. Angehrn, Salome Dell-Kuster. Writing–Review and Editing: All authors.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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