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A new medication-based prediction score for postoperative delirium in surgical patients: Development and proof of feasibility in a retrospective patient cohort

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Structured risk screening for postoperative delirium (POD) considering prehospital medication is not established. We aimed to develop a POD-risk prediction score based on known risk factors and delirium-risk increasing drugs to be used by pharmacists during medication reconciliation at hospital admission, and to test for feasibility in a retrospective cohort of surgical patients. Therefore, established POD-risk factors and drugs were extracted from the literature and a score was generated. Following this, the score was tested for feasibility in a retrospective 3-month-cohort of surgical patients. For patients with higher scores suggesting higher probability of POD, patient charts were screened for documentation of POD. For development of the score, the following POD-risk factors were defined and points assigned for score calculation: age (≥65 years=1 point/≥75 years=2), male sex (1), renal insufficiency (RI; 1), hepatic impairment (HI; Model-of-endstage-liver-disease (MELD) 10-14=1/≥15=2), delirium-risk increasing drugs (1 point per drug class), anticholinergic drug burden (ACB; ≥3=1). In the retrospective test cohort of 1174 surgical patients these factors concerned: age ≥65 years 567 patients (48%)/≥75 years 303 (26%), male 652 (55%), RI 238 (20%), MELD 10-14 106 (9%)/≥15 65 (5%), ≥ 1 delirium-risk increasing drug 418 (36%), ACB ≥3 106 (9%). The median POD-risk prediction score was 2 (range 0-9). Of 146 patients (12%) with a score ≥ 5, POD was documented for 43 (30%), no evidence for POD for 91 (62%) and data inconclusive for 12 (8%). For scores of ≥ 7, POD was documented for 50% of the patients with sufficient POD documentation. Overall, POD documentation was poor. To summarize, we developed and successfully tested the feasibility of a POD-prediction-score assessable by pharmacists at medication reconciliation at hospital admission.

1. Introduction

Delirium is an acute confusional state characterized by a disturbance in attention and awareness (American Psychiatric Association 2013). It develops rapidly, usually within hours or days, and is typically caused by medical conditions, drugs, substance intoxication or withdrawal (Francis 2019; Wilson et al. 2020). In hospitalized patients, incidences are 20-30% on peripheral wards and up to 80% on intensive care units (ICU) (Aldecoa et al. 2017; NICE 2010, Wilson et al. 2020). Postoperative delirium (POD) is an adverse postoperative complication affecting 3-54% of all surgical patients (Francis 2019; Hernandez et al. 2017; Wilson et al 2020). POD can occur as early as in the recovery room up to five days after surgery and last one to 30 days (Aitken et al. 2017; Aldecoa et al. 2017). The clinical consequences are severe with increased short and long-term mortality, prolonged ICU and overall hospital stay, long term cognitive impairment, dementia and care dependency (Francis 2019; Olotu 2020).

A number of predisposing and precipitating factors have been identified for POD. Higher age is a well-studied risk factor with growing importance in view of an ageing population (Aldecoa et al. 2017). Several co-morbidities increase the risk like cerebro- and cardiovascular diseases, anaemia, diabetes mellitus, renal insufficiency (RI), hepatic impairment (HI), Parkinson´s disease, depression and anxiety disorders (Aldecoa et al. 2017; Bowman et al. 2020; Francis 2019). Precipitating factors may cause acute delirium in a susceptible patient, e.g. pain, infection, dehydra-

tion, metabolic disturbances, stress and disorientation (Aitken et al. 2017; Aldecoa et al. 2017; Francis 2019). Importantly, drugs cause 12-39% of all delirium cases (Francis 2019). This especially concerns drugs targeting the central nervous system (CNS) with sedative, hypnotic, antidepressant and anticholinergic effects (Francis 2019; Kassie et al. 2017; NICE 2010). Analogous to the established term of `fall-risk increasing drugs´ (FRIDS), those drugs could be summarized as `delirium-risk increasing drugs´ (DRIDS). Interestingly, the CNS adverse effect burden arising from a medication list was positively associated with delirium diagnosis (McCoy et al. 2021). Moreover, for at least every third in-hospital patient with delirium, pre-hospital intake of DRIDS was found (Kassie et al. 2019).

To avoid the severe clinical consequences of delirium, screening for patients at risk is recommended. For high-risk patients, preventive measures could be implemented in anaesthesia and on the ward (Francis 2019; NICE 2010; NHS Scotland 2019). Interestingly, the occurrence of delirium was predictable from risk factors extracted from electronic patient charts (Bowman et al. 2020). A preoperative medication review can decrease the delirium-risk and is recommended by the European Association of Anaesthesiology (De Hert et al. 2018; Francis 2019). However, despite their well-known role in delirium development, recently published POD-risk prediction scores do not consider drugs as a variable (De la Varga-Martinez et al. 2021; Kim et al. 2016; Kim et al. 2020; Menzenbach et al. 2022; Oberai et al. 2021).

In addition, for the timely implementation of preventive measures it is important to detect patients at risk early. This task could be part of the medication reconciliation (MR) by pharmacists at hospital admission. A useful tool for quick identification of patients at risk are scores which could be integrated in clinical decision support systems (CDSS). Therefore, we aimed to develop a POD-risk prediction score based on pre-hospital medication and established POD-risk factors available for pharmacists at MR. Subsequently, this score was to be tested for feasibility in a retrospective cohort of surgical patients.

2. Investigations and results

2.1. Development of the POD-risk prediction score

A thorough literature search was performed to identify established DRIDS and POD-risk factors (Aitken et al. 2017; Aldecoa et al. 2017; Bowman et al. 2020; De Hert et al. 2018; Francis 2019; Galyfos et al. 2017; Iamaroon et al. 2020; Kassie et al. 2017; NICE 2010; NHS Scotland 2019; Scholz et al. 2016; Wilson et al. 2020). In interprofessional discussion (pharmacist, neurologist, anaesthesiologist), score variables were selected and points assigned for score calculation. We excluded factors not reliably assessable at MR by pharmacists (e.g. intraoperative factors, dehydration, cognitive diseases) or with uncertain evidence.

Table 1: Parameters defined for the POD-risk prediction score

Parameter	Rating
Age	
≥ 65 years	1 point
≥ 75 years	2 points
Male sex	1 point
Renal insufficiency[1]	1 point
Hepatic impairment[2]	
MELD 10-14 (CPS-B)	1 point
MELD ≥ 15 (CPS-C)	2 points
ACB-Score[3] ≥ 3	1 point
DRIDS (ATC-Code)[4]	1 point per drug taken
Drugs used in diabetes (A10)	
Opioid drugs (N02A)	
Antiepileptic drugs (N03)	
Antiparkinson drugs (N04)	
Antipsychotic drugs (N05A)	
Benzodiazepines (N05BA, N05CD, N03AE)	
Hypnotics and sedative drugs (except Benzodiazepines (N05C)	
Antidepressant drugs (N06A)	
Dementia drugs (N06D)	
Antihistamines for systemic use (R06)	

[1] eGFR < 60 ml/min/1.73 m²
[2] MELD: Model of endstage liver disease; CPS: Child-Pugh-Score; MELD-ranges corresponding to CPS-classes
[3] ACB: anticholinergic burden
[4] DRIDS: delirium-risk increasing drugs; ATC-Code: anatomic therapeutic chemical code

Table 1 summarizes the parameters chosen for the POD-risk prediction score and the assigned points for score calculation. All considered risk factors can be assessed by pharmacists during MR at hospital admission. For male sex, elevated risk (OR 1.2-5.8) has been shown compared to women (Galyfos et al. 2017). Evidence for older age as a risk factor is high (OR 3.4 – 4.8), but, inconclusive regarding the exact threshold. We set thresholds at 65 and 75 years as these are frequently used (Aitken et al. 2017; Aldecoa et al. 2017; Galyfos et al. 2017; Iamaroon et al. 2020; Scholz et al. 2016). Studies describing RI as a risk factor used very different thresholds regarding severity of kidney disease and reported OR vary between 1.3-5 (Bowman et al. 2020; Galyfos et al. 2017). We decided to set a threshold at <60 ml/min/1.73 m², which in general defines impaired renal function (KDIGO 2013). HI as a risk factor has not been very well studied but proven for liver cirrhosis (OR 2.08) (Bowman et al. 2020; Francis 2019; Scholz et al. 2016). HI was defined as CPS classes B (MELD 10-14) and C (MELD ≥15) (Albarmawi et al. 2013). Other diseases described as possible risk factors were excluded since documentation in the electronic patient chart at the time of MR is usually not available or incomplete.

Despite the anticholinergic burden has frequently been described as a risk factor for in-hospital delirium *per se* and also in studies focusing on POD, conflicting result have been published recently (Francis 2019; Heinrich et al. 2021; Herrmann et al. 2022). However, the evidence to represent a relevant risk factor was weighted positive and a threshold of ≥3 points was set as high risk as described in the literature (Kiesel et al. 2018).

Of the high number of DRIDS discussed in the literature, we decided to consider the drug classes with proven evidence listed in Table 1. For other drugs, evidence was inconclusive, effects time dependent or relevant in intoxication (e.g. cardiovascular drugs, antibiotics, digitalis glycosides) (Bowman et al. 2020; Francis 2019; Galyfos et al. 2017; Iamaroon et al. 2020; Kassie et al. 2017; NHS Scotland 2019; NICE 2010). The number of drugs was excluded as parameter, since a recent review found no evidence (Kassie et al. 2017).

The POD-risk prediction score for a patient was defined as sum of the assigned points for risk factors and DRIDS at hospital admission. Preliminary, low (≤3 points), moderate (4-5) and high risk (>5) were defined. Thus, at least three to four risk factors or DRIDS had to be present for high risk and over-alerting prevented.

2.2. Feasibility testing of the POD-risk prediction score

We retrospectively evaluated a cohort of patients admitted to the surgical department of a large teaching hospital in Bavaria, Germany, January to March 2019 (3 months). Inclusion criteria were age over 18 years and pharmacist-led medication reconcil-

Table 2: Characteristics of the retrospective surgical patient cohort (n=1174)

Parameter	No. of patients/*median (range)*	%
Sex		
Male	652	55.5
Female	522	44.5
Age [years]	*63 (18-99)*	
< 65	607	51.7
65-74	264	22.5
≥ 75	303	25.8
eGFR [ml/min/1.73 m²][1]	*87 (10-157)*	
< 60	238	20.3
≥ 60	883	75.2
Not available	53	4.5
MELD[2]	*7.5 (6.4-36.8)*	
< 10	585	49.8
10-14 (CPS-B)	106	9.0
≥ 15 (CPS-C)	65	5.5
Not calculable	418	35.6
ACB-Score[3]	*Median 0 (0-11)*	
0	697	59.4
1	260	22.1
2	111	9.5
3	55	4.7
4	26	2.2
5	15	1.3
>5	10	0.8
No. of drugs at admission[4]	*5 (0-22)*	
0	122	10.4
1-5	529	45.1
6-10	344	29.3
> 10	179	15.2
No. of DRIDS at admission[5]	*Median 0 (0-5)*	
0	756	64.4
1	290	24.7
2	89	7.6
3	29	2.5
4	8	0.7
5	2	0.2

[1] eGFR: estimated glomerular filtration rate
[2] MELD: Model of endstage liver disease; CPS: Child-Pugh-Score; MELD-Ranges corresponding to CPS-classes; not available: mostly bilirubin missing for MELD-calculation
[3] ACB: anticholinergic burden; scores ≥ 3 represent high risk
[4] Number of drugs assessed, but not included in POD- prediction score
[5] DRIDS: delirium-risk increasing drugs

iation (PhMR) at admission. The study cohort consisted of 1180 patients admitted to the surgical department. Six patients were excluded due to missing medication lists resulting in a final cohort of 1174 patients with a median age of 63 years (18-99) and 55.5% (652) male patients. Table 2 presents details on overall patient characteristics and risk factors of the POD-risk prediction score. While renal function could be determined for almost all patients, MELD was calculable for only 64.5% of the patients, mainly due to missing bilirubin parameters (393; 33.5%).
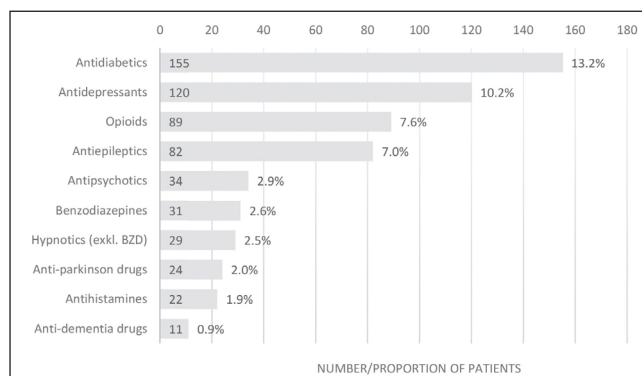

Fig. 1: Delirium-risk increasing drug classes taken by patients (n=418) of a retrospective surgical patient cohort (n=1174).

ACB-scores differed widely with the majority of patients (59.4%) scoring zero, while maximum scores of 8 and 11 were reached by one patient each. An ACB-score ≥3 was found in 106 patients (9%). One or more DRIDS were taken by 418 (35.6%) patients with a median number of zero (range 0-5) Fig. 1 shows details on involved drug classes. Antidiabetic drugs represented the most often used drug class (155 patients), followed by antidepressants (120), opioids (89) and anticonvulsives (82). The most often found risk factors were male sex (652 patients), age >65 years (567) and intake of at least one DRID (418) (Fig. 2). Following the preliminary classification, 898 patients (76.5%) had low risk (score 0-3), 210 (17.9%) moderate risk (score 4-5) and 66 (5.6%) high risk (score >5) for developing POD according to our score (Fig. 3). The overall median number of drugs per patient was 5 (0-22). In detail, the median number was 4 (0-20) for low POD risk, 9 (0-20) for moderate and 11 (3-22) for high risk.
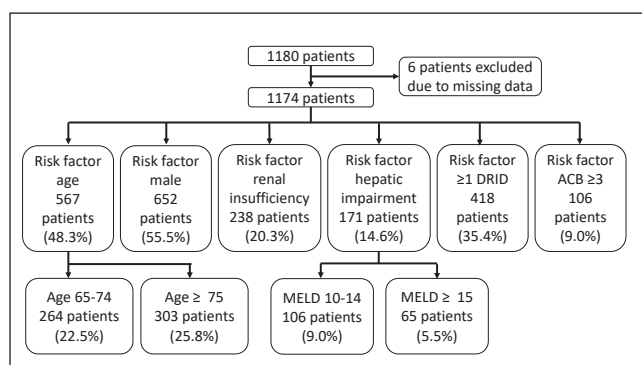

Fig. 2: Frequency of POD-risk factors of the risk-prediction score in the evaluated cohort of surgical patients (n=1174).

Finally, Fig. 4 presents results of delirium documentation for the 146 patients (12.4% of all 1174 patients) with a calculated score ≥5. Overall, documentation was poor and not following a structured approach. Electronic documentation of signs and symptoms for POD was found for 43 patients (29.5%) and inconclusive in 12 (8.2%). At scores of 5 (n=80) and six (n=37), delirium was documented for about a quarter of the patients, no delirium for the majority and documentation inconclusive in some cases. However, at a score of 7 (n=15), the percentage of patients (40% each) with and without delirium documentation was at the same level while documentation
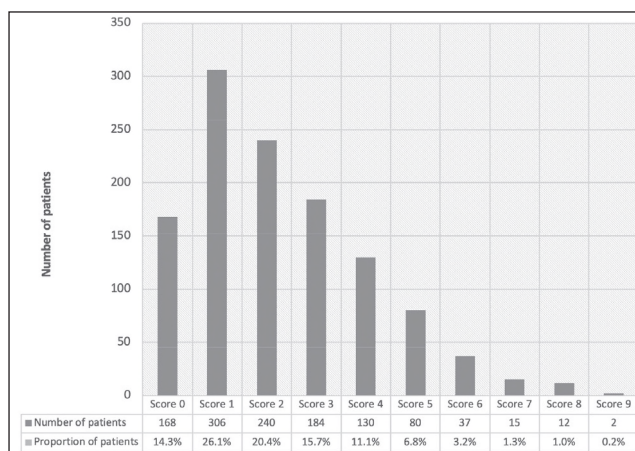

Fig. 3: Results of POD-risk prediction score calculated for a retrospective cohort od surgical patients (n=1174).
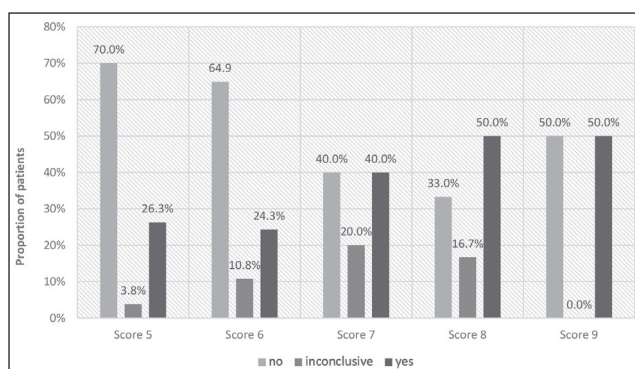

Fig. 4: Documented delirium for patients with a calculated POD-risk prediction score ≥ 5 (n=146)

was inconclusive for 20%. At a score of eight (n=12) and nine (n=2), delirium was documented for 50% of the patients. Taken together, starting with a score of seven, for at least half of the patients with conclusive documentation, delirium was found (Fig. 4).

When looking in detail at the 43 patients with documented POD, the most often found risk factors were intake of DRID (37; 86%), age ≥75 years (35; 81.4%) and male sex (32; 74.4%). An ACB ≥3 had 17 (39.5%) patients. POD-risk scores were five for 21 patients (48.8%) and 6-9 for 22 (51.2%).

3. Discussion

POD is a severe clinical complication affecting at least 20% of surgical patients. However, although up to 40% of all delirium cases are preventable and screening for patients at risk including preoperative medication review is recommended, implementation in clinical routine is often lacking (Aldecoa et al. 2017; De Hert et al. 2018; Francis 2019; NHS Scotland 2019; NICE 2010; Wilson et al. 2020). For timely identification of patients at risk, we developed a new POD-risk prediction score based on known risk factors assessable by pharmacists at MR at hospital admission. Feasibility testing of the score in a retrospective cohort of surgical patients revealed that all chosen factors were assessable to a satisfying extent with the exception of hepatic impairment. Further, preliminary classification of calculated POD-risk score assigned `low risk´ (0-3) for 76,5%, `moderate risk´ (4-5) for 17.9% and `high risk´ (>5) for 5.6% of the surgical patients. However, when evaluating all patients with a score of ≥5, POD was documented for around a quarter at scores five and six, but for at least 50% of all evaluable patients starting with a score of seven, implementing that the threshold for `high risk´ has to be redefined. Unfortunately, overall delirium documentation was poor. Taken together, the new medication-based delirium-risk prediction score proved to be a feasible instrument to screen for patients at risk and the current study results give important insights needed for further refinement.

3.1. Current developments of POD-prediction tools

The research interest in POD-prediction has increased considerably in the last years. However, intake of DRIDS or any other drug was not considered in most tools despite the high evidence for their potential harmful effect. Regarding drug impact, a recently published study by McCoy et al. (2021) could stratify patients for delirium risk by aggregating brain-related medication adverse effects. In another recent study concerning geriatric patients, the intake of potentially inappropriate drugs according to PRISCUS or EU(7)-PIM list was not correlated to POD occurrence (Heinrich et al. 2021). Thus, screening by these established lists seems to be insufficient to detect vulnerable patients and more specific approaches are needed. Taken together, there is great interest in the development of POD-prediction tools but approaches differ widely and often neglect drugs as a risk factor so far. The score presented here is of importance, since strong evidence exists regarding the impact of DRIDS and preoperative drug therapy has to be assessed anyway. Of note, our score could be automatically calculated out of electronic prescribing tools, thereby offering an easy implementation.

3.2. Characterization of POD-risk factors in surgical patients

The retrospective evaluation of surgical patients provided a comprehensive view on POD-risk factors in a real-life setting. As a strength of this study, we considered adult patients of all kinds of surgery and did not exclude any patient groups. The risk factor `age´ affected nearly half of all patients (48.3%) which is in concordance with the general age pattern for hospitalized patients in Germany (Statistisches Bundesamt 2020). However, the thresholds for point assignment for the POD-risk prediction score could be discussed. To determine the sensitivity and specificity of the score, additional threshold at 70 and 80 years should be tested in following studies. This was not possible for this patient cohort because of irreversible anonymization of data, including elimination of date of birth, after assessment.

Information on renal function was available for almost all patients and the percentage of patients presenting with RI (20.3%) was similar to other studies in hospitalized patients (Seiberth et al. 2020). A systematic screening for hepatic impairment at hospital admission is not yet established for surgical patients. When referring to MELD, 14% of the patients were classified as potentially having liver disease. The overall prevalence of liver cirrhosis in the general population has been reported with 4.5-9.5% (Starczewska et al. 2017). However, chronic liver disease often develops silently, is judged to be heavily underestimated and up to 50% of cirrhosis cases are discovered by chance, e.g. at hospital admission (Härmälä et al. 2019). MELD is based on laboratory parameters only, therefore calculable by pharmacists, corresponds to CPS-classes and has been suggested as screening tool (Albarmawi et al. 2013; Roth et al. 2017). However, availability of bilirubin was a limiting factor in this study and the use of MELD as a screening instrument for HI has to be further evaluated.

The anticholinergic burden concerning pre-hospital medication was high for 9% of the patients in our retrospective cohort. This is in contrast to findings for internal medicine wards with 27.3% of the patients having high ACB-cores (Rigor et al. 2020). For patients already admitted with high ACB-scores, avoidance of anticholinergic in-hospital medication can be recommended as a preventive measure, especially in the context of anaesthesia, where strongly anticholinergic drugs are commonly used.

DRIDS were taken by 35.6% of the patients and represented the third-often found risk factor. Since drugs cause 12-39% of all delirium cases, medication review at hospital admission is a highly important step to identify vulnerable patients (De Hert et al. 2018; Francis 2019). One study found intake of DRIDS at hospital admission for at least every third in-hospital patient with delirium (Kassie et al. 2019). Dosage adjustment, need to continue or possibility of stopping DRIDS should be checked to decrease POD-risk. Implementation of our POD-prediction score would allow for a structured assessment of DRIDS in vulnerable patients for the first time.

3.3. Limitations

The main limitations of this study are its retrospective design and the poor documentation of POD. Missing parameters could not be assessed afterwards and statistical correlations regarding impact of score parameters were not possible due to unreliable POD documentation. In addition, we did not include POD-risk factors not assessable by pharmacists at MR at hospital admission. For accuracy of the POD-prediction tool, intraoperative factors could as well play a major role which should also be considered in future studies.

3.4. Further refinement of the POD-risk prediction score

The results of this study will be the basis for prospective evaluations to follow. We defined three areas to be addressed for further development of the score. First, delirium documentation has to be improved. For patients with a POD-risk prediction score ≥5, delirium was found in 29.5%, but for a considerable number of patients documentation was inconclusive. Higher scores mirrored higher POD-reporting and for lower scores lower numbers of documented POD are expected. Numbers reported in the literature range from 20% for all surgical patients, 35% for gastrointestinal surgery, 39% in hip fracture patients and up to 46% for heart surgery. Thus, underreporting is strongly suspected (Aitken et al. 2017; Aldecoa et al. 2017; Oberai et al. 2021).

Second, weighting of risk factors for score calculation has to be reassessed. Poor documentation of POD prevented further statistical evaluations on the impact of single factors in this feasibility study. However, point assignment and thereby impact of single factors should be tested in subsequent studies regarding specificity and sensitivity of the score. Special emphasize should be put on impact of drug dose and the not very well characterized risk factors renal and hepatic impairment.

Third, the integration of additional risk factors, like smoking, consumption of alcohol or illicit drugs, hearing and visual impairment in the score has to be tested. Reliable assessment and rating tools would have to be determined. Moreover, starting with a POD-risk score assessed by the pharmacist at MR, the anaesthesiologist could add further factors identified during preoperative evaluation of patients.

3.5. Conclusion

We developed and successfully tested the feasibility of a new medication-based POD-prediction-score assessable by pharmacists at MR at hospital admission. The score offers the possibility to identify patients at risk for POD, thereby allowing early preventive measures and increasing patient safety, and to heighten the overall awareness for POD.

4. Experimental

For renal function, the estimated glomerular filtration rate (eGFR) calculated by the Chronic Kidney Disease Epidemiology (CKD-EPI) equation was used (KDIGO 2013). For hepatic function, the model-of-endstage-liver-disease-score (MELD) was assessed (Wiesner et al. 2003). MELD is based on laboratory parameters only, therefore calculable by pharmacists and MELD-ranges can be assigned to corresponding classes A, B and C of the Child-Pugh-Score (CPS) (Albarmawi et al. 2013). To determine the anticholinergic burden (ACB), the ACB-score published for German market drugs was used assigning points for anticholinergic effects from 0-3 per drug (Kiesel et al. 2018).

To test for feasibility, patients of the surgical department including general, visceral, transplant, vascular, trauma and reconstructive surgery were retrospectively evaluated. PhMR is routinely performed for all admitted surgical patients Monday to Friday assessing a detailed drug history and generating a full medication list. Clinical data were extracted from the electronic patient information system (SAP-i.s.h. med, Cerner Corporation, North Kansas City, USA). Information on drugs was derived from the medication list of PhMR. The following data was documented:

- Patient characteristics (age, sex)
- Laboratory parameter from the day of admission: serum creatinine (SCrea), eGFR [ml/min/1.73 m²], bilirubin, International Normalized Ratio (INR)
- Number of drugs, number and kind of DRIDS, anticholinergic burden at hospital admission

Drugs taken permanently or on demand were taken into account. Antidepressant, anticonvulsive and antiparkinsonian drugs were considered in all possible indications since CNS adverse drug reactions (ADR) and delirium risk will always be of concern.

For antidiabetics, oral drugs as well as insulin and glucagon-like-peptide-1-analoga were considered since hypoglycemia may occur.

In addition, for patients with a POD-risk prediction score ≥5 we searched for documentation of delirium in electronic diagnoses, anesthesia and surgery protocols, electronic nurses´ notes, paper patient charts (electronically available after scanning post discharge), and discharge letters as described as validated method by others (Inouye et al. 2005). Any possible sign of POD like altered cognition, perception or level of consciousness was rated as positive proof. POD was rated yes, no or uncertain (documentation inconclusive).

Descriptive statistics were performed with Microsoft Excel® 2016 (Seattle, WA, USA). Median and range were calculated for non-normal distribution and mean and standard deviation (SD) for normal distribution of data. The frequency distribution was shown for qualitative variables.

The study was conducted in accordance with the Declaration of Helsinki. Approval was obtained by the ethics committee of the University Hospital Munich (20-588). Because of the retrospective design, patient informed consent was not requested and not obtained in accordance with the applicable statutory provisions under the Bavarian State Hospital Act (Art. 27 Para. 4 BayKrG).

Conflicts of interest: None declared.

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