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Use of electronic adverse drug reaction check to identify inpatients with a high drug-associated risk of falling: a case-control study at the Department of Neurology

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Background: In hospital, falls are frequent adverse events. Certain drugs affect the fall risk, therefore studying prescriptions may reveal perilous combinations and support falls prevention. As neurologic diseases frequently increase fall risk, neurologic patients require special attention concerning fall prevention. *Aim*: To analyse the performance of the electronic adverse drug reaction check programmes VERIKO® and SCHOLZ Datenbank® in identifying neurologic patients with a high drug-associated fall risk. *Method*: Falls in the Department of Neurology in 2016 were matched to fall-free control patients of the same age, sex and principal diagnosis. Their estimated fall risk and other risk factors were compared using univariate and a multifactorial conditional logistic regression. Receiver operating characteristic curves visualised the performance of both programmes. R^2 for a model with and without software was calculated. *Results*: Eighty-seven matched pairs were analysed. In the univariate analyses, VERIKO risk estimations showed a significant correlation to fall events (OR=1.448, CI=1.061-1.975). Additionally, the number of comorbidities (OR=1.086, CI=1.013-1.164), the Hospital Frailty Risk Score (OR=1.085, CI=1.025-1.149), impaired balance (OR=3.6, CI=1.337-9.696), gait abnormality (OR=4.75, CI=1.616-13.962), presence of delirium (OR=3.4, CI=1.254-9.216) and previous falls (OR=8.0, CI=1.839-34.793) were related to high fall risk. Polypharmacy and the number of potentially inappropriate medications did not correlate with fall events. In the multivariate analysis, the Hospital Frailty Risk Score was associated to fall risk (OR=1.390, 95%-CI=1.049-1.842). Both programmes showed an area under the receiver operating characteristics curves < 0.6 and improved the model performance slightly ($\Delta R^2 \leq 0.0006$). *Conclusion*: VERIKO risk estimations correlated significantly to fall events. Nevertheless, both programmes showed little accuracy in identifying drug-associated fall risk.

1. Introduction

Falls, defined as 'inadvertently coming to rest on the ground or other lower level' (WHO 2008), are the most frequent adverse event during hospitalisation (LeLaurin and Shorr 2019) with approximately 3 to 5 falls per 1000 patient days (Oliver et al. 2010). The consequences are extensive, making falls a major public health issue. They often result in injury, lengthening of hospitalisation and nursing care dependency (Silva et al. 2019). This further medical assistance explains their substantial economic burden of $49.5 billion in the US in 2015 (Florence et al. 2018).

The primary issue in fall prevention is the identification of high risk patients (Park 2018). Existing risk assessments try to cover the complex aetiology of accidental falls and have been implemented globally into clinical routine (LeLaurin and Shorr 2019). In the setting of acute care especially the Hendrich II Fall Risk Model, the St. Thomas's Risk Assessment Tool in Falling elderly inpatients (STRATIFY) and the Timed Up and Go test play an important role. Despite their high sensitivity values and thus effective identification of risk patients, the fall incidence remains disturbingly high, underlining the need for further research (Park 2018; Rasche et al. 2019; Royset et al. 2019).

Systematic investigations show the multiple causes for accidental falls (Severo et al. 2018; LeLaurin and Shorr 2019). Major individual risk factors comprise female sex, cognitive impairment, reduced balance capacity, restricted mobility, frailty, hyponatremia, low creatinine clearance, poor nutritional state, orthostatic dysfunction and a history of falls (Fehlberg et al. 2017; Hubbard et al. 2017; Severo et al. 2018; Boyer et al. 2019; Silva et al. 2019; Goto et al. 2020; Maly et al. 2020). Certain diagnoses are considered to increase the fall risk as well, such as urinary incontinence, depression, delirium, osteoporosis, poor vision, diabetes and hyper-/hypotension, which all affect the capacity of postural stability (Lord 2006; Mazur et al. 2016; Bittencourt et al. 2017; Najafpour et al. 2019; Oshiro et al. 2019).

Since numerous neurologic disease patterns alter a patient's state of cognition, balance, muscle strength and postural stability, a Department of Neurology seems to require special attention in terms of fall prevention. Especially a diagnosis of Parkinson's disease, stroke, epileptic syndromes requiring anticonvulsive therapy or dementia affects the patient's individual fall risk (Haasum and Johnell 2017; Kim et al. 2018; Mansfield et al. 2018; Schniepp et al. 2021).

A main fall risk factor is age (Jacobi et al. 2017). Elderly patients are particularly susceptible to adverse events due to the increased prevalence of chronic diseases, comorbidities and polypharmacy (Morin et al. 2019). One third of people aged over 65 experience at least one fall event per year (WHO 2008). Their frailty results in weakened coping mechanisms to deal with stress factors including

acute illness or adverse drug reactions (ADR) (Hubbard et al. 2017). Here, the Hospital Frailty Risk Score is an efficient tool to detect high risk for frailty and therefore a greater probability of adverse clinical outcomes. Its numeric value is calculated with the International Statistical Classification of Diseases and Related Health Problems, Tenth version (ICD-10) codes as written in the patient's "electronical health record (EHR)" and classifies the patient in low, intermediate or high risk for frailty (Gilbert et al. 2018). Another important topic is drug therapy. Polypharmacy, drug interactions and certain drug classes are considered to elevate fall risk (Schiek et al. 2019). Drugs with ADR which lead to an increased fall risk such as gait abnormality, reduced balance capacity or sedation are called fall risk-inducing drugs (FRID). Their use is associated with high fall risk (Bor et al. 2017) and has turned out to be a significant fall predictor (Morin et al. 2019). Since elderly are more vulnerable to ADR in general, guidelines to reduce high risk agents have been compiled in terms of potentially inappropriate medication use in older adults (PIM).

Multiple PIM lists offer the possibility of lowering the drug-associated fall risk by identifying high risk agents (such as FRID) and optimising the prescription procedure. The Beers Criteria® are a well-known example in the Anglo-American region (American Geriatrics Society 2019). In Germany the use of the Fit fOr The Aged-Criteria (FORTA) (Pazan et al. 2019) or the PRISCUS list (Holt et al. 2010) is prevalent due to their suitability for the German market but there is ongoing effort to adapt them for international use as the EURO-FORTA (Pazan et al. 2018) respectively EU(7)-PIM list (Renom-Guiteras et al. 2015).

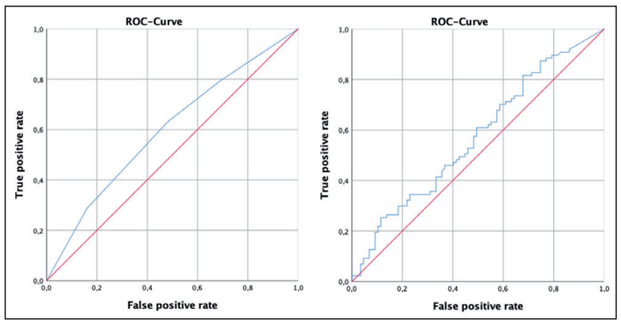
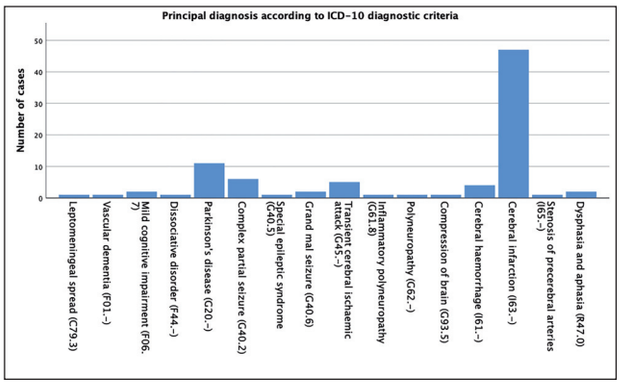
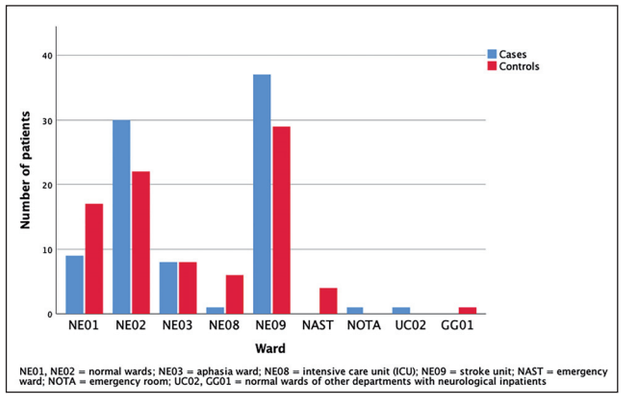


Fig. 1: Receiver operating characteristics curves of the VERIKO risk class (left) and the SCHOLZ Datenbank risk estimation (right) to predict falls.

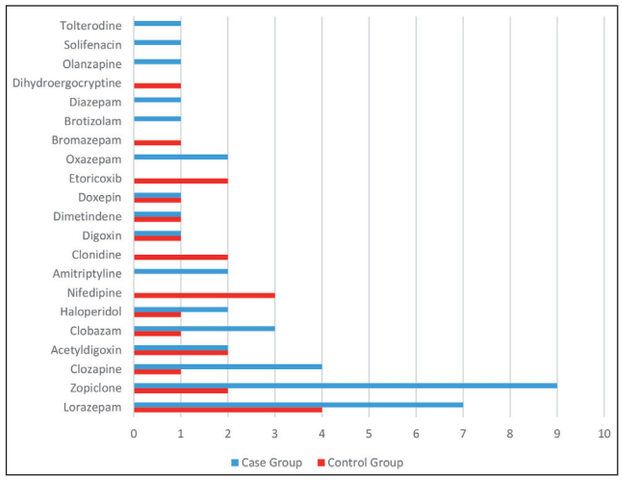


ESM Fig. 1: Principal diagnoses of the cohort. Notes. ICD – International Statistical Classification of Diseases and Related Health Problems.

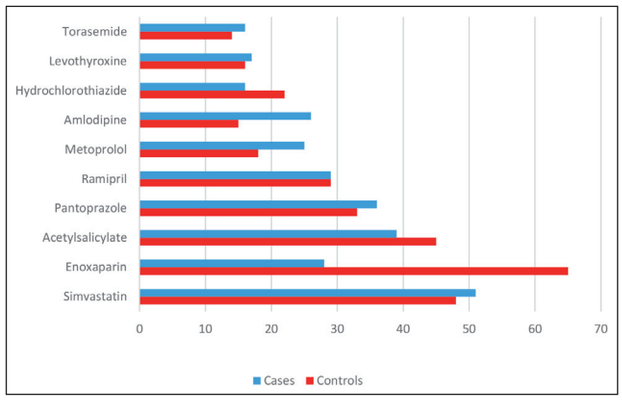
However, to cope with the variety of information on drug-associated fall risk is a challenging task in clinical routine. At this point electronic programmes could be used efficiently to introduce existing pharmacological data and individual patient characteristics into a clinical decision support system in order to raise physician's attention on high fall risk patients (Schiek et al. 2019).



ESM Fig. 2: Distribution by wards.



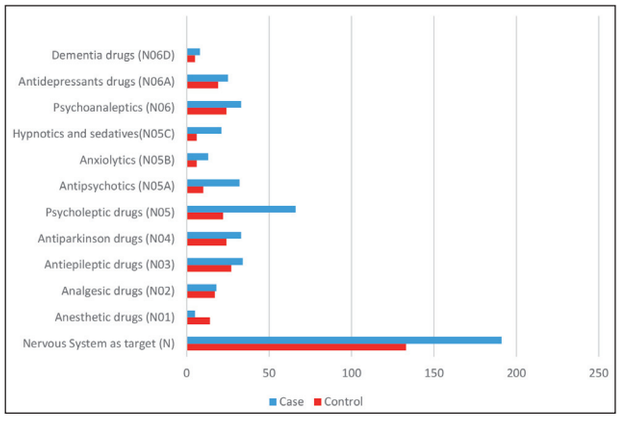
ESM Fig. 3: Number of prescribed PIM per active agent and group ordered by frequency.



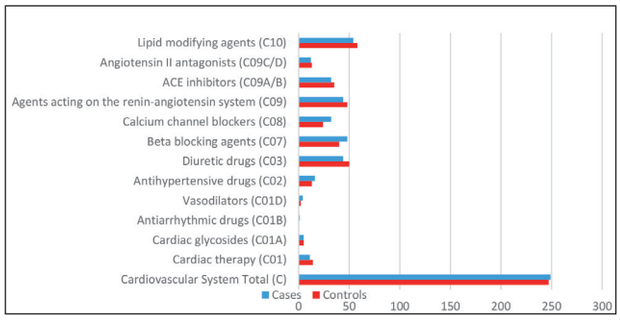
ESM Fig. 4: Top ten prescribed active agents in the study group.

The Department of Neurology at Aachen's University Hospital observes a high number of in hospital falls due to their mainly elder and frail patients with disease-related fall risk and frequent use of FRID like neuroleptics, antiepileptics, antidepressants and dopaminergic agents (Seppala et al. 2018a, b).

The aim of this cooperative investigation of the Departments of Pharmacy and Neurology was to determine the accuracy of two selected ADR check programmes on estimating the drug-associated fall risk, based on inpatient prescriptions in a Department of Neurology and thus identify high risk patients.



ESM Fig. 5: Nervous system drug use in the case and control group. Notes. ATC-codes (Anatomical Therapeutic Chemical Classification System) in parentheses.



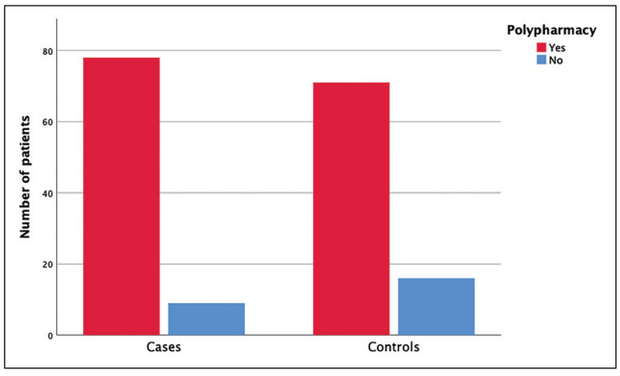
ESM Fig. 6: Cardiovascular drug use in the case and control group. Notes. ATC-codes (Anatomical Therapeutic Chemical Classification System) in parenthesis.

2. Investigations and results

Throughout the study period, 135 patients experienced an in hospital fall in the neurological department within a total of 3798 admitted patients, resulting in 0.36 falls per patient and 4.21 falls per 1000 patient-days.

We identified 90 matched pairs of the same age, sex and principal diagnosis. Three were excluded due to missing medication information or death during admission, meaning that 87 cases and 87 controls were included in the study (Fig. 1). Table 1 shows the characteristics of subjects included in the study. An elevated age (mean 73.9 years) was identified, with only 27 subjects aged under 65 years. The gender distribution was almost balanced.

In the study cohort the most common principal diagnoses were stroke (I63.-) followed by Parkinson's disease (G20.-) and seizures (G40.-) (see electronic supplementary material [ESM] Fig. 1). Most patients were admitted to the stroke unit and the principal standard care ward 'NE02' (see ESM Fig. 2). There was no significant difference between the case and the control group concerning the admitting unit and a fall event in a conditional logistic regression



ESM Fig. 7: Polypharmacy and fall events.

model. Also, the fall rate in intensive care was not significantly lower than in other wards.

We found a positive correlation of 0.247 (95%-CI=0.1-0.38) between age and number of prescribed drugs using spearman's rank correlation coefficient (p=0.01). A graphic demonstrating the ten most frequent active agents is presented in the ESM (Fig. 3). Since the cohort consisted largely of elderly patients, we expected a considerable number to present with polypharmacy i.e. more than five prescribed drugs. Nevertheless, the prevalence of patients with polypharmacy was high without regards to a fall event (see ESM Fig. 4).

The number of prescribed PIM per patient was 0.36 in the case group and 0.23 in the control group. The most commonly prescribed PIM were Lorazepam and Zopiclone. For further information about the observed PIM frequency see ESM Fig. 5.

In the conditional logistic regression models a significant association with an increased fall risk was found for activity/mobility and fatigue items of the ePA-AC® ('ergebnisorientiertes Pflegeassessment–Acute Care', i.e. goal-orientated acute care assessment; ePA-CC GmbH, Wiesbaden, Germany) before fall, gait abnormality, impaired balance or previous fall events as documented by the nursing staff, the Hospital Frailty Risk Score (HFRS), the number of comorbidities and the presence of delirium. For all results of the univariate analyses see Table 2.

The fall risk estimations according to both ADR check programmes VERIKO® (Gero PharmCare GmbH, Köln, Germany) and SCHOLZ Datenbank® (ePrax GmbH, Lüdenscheid, Germany) ('Datenbank', i.e. database) were tested with conditional logistic regression models, as well. The risk estimations by VERIKO were significantly related to fall events, whereas the fall risk by SCHOLZ Datenbank did not have a significant outcome. Comparing the VERIKO risk classes with each other, there is a significantly lower chance for high fall risk patients to be grouped into Class 0 ("No risk detectable"). Both risk estimations were used to calculate standard receiver operating characteristic (ROC) curves to allow a better comparison unless their different output characteristics.

VERIKO risk classes form an area under the ROC curve (AUC) of 0.597±0.43 (asymptotic p-value=0.027, asymptotic 95%-CI=0.513-0.681) and SCHOLZ Datenbank risk estimations

Table 1: Characteristics of cases and controls as arithmetic mean±SD

	Cases (n = 87)	Controls (n = 87)
Age [years]	73.9 ± 12.0	73.9 ± 12.0
Sex female/male	41 (47.1%)/ 46 (52.9%)	41 (47.1%)/ 46 (52.9%)
BMI [kg/m^2]	25 ± 5[a]	26 ± 4[b]
Systolic blood pressure [mmHg]	138.4 ± 26.5	137.4 ± 20.8[c]
Serum sodium level [mmol/l]	140.5 ± 3.9	140.7 ± 3.7
Serum creatinine level [mg/dl]	0.98 ± 0.73	0.91 ± 0.27

SPI		SPI score at admission		26.8 ± 9.6[d]	30.6 ± 10.7[e]
		SPI score before fall		27.2 ± 9.3[f]	31.2 ± 10.6[e]
		Level of activity [n (%)][g]	Class 1	7 (8.5%)	8 (11%)
			Class 2	36 (43.9%)	22 (30.1%)
			Class 3	31 (37.8%)	22 (30.1%)
			Class 4	8 (9.8%)	21 (28.8%)
		Level of mobility [n (%)][h]	Class 1	3 (3.6%)	6 (8.2%)
			Class 2	21 (25.3%)	13 (17.8%)
			Class 3	39 (47%)	17 (23.3%)
			Class 4	20 (24.1%)	37 (50.7%)
		Change of position [n (%)][h]	Class 1	17 (50%)	17 (50%)
			Class 2	30 (69.8%)	13 (30.2%)
			Class 3	36 (45.6%)	43 (54.4%)
		Gait abnormality [yes (%)][i]		65 (86.7%)	40 (62.5%)
		Impaired balance [yes (%)][j]		50 (71.4%)	28 (45.2%)
		Previous fall event [yes (%)][k]		27 (37%)	9 (14.3%)
		Current fall event [yes (%)][h]		10 (12%)	1 (1.4%)
		Fatigue level [n (%)][i]	Class 1	5 (6%)	9 (12.3%)
			Class 2	22 (26.5%)	9 (12.3%)
			Class 3	33 (39.8%)	18 (24.7%)
			Class 4	23 (27.7%)	37 (50.7%)
Level of long-term care				0.58 ± 0.82[l]	0.35 ± 0.72[m]
Hospital Frailty Risk Score				11.7 ± 6.2[n]	8.7 ± 5.8
Estimated fall risk according to VERIKO				1.71 ± 1.10	1.33 ± 1.09
Class 0 (“No risk detectable”)				18 (20.7%)	28 (32.2%)
Class 1 (“Low risk”)				14 (16.1%)	18 (20.7%)
Class 2 (“Elevated risk”)				30 (34.5%)	27 (31%)
Class 3 (“High risk”)				25 (28.7%)	14 (16.1%)
Estimated fall risk according to SCHOLZ [%]				12.35 ± 14.60	9.65 ± 11.42
Number of prescribed drugs				8.5 ± 3.6	8.4 ± 4.1
Polypharmacy [yes (%)]				78 (89.7%)	71 (81.6%)
Potentially inappropriate drugs per patient				0.36 ± 0.7	0.23 ± 0.42
Number of comorbidities				11.3 ± 5.3	9.5 ± 4.8
Comorbidities: [yes (%)]		Auditory defect		0	0
		Cognitive impairment		9 (10.3%)	10 (11.5%)
		Delirium		18 (20.7%)	6 (6.9%)
		Depression		3 (3.4%)	3 (3.4%)
		Diabetes type I		0	0
		Diabetes type II		24 (27.6%)	22 (25.3%)
		Gait abnormality		17 (19.5%)	14 (16.1%)
		Hemiparesis		41 (47.1%)	33 (37.9%)
		Hypertension		54 (62.1%)	59 (67.8%)
		Hypotension		0	3 (3.4%)
		Myopathy		1 (1.1%)	0
		Osteoporosis		0	0
		Parkinson’s disease		13 (14.9%)	12 (13.8%)
		Rheumatism		0	0
		Seizure		19 (21.8%)	15 (17.2%)
		Urinary incontinence		7 (8%)	6 (6.9%)
		Vertigo		6 (6.9%)	8 (9.2%)
		Visual defect		7 (8%)	3 (3.4%)

Notes. SD – standard deviation. BMI – body mass index. SPI – Selbstpflegeindex. [a]43 values missing, [b]51 values missing, [c]one value missing, [d]5 values missing, [e]14 values missing, [f]4 values missing, [g]5 values of the case group missing and 14 values of the control group missing, [h]four values of the case group missing and 14 values of the control group missing, [i]12 values of the case group missing and 23 values of the control group missing, [j]17 values of the case group missing and 25 values of the control group missing, [k]14 values of the case group missing and 24 values of the control group missing, [l]current fall event according to ePA-AC (goal-orientated orientated acute care assessment) (not registered in the electronic health record and thus no inpatient fall pursuant to the chosen definition), [m]6 values missing, [n]15 values missing, [o]2 values missing.

Table 2: Results of the univariate analyses

			Odds Ratio	95% CI	*p* value
BMI [kg/m^2]			1.018	0.908-1.140	0.764
Systolic blood pressure [mmHg]			1.002	0.989-1.016	0.721
Serum sodium level [mmol/l]			0.986	0.913-1.065	0.725
Serum creatinine level [mg/dl]			1.276	0.714-2.280	0.411
SPI	SPI score at admission		0.968	0.931-1.007	0.108
	SPI score before fall		0.968	0.932-1.005	0.087
	Activity item		-	-	0.059
		Class 1 vs. 4	3.810	0.707-20.537	0.120
		Class 2 vs. 4	5.562	1.454-21.274	***0.012**
		Class 3 vs. 4	5.177	1.430-18.735	***0.012**
	Mobility item		-	-	0.10
		Class 1 vs. 4	0.750	0.132-4.281	0.747
		Class 2 vs. 4	3.354	1.051-10.699	***0.041**
		Class 3 vs. 4	4.902	1.801-13.341	***0.002**
	Positioning item		-	-	0.102
		Class 1 vs. 3	1.114	0.449-2.760	0.817
		Class 2 vs. 3	2.420	1.044-5.609	***0.039**
	Gait abnormality		4.75	1.616-13.962	***0.005**
	Impaired balance		3.6	1.337-9.696	***0.011**
	Previous fall		8.0	1.839-34.793	***0.006**
	Current fall		7.0	0.861-56.894	0.069
	Fatigue item		-	**-**	***0.025**
		Class 1 vs. 4	0.789	0.179-3.471	0.753
		Class 2 vs. 4	3.907	1.319-11.579	***0.014**
		Class 3 vs. 4	2.869	1.116-7.376	***0.029**
Level of long-term care			1.616	0.937-2.787	0.085
Hospital Frailty Risk Score			1.085	1.025-1.149	***0.005**
Estimated fall risk according to VERIKO[a]			1.448	1.061-1.975	***0.02**
	Class 0 vs. 3		0.306	0.115-0.819	***0.018**
	Class 1 vs. 3		0.389	0.141-1.077	0.069
	Class 2 vs. 3		0.584	0.246-1.384	0.222
Estimated fall risk according to SCHOLZ [%]			1.019	0.992-1.046	0.178
Number of prescribed drugs per patient			1.004	0.926-1.089	0.918
Polypharmacy (≥5 prescribed drugs)			2.167	0.824-5.7	0.117
Potentially inappropriate drugs per patient			1.490	0.849-2.615	0.164
Number of comorbidities			1.086	1.013-1.164	***0.02**
Comorbidities	Auditory defect		No case with condition		
	Cognitive impairment		0.875	0.317-2.413	0.796
	Delirium		3.4	1.254-9.216	***0.016**
	Depression		Less than 5 cases		
	Diabetes type I		No case with condition		
	Diabetes type II		1.111	0.588-2.1	0.746
	Gait abnormality		1.333	0.562-3.164	0.514
	Hemiparesis		1.667	0.815-3.409	0.162
	Hypertension		0.722	0.354-1.474	0.371
	Hypotension		Less than 5 cases		
	Myopathy		Less than 5 cases		
	Osteoporosis		No case with condition		
	Parkinson's disease		2.0	0.181-22.056	0.571
	Rheumatism		No case with condition		

	Seizure	2.0	0.602-6.642	0.258
	Urinary incontinence	1.2	0.366-3.932	0.763
	Vertigo	0.75	0.260-2.162	0.594
	Visual defect	3.0	0.606-14.864	0.178
Admitting unit		-	-	0.688

*Notes. *Significant at the level of p<0.05. CI – confidence interval. BMI – body mass index. SPI – Selbstpflegeindex. [a]Analysed as a continuous variable.*

result in an AUC of 0.572 ± 0.43 (asymptotic p-value=0.101, asymptotic 95%-CI=0.487-0.657) (see Fig. 1).
We included the significant variables of the univariate analysis, i.e. HFRS, presence of delirium, number of comorbidities and the drug-associated fall risk according to VERIKO, into a multivariate analysis. Of the significant variables related to the SPI ('Selbstpflegeindex', i.e. self-care index), we used the fatigue, gait abnormality and impaired balance items of the ePA-AC for the multifactorial model, as these are the variables most easily to assess at admission without the need for further patient observation. For the result of the multivariate conditional logistic regression see Table 3. As a result, the HFRS shows significant association to fall events in a multifactorial model.
Nagelkerke's pseudo-R^2, a measure ranging between 0 and 1, was used to compare the similar models regarding their prognostic accuracy. For the intercept-only model pseudo-R^2 was 0.4771, for the full model including VERIKO 0.4777 and SCHOLZ Datenbank 0.4773.

Table 3: Multivariate analysis

	Odds Ratio	95% CI	*p* value
HFRS	1.390	1.049-1.842	***0.022**
Impaired balance item	1.929	0.450-8.274	0.377
Gait abnormality item	0.888	0.162-4.870	0.891
VERIKO risk class	1.055	0.603-1.847	0.850
Number of comorbidities	0.946	0.770-1.162	0.946
Delirium	0.123	0.003-5.374	0.123
Fatigue item	-	-	0.052
Class 1 vs. 4	0.106	0.01-1.164	0.066
Class 2 vs. 4	14.679	0.646-333.331	0.092
Class 3 vs. 4	2.085	0.518-8.384	0.301

*Notes. *Significant at the level of p<0.05. CI – confidence interval. HFRS – Hospital Frailty Risk Score.*

3. Discussion

To our knowledge, this is the first analysis of electronic ADR check programmes to predict fall risk, although other studies indicate the beneficial use of drug information to estimate the predisposition to falling (Schiek et al. 2019, Silva et al. 2019).
As our conditional logistic regression model shows, there is a significant correlation between VERIKO risk estimations and patient outcomes. Nevertheless, its ROC curve with an AUC <0.6 displays a relatively weak efficiency (Fischer et al. 2003). Furthermore, the pseudo-R^2 containing VERIKO risk calculations improves the prognostic accuracy only slightly. Looking closely at the different risk classes, the low discriminatory power is striking. Only the comparison of the highest and the lowest risk class results in significant outcomes, whereas the prognostic accuracy of accidental falls in Class 1 and 2 ("low" and "elevated" fall risk) becomes blurred. Yet, the programme was tested in residential homes with a significant reduction of fall events of 57.7% per month after an assessment period of 14 months (Hanke et al. 2013). Further improvement of its risk calculation and classification, prospective clinical trials as well as guidelines for the management of high-risk in hospital patients according to VERIKO are needed.
The SCHOLZ Datenbank developed the fall risk estimations only recently. ePrax GmbH itself describes the calculation merely as an indicator for a drug-associated fall risk (Scholz 2016; Scholz 2020). In our study population we found no correlation between the estimations and fall events. This is also reflected by a small AUC of <0.6 and an improvement of the model fit by only 0.02%. Further investigation of specific cut-offs or an adaptation of the risk potentiation factor according to the synergistic effects of ADR are needed.
The SPI seems to be important for evaluating the patient's overall condition but was not associated with fall risk. This may be due to many nursing specific items within it, which reduce its sensitivity to identify specific risks.
In general, daily updating of a 50-item-score is of questionable feasibility. Ongoing research should investigate its cost-value ratio. In contrast to this large-scale questionnaire, an electronic programme suggests to be a labour- and time-saving screening tool to complement fall risk scores in identifying high risk patients.
In our analysis polypharmacy is not significantly related with fall events. Literature research shows discordant results on this question (Morgado et al. 2017; Najafpour et al. 2019; Schiek et al. 2019) and mentions it as possible confounder of chronic multimorbidity or the use of FRID (Morin et al. 2019), which substantially contribute to fall events (Bennett et al. 2014; Hart et al. 2020). This could not be investigated in our study since cases and controls did not show significant differences in the total number of drugs, nor prescribed PIM. In fact, the low number of PIM in our cohort reflect the common use of PIM lists, especially the PRISCUS list and the FORTA criteria at our study site. However, the potential for pharmacological interactions and ADR, which are not routinely identified by professionals in their daily practice, opens up the possibility of drug-associated falls risk beyond current awareness (Morgado et al. 2017; Krause et al. 2019; Schiek et al. 2019). Here, an electronic evaluation of ADR and interactions could be beneficial. Especially the frequency of the ADR as listed in the Summary of medicinal Product Characteristics (SmPC) have turned out to be a helpful source to identify FRID and assess drug-associated fall risk (Michalcova et al. 2020). Moreover, avoiding FRID is crucial. Facilitating the deprescribing process are the STOPPFall and the STOPP/START criteria which suggest to stop perilous medication (O'Mahony et al. 2014; Seppala et al. 2020). Inserting deprescribing lists into an ADR check programme may help realising the criteria in daily routine.
Studying in detail the most frequently prescribed drugs and the used PIM in our study group the amount of agents affecting the nervous or the cardiovascular system is striking. Considering the study population in a department of Neurology this is expectable since neurological diseases require drugs of nervous targets and cardiovascular diagnoses are of high prevalence in the whole society. Yet, the more frequent use of psycholeptics, anxiolytics, hypnotics and antipsychotics in the case group underline their fall risk increasing potential as named in several PIM lists (see ESM Fig. 6). In contrast, the application of cardiovascular drugs is comparable in our case and control group (see ESM Fig. 7). The impact of antihypertensive medication on fall risk is the topic of numerous studies with inconsistent results (Kuschel et al. 2014; Shao et al. 2021).
Regarding comorbidities there is a questionable number of certain diagnoses like depression or osteoporosis. The encoding of diagnoses during hospitalisation is only of economic value if it has

diagnostic or therapeutic consequences which may lead to incomplete documentation.

Nevertheless, the HFRS confirms the relationship of frailty, comorbidities and falls. This assessment completely based on existing data, makes a cost- and time-efficient tool to detect frailty and is associated with adverse events such as a high risk of falling (Gilbert et al. 2018; Eckart et al. 2019). In fact, fall risk estimation by medical record has demonstrated to allow reliable fall risk prediction under the premise of further research (Choi et al. 2018; Cho et al. 2019; Oshiro et al. 2019). This highlights the importance of thorough documentation of the patient's medical history.

Our investigations underline the role of other intrinsic risk factors in literature such as previous falls (Schiek et al. 2019), frailty (Hubbard et al. 2017), delirium (Mazur et al. 2016), gait abnormality (Oshiro et al. 2019), impaired balance (Najafpour et al. 2019) and a reduced level of mobility (Severo et al. 2018). These are not represented in the investigated software which might explain our inaccurate results.

We observed a rate of 4.21 falls per 1000 patient-days. Single-centre studies report a fall rate between 0.41 and 8.67 falls per 1000 patient-days (Dykes et al. 2020; Liang et al. 2021; Melin 2018; Royset et al. 2019). This inconsistency is explainable. Firstly, by regarding the observed units. Neurological, geriatric and rehabilitation care usually experience a higher fall rate only topped by mental health clinics (Oliver et al. 2010). Secondly, fall events are not always documented in a fall report and therefore escape statistics. On the other hand, due to the recent focus on the importance of fall prevention, an overrated fall incidence cannot be excluded. In general, the continuous research on this topic has led to a reducing fall rate in the past years (Walsh et al. 2018).

Throughout the revision of the electronic health record (EHR), seldomly protective measures were taken after a fall. Therefore, further studies should focus on efficient actions to be taken in response to high risk of falling.

In conclusion, our findings show that an electronic ADR check by the two tested programmes only shows little accuracy in identifying high risk patients. Since in hospital falls are of multifactorial genesis, a simple electronic programme does not address this complex problem adequately.

We suggest to improve the used algorithms and insert deprescribing tools for FRIDs in order to counteract high drug-associated risk situations at an early stage. However, a combination of different fall risk assessments and a multidisciplinary approach including medication review by a clinical pharmacist seem to be inevitable to reduce in hospital falls. There is undeniable evidence of the extensive consequences of accidental falls, therefore it is crucial to improve falls prevention for inpatients.

The study at hand has some limitations. It was a case-control study where the results are dependent on the suitability of the control group. Matching the cases to controls by our selected criteria resulted in groups of the same age, sex and diagnosis. However, different results on whether age and sex are considerable risk factors for falling can be found in literature (Najafpour et al. 2019; Oshiro et al. 2019; Silva et al. 2019). Further studies are needed to evaluate the effect of gender, age and principal diagnosis on falling compared to drugs (Gale et al. 2016).

Our study results may be influenced by the limited number of observations which may hide further interrelations.

Since the subjects of our study all suffered from neurological diseases, the cohort is not representative for other patient collectives.

We suggest to conduct a randomized prospective clinical trial with a larger cohort of different clinical units to examine the effectiveness of an ADR check programme to reduce fall risk.

4. Experimental

4.1. Ethics approval

Ethics approval was obtained by the ethical review board of the Medical Faculty of RWTH Aachen University (EK358/17). All patient data was anonymised.

4.2. Setting and study design

The study was conducted at the Department of Neurology, RWTH Aachen University Hospital, Aachen, Germany. This department has a capacity of 62 beds divided into 3 standard care wards, 10 intensive care beds and a stroke unit with 28 beds, 12 of which are equipped with monitoring devices.

The study protocol followed a case-control design. The cohort consisted of patients admitted to the neurological department between January and December 2016. A case was defined as a patient who fell at least once during the study period as reported in the EHR. Repeated fall events were not analysed separately. For each case, we identified one fall-free control of the same age, sex and principal diagnosis who was also admitted to this department in 2016. To ensure a blinded 1:1-matching, an automated procedure was programmed using SQlite (open source). In case of multiple possible matches the code matched the pair by chance. Controls with missing information or death during admission were excluded and replaced by another match. Cases without a matching control, missing information on the medication or in case of death during the admission were excluded (see Fig. 2).

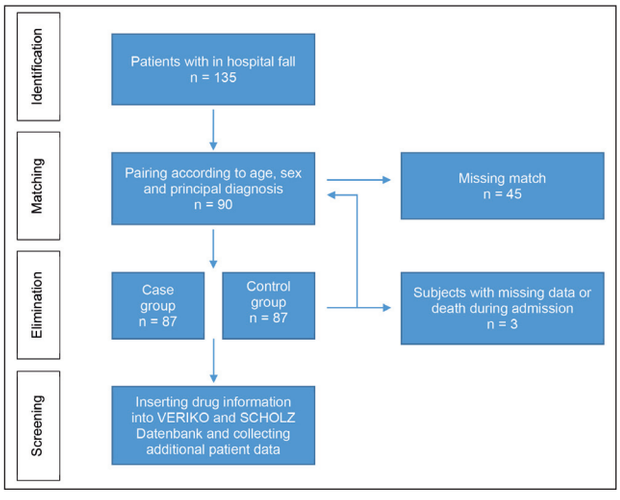


Fig. 2: Flowchart depicting sample selection.

Table 4: ePA-AC ('Ergebnisorientiertes Pflegeassessment–Acute Care', i.e. goal-orientated acute care assessment) items on activity/ mobility

Item	Score
Activity	4 = walks frequently, 3 = walks alone but scarcely, 2 = needs help to sit up/walk, 1 = bed-ridden/bed rest
Mobility	4 = fully preserved, 3 = slightly restricted, 2 = highly restricted, 1 = completely immobile
Change in position	3 = without danger, 2 = needs minor support, 1 = needs strong support
Gait abnormality	0 = no, 1 = yes
Impaired balance	0 = no, 1 = yes
Previous fall in the last 2 months	0 = no, 1 = yes
Current fall event (fall event that day)	0 = no, 1 = yes
Fatigue	4 = sufficient strength, 3 = several extensive activities possible, 2 = small activities possible, 1 = no autonomous activity possible

Based on the clinical record, further fall risk factors of each patient were collected. In order to compare cases and controls in a defined time frame of the admission, the fall-day-to-length-of-stay-ratio was calculated and transferred to the stay of control patients to create a corresponding fall date. For dynamic parameters the closest values before and after the fall event/corresponding fall date were taken into account.

In the analysed department the only fall risk assessment conducted by the nursing staff for every patient and updated on a daily basis is the ePA-AC and consists of 50 items. The result is the SPI, a score between 10 and 40 points which predicts the risk of an increased need of care after hospitalisation (Hunstein 2009; Koch et al. 2020). These items are also used to detect common fall risk factors and – if present – display an alert. In particular, the items on activity/ mobility help to determine the subject's condition and form the basis of the high fall risk alert (see Table 4).

We used the SPI score at admission and the last SPI before the fall event, the ePA-AC activity/mobility items before the fall, the HFRS (Gilbert et al. 2018; Eckart et al.

2019) and the long-term care level to describe the patient's frailty and autonomy and to investigate its association to fall events. General information about the drug therapy were collected such as the total number of agents and the use of PIM (Bennett et al. 2014). We defined PIM according to the PRISCUS list (Holt et al. 2010) since it does not need further information like the indication as needed for the FORTA list for instance. An overview of the collected data is shown in Table 5.

Table 5: Overview of collected data

Category	Items	Differentiation
Patient characteristics	Age, sex, height, weight, body mass index (calculated)	At hospital admission
Diagnoses	Principal diagnosis/secondary diagnoses	According to ICD-10 diagnostic criteria
Laboratory parameters	Serum sodium and serum creatinine level	Before fall event/corresponding fall date
Vital parameters	Blood pressure	Before fall event/corresponding fall date
Setting	Admitting unit, hour of fall	
Assessments	Level of long-term care, HFRS, score of the SPI, items on activity	
Medication	Number of prescribed drugs, number of PIMs	According to PRISCUS list
Medication review programme	Estimated fall risk using VERIKO and SCHOLZ Datenbank software	Based on FRIDs, agent, dose rate, posology of the medication given in the last 24 hours before the fall event

Notes. ICD – International Statistical Classification of Diseases and Related Health Problems. HFRS – Hospital Frailty Risk Score. SPI – Selbstpflegeindex. PIM – potentially inappropriate medication. FRID – Fall risk-inducing drugs.

The examined pharmaceutical software in this study were VERIKO and SCHOLZ Datenbank. Both ADR check programmes calculate a drug-associated fall risk based on pharmacological interactions and adverse effects. VERIKO uses an electronic data processing-risk analysis of active agents and their typical ADR. Every compound contributes with its own weighting factor to the cumulative risk (Hanke n.d.; Hanke 2016). The SCHOLZ Datenbank calculates the fall risk considering the frequency of the ADR as listed in the Summary of medicinal Product Characteristics, the risk severity as an estimation of the relevance of every adverse effect in causing fall events and the risk potentiation factor, which represents synergistic effects of different active agents in the probability to experience a fall (Scholz 2020). Further algorithm details for both software packages were not studied due to confidentiality constraints.
VERIKO classifies the fall risk into four classes ("No risk detectable", "low", "elevated" and "high" fall risk) whereas SCHOLZ Datenbank calculates the fall risk as a percentage. The drug-associated fall risk calculated by the two software programmes was linked to the patient data respectively. To compare the performance of both calculations the ROC curves were calculated and analysed.

4.3. Statistical analysis

Data analysis was performed using SPSS software (Statistical Package of the Social Sciences) 25.0 for Mac OS X (IBM, Armonk, New York, USA). Demographic and clinical characteristics such as age, sex, admitting unit and principal diagnoses were analysed descriptively. Continuous data are described as mean ± standard deviation (SD). Categorical data were summarised as absolute and relative frequencies. Falls per 1000 patient-days ratio was calculated. Spearman's rank correlation coefficient with 95%-confidence interval was calculated to describe the relationship between age and number of prescribed drugs.
Conditional logistic regression models were used for every independent variable respectively to calculate the odds ratio for fall events. For a better comparison of both programmes with different output characteristics their ROC curves were contrasted. Significant variables of the univariate analyses were included in a multivariate conditional regression model. In case of resembling variables, the more clinically relevant one or accurately assessable was chosen. The level of significance was set at 5%. No adjustments were made for multiple comparisons. To test the model fit, Nagelkerke's pseudo-R^2 was calculated for a reduced model without any of the two programmes compared to the full models including either one of them.

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