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Adrenomedullin for Risk Stratification of Emergency Patients With Nonspecific Complaints

An Interventional Multicenter Pilot Study

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Abstract: Patients with nonspecific complaints (NSC) presenting to the emergency department (ED) are at risk of life-threatening conditions. New stress biomarkers such as the midregional portion of adrenomedullin (MR-proADM) promise to support decision-making. This study tested the following hypotheses: biomarker-assisted disposition of patients with NSC will not increase mortality. Second, discharge from the ED will increase if clinical risk assessment is combined with low MR-proADM levels. Third, inappropriate disposition to a lower level of care will decrease, if clinical assessment is combined with high MR-proADM levels, and fourth that this algorithm is feasible in the ED setting.

Prospective, multicenter, randomized, controlled interventional feasibility study with a 30-day follow-up, including patients with NSC. Patients were randomly assigned to either the standard group (decision-making solely based on clinical assessment) or the Novum group (biomarker-assisted). Regarding disposition, patients were assigned to 1 of 3 risk classes: high-risk (admission to hospital), intermediate risk (community geriatric hospital), and low-risk patients (discharge). In the Novum group, in addition to clinical risk assessment, the information of the MR-proADM level was used. Unless there were overruling criteria, patients were transferred or discharged according to the risk assessment. Primary endpoint was 30-day mortality. Secondary endpoints were comparisons of patient disposition and related mortality rates, ED, and hospital length of stay and readmission.

The final study cohort consisted of 398 patients (210 in the Standard group and 188 in the Novum group). Overruling, that is, disposition not according to the result of the proposed algorithm occurred in 51 cases. Baseline characteristics between Standard and Novum groups were similar. The mortality rate in the Novum group was 4.3%, as compared to the Standard group mortality of 6.2%, which was not significantly different (intention-to treat analysis). This was confirmed by the perprotocol analysis as well as by sensitivity analysis. For the secondary endpoints, no significant differences were detected.

Biomarker-assisted disposition is safe in patients with NSC. Discharge rates did not increase. Feasibility could only partly be shown due to an unexpectedly high overruling rate. Inappropriate disposition to lower levels of care did not change.

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Abbreviations: BANCStudy = Basel Nonspecific Complaints Study, BMI = body mass index, CCI = Charlson Comorbidity Index, CGRP = calcitonin gene-related peptide, CTUU = niversity Hospital Basel Clinical Trial Unit, ED = emergency department, EP = emergency physician, ESI = emergency severity index, ET = effective transfer, FU = follow-up, IQR = interquartile ranges, ITT = intention to transfer, Katz ADL = Katz Index of Independence in Activities of Daily Living, LOS = length of stay, LRTI = lower respiratory tract infection, MR-proADM = midregional portion of adrenomedullin, NSC = nonspecific complaints, SaO_2 = oxygen saturation.

INTRODUCTION

Demographic change in western countries is a well-known phenomenon.[1] The shift in age structure leads to continuously increasing presentations of elderly people to the emergency department (ED).[2–4,5] Older patients consume more resources, are at risk of adverse outcomes, and hospitalization rates are higher than in younger patients.[6,7]

Among older ED patients the prevalence of nonspecific complaints (NSC), such as weakness, is ~20%.[8–10] The lack of typical symptoms in these patients may originate from multiple underlying diseases, complicated by polypharmacy, as well as cognitive and functional impairment.[11–14] Therefore, workup of patients with NSC may be challenging. Potentially life-threateningg conditions need to be excluded immediately, as almost 60% of the patients with NSC are in need of rapid treatment.[10] The spectrum of underlying conditions is extremely broad, ranging from social problems to acute life-threatening disease [15–18] and may lead to excessive diagnostic efforts, increasing throughput times.[19] As patients with NSC are often hospitalized, risk stratification tools for timely disposition planning in order to reduce excessive admission rates for patients with NSC without acute morbidity are needed.[20,21]

New stress biomarkers have emerged as useful risk stratification tools in the emergency setting. Adrenomedullin belongs to the Calcitonin Gene-Related Peptide (CGRP) family [22] and is a member of hormokines, a circulating substance group, with both

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hormonal properties like expression in neuroendocrine cells and systemic action, as well as cytokine behavior like expression in numerous cell types in the entire body and local action in response to inflammation or other physiological stress.[23,24] The midregional fragment of the prohormone (MR-proADM) has been shown to be a prognostic marker improving the accuracy of outcome prediction by clinical scores and risk assessments in different clinical situations such as acute and chronic heart failure,[25,26] myocardial infarction,[27,28] lower respiratory tract infections,[29–34] sepsis,[35] urinary tract infections, and kidney disease.[36,37]

We have recently shown that stress biomarkers including MR-proADM can be used to predict 30-day mortality in patients with NSC. Applying simulation, the potential usefulness of this prognostic information for disposition could be demonstrated, ideally leading to decreasing admissions to acute care, increasing transfers to geriatric care, and additional discharges. Using 30-day mortality as endpoint, a simulated algorithm was not inferior in terms of safety.[38]

Therefore, this interventional pilot study was performed to validate the proposed algorithm focusing on the following hypotheses: first, we hypothesized that biomarker-assisted disposition will not increase mortality. Second, we hypothesized that discharge will increase if clinical risk assessment is combined with low MR-proADM levels. Third, we hypothesized that inappropriate disposition to a lower level of care will decrease, if the clinical assessment is combined with high MR-proADM levels, and fourth, we hypothesized that this algorithm is feasible in the real-life ED setting.

METHODS

Study Design and Study Setting

The fourth part of the Basel Nonspecific Complaints (BANC) Study is a prospective, multicenter, randomized, controlled interventional feasibility study with a 30-day follow-up. The study was carried out in 3 EDs in Switzerland, coordinated by the University Hospital Basel (urban, tertiary-care university referral center with access to all specialties). Two regional hospitals (Kantonsspital Liestal and Kantonsspital Olten) contributed to inclusion of patients for this study. The annual census of including institutions ranges from 12.000 to 45.000 ED visits. Additionally, geriatric hospitals in the urban regions of the study centers admit older patients after initial ED evaluation and treatment. These facilities are specialized in geriatric care, providing not only medical care but also rehabilitation.

Ethics, Consent, and Permissions

The study was approved by the local ethics committee (EKBB 187/11) in charge. It is registered with Clinical Trials.gov (NCT00920491) and is in compliance with the Helsinki Declaration. Patient's participation was based on obtaining written informed consent.

Inclusion and Exclusion Criteria

Provided informed consent, all nontrauma patients aged 18 years and older with an Emergency Severity Index (ESI)[39] of 2 or 3 presenting to the emergency department with nonspecific complaints such as generalized weakness were considered for inclusion during office hours. The ESI is a widely used triage tool with proven reliability and validity.[39,40]

Patients presenting with specific complaints (eg chest pain), or clinical features suggestive of a working diagnosis (eg anemic pallor), <18 years or with an ESI 1, 4, or 5 were not eligible. Furthermore, patients whose vital signs were out of predefined limits (blood pressure < 80 mm Hg, heart rate < 55 or > 120 beats/min, respiratory rate >20 breaths/min, tympanic temperature > 38.5 degrees Celsius, oxygen saturation (SaO_2) < 92%) were not included. The ESI was used to exclude patients with predicted low resource use and very low mortality (ESI 4, 5), and to identify patients with a life-threatening condition requiring immediate life-saving interventions (ESI 1).[39,40] Patients who were not able or did not want to participate in the trial were not considered for inclusion.

RANDOMIZATION

After inclusion, all patients were randomly assigned to one of the study groups, either the Standard group or the Novum group. Due to the multicenter design of the study, a web-based tool was applied, provided by the University Hospital Basel Clinical Trial Unit (CTU) with a randomization stratified by center. Randomization with a fixed block size of 4 was used. Study physicians had access to the web-based tool at the bedside by using a tablet device for inclusion of participants.

Treatment and Disposition Decisions

All patients were treated at the discretion of the emergency physician in charge. In the Standard group, this was solely based on clinical assessment. A first disposition plan was made after initial patient work-up including diagnostics in the acute assessment unit and documented in the electronic health record. With the preliminary disposition plan, patients were assigned to 1 of 3 risk classes. If acute morbidity requiring inpatient treatment was identified, admission to an inpatient ward was planned ("A" for "acute," high-risk) as previously described in detail.[20] Patients who did not need inpatient tertiary care were transferred to a community geriatric hospital (labeled "G" for "geriatric," intermediate risk) providing immediate early rehabilitation for older patients. These community hospitals continue acute care, using, for example, i.v. antibiotics or i.v. diuretics. Low-risk patients who did not need further inpatient treatment were discharged for outpatient treatment (labeled "D" for discharge, low-risk).

The Novum group was treated according to the same standards including the additional information of the MR-proADM level. The algorithm combining the preliminary decision for the patient's disposition (intention to transfer; ITT) and the biomarker information is shown in Figure 1.

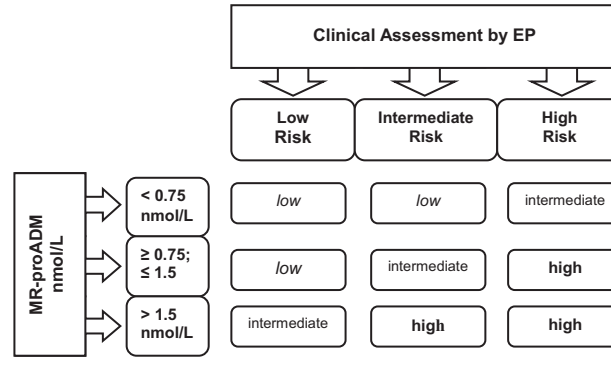

FIGURE 1. Algorithm combining the clinical risk assessment with biomarker risk classes. MR-proADM = midregional proadrenomedullin, EP = emergency physician.

The resulting risk assessment is 3-staged as well, based on the MR-proADM cutoffs 0.75 and 1.5 nmol/L with a primacy of clinical assessment. According to their risk assessment, patients were transferred to tertiary care in-hospital beds, a geriatric ward, or outpatient care unless there were overruling criteria. Effective transfer (ET) was recorded as well as overruling criteria leading to a change of disposition between ITT and ET.

Overruling Criteria

In every single case, the final disposition decision was made by the physician in charge. Therefore, in deviation from the underlying algorithm, 3 possibilities for overruling were given:

(1) medical or social reasons, for example, instability after initial assessment, or concern about the patients' ability for self-care;
(2) patients' preferences or decisions for disposition to palliative care.
(3) institutional reasons, for example, exit-block.

In these cases, the disposition suggested by the algorithm was overruled and the patient was transferred to the appropriate facility.

Data Collection and Outcome Ascertainment

Data collection was performed as previously described.[19] In brief, standardized data collection forms were made available on a tablet device used to record demographic data, patients' complaints, and comorbidities as assessed by the Charlson Comorbidity Index (CCI),[41] the patients' prescribed medications, and physical examination information. Furthermore, the Katz Index of Independence in Activities of Daily Living (Katz ADL)[42] was recorded. Each patient was followed up to 30 days after inclusion. Information on discharge, transfer to other care facilities/hospitals, and rehospitalization were obtained from hospital discharge reports or the patients' primary care providers.

MR-proADM Measurement

ProADM measurement was performed from EDTA plasma with a commercially available automated sandwich immunofluorescent assay (BRAHMS MR-proADM KRYPTOR, Thermo Scientific Biomarkers, Hennigsdorf, Germany) in hospital laboratories by technicians unaware of patients' clinical data. The MR-proADM assay has a 0.05 to 100 nmol/L measuring range and a functional sensitivity of 0.25 nmol/L.

Results were routinely available within 2 h during office hours after ordering and visible only in the case of patients randomized to the Novum group.

ENDPOINTS

The primary endpoint was mortality up to 30 days after effective transfer (ET) comparing the Novum (MR-proADM-) with the Standard-of-care-group. Secondary endpoints were comparisons with regard to patient disposition and related mortality rates, ED length of stay, hospital length of stay (LOS), and re-hospitalization (number, time to readmission, LOS during readmission).

Data Analysis

As predefined in the study protocol, the full analysis set included all patients randomized, and analysis followed the intention-to-treat principle. All patients enrolled and randomized were followed up for 30 days. The final analysis covered both an intention-to-treat analysis and a per-protocol analysis (assigning patients to study arms according to the real disposition [effective transfer, ET]—based on the algorithm or on the standard approach).

Patient characteristics values are expressed as means and standard deviations, medians and interquartile ranges (IQR), or counts and percentages as appropriate. Comparisons of Novum and Standard of care groups of continuous variables were performed using Students' t test or Mann–Whitney U test, as appropriate. Biomarker data were log-transformed if necessary. Categorical data were compared using Fisher's exact test or the x^2-test, as appropriate, numerical variables (median [IQR]) using the Wilcoxon test.

All statistical tests were 2-tailed and a 2-sided P-value of 0.05 was considered for significance.

For the primary endpoint asymptotic 95%-confidence intervals were calculated. Confidence intervals for differences were calculated as 2-sided asymptotic 95.0%-confidence intervals.

A sensitivity analysis was performed imputing patients lost to follow-up with either as survivors in a best-case analysis or as deaths in a worst-case analysis.

For all evaluations, special focus was given to patients in the biomarker disposition group, in whom the disposition decision according the algorithm was overruled.

The statistical analyses were performed using R version 2.5.1 (http://www.r-project.org).

Sample Size Considerations

The aim of the current interventional study was to evaluate for the first time the safety of a biomarker-based algorithm in patients with nonspecific complaints, while improving patient management. Calculations of sample size were performed based on previous observational studies.[19,38] We estimated that a power of at least 80% for the primary endpoint mortality and secondary endpoints could be reached if a total of 400 patients were enrolled. The noninferiority margin was set to 0.1 and a 2-sided α of 5% was assumed for all scenarios. Power calculations were performed using software PASS 2005.

RESULTS

During the study period, of the 411 patients included, 1 patient withdrew the consent and 12 patients (3%) were lost to follow-up. Therefore, the final study cohort for analysis consisted of 398 patients, randomly assigned to 210 in the Standard group, and 188 in the Novum group (see Figure 2).

Overruling occurred in 51 cases (27%) of which 30 cases were due to "medical reasons," 6 due to "patient's preference," 1 due to a "palliative situation," and 6 due to "institutional reasons" (eg exit block). In 8 cases, overruling reasons were multiple or unclear. In additional 12 cases (6%), MR-proADM values could not be considered by the responsible physician at the time of disposition as levels were either transmitted too late or levels could not be estimated. In all these 63 patients (overruled cases plus biomarker not available, 33.5%), the standard clinical disposition decision was applied.

Baseline characteristics of the study populations in each arm (intention-to-treat analysis) are shown in Table 1. There

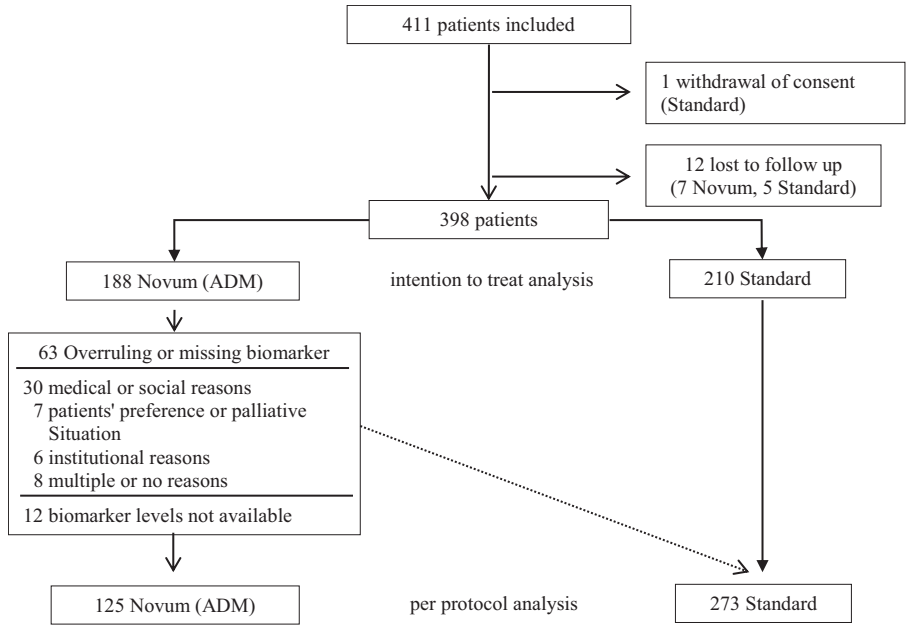

FIGURE 2. Inclusion procedure.

were no statistically significant differences between both patient groups (Standard, Novum) in all investigated parameters. Median age was 79.0 in the Standard group and 78.5 in the Novum group. Charlson Comorbidity Index and the Katz index were equal in both groups. Referral of patients to Emergency Departments occurred to one-third by self-referral or by proxy, to one-third by ambulance, and to one-third by family physicians or others. The respective data for the per-protocol analysis are provided in the Online Appendix, Table 3 (uploaded to "Supplemental Digital Content," http://links.lww.com/MD/A589).

A separate analysis of the 63 patients randomized to the Novum group, but treated as standard of care ("overruled" patients) revealed no differences in baseline characteristics

TABLE 1. Patient Characteristics (Intention to Treat Analysis)

Patient Characteristics		Novum (N = 188)	Standard (N = 210)	*P* Value
Age, median (IQR)		78.5 (62.0–87.0)	79.0 (61.0–86.0)	0.710
Sex, % male		81 (43.1%)	106 (50.5%)	0.69
BMI, mean (STD)		25 (5.2)	25 (4.8)	0.633
Heart rate, mean (STD)		79 (17.2)	82 (16.4)	0.083
Temperature, mean (STD)		36.9 (0.7)	37.0 (0.7)	0.446
Systolic BP, mean (STD)		141 (23.6)	137 (22.2)	0.126
Diastolic BP, mean (STD)		75 (14.7)	74 (14.4)	0.366
Respiratory Rate, mean (STD)		16.8 (5.1)	17.1 (5–6)	0.955
Charlson score, median (IQR)		1 (0–3)	1 (0–3)	0.748
KATZ, median (IQR)		6 (5–6)	6 (5–6)	0.997
Living situation, n (%)	alone, independent	40 (21.3%)	36 (17.1%)	0.248
	help of family	17 (9.0%)	24 (11.4%)	
	nursing home	11 (5.9%)	4 (1.9%)	
	other support systems	46 (24.5%)	63 (30.0%)	
	Partner	73 (38.8%)	82 (39.1%)	
	Unknown	1 (0.5%)	1 (0.5%)	
Mode of admission, n (%)	by ambulance	72 (38.3%)	75 (35.7%)	
	by proxy	12 (6.4%)	18 (8.6%)	
	family doctor	50 (26.6%)	54 (25.7%)	0.863
	Others	11 (5.9%)	10 (4.8%)	
	self-referred	43 (22.9%)	53 (25.2%)	

BMI = body mass index, IQR = interquartile ranges, KATZ = activities of daily living, STD = standard deviation.

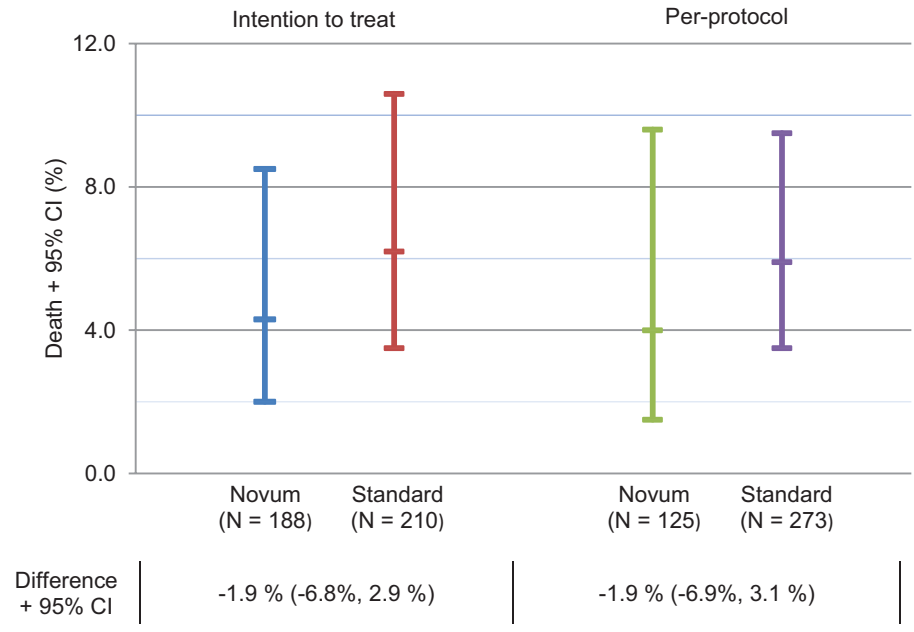

FIGURE 3. All-cause 30-day mortality. Intention-to-treat analysis: patients assigned to study arms according to randomization, irrespective of real disposition. Per-protocol analysis: patients assigned to study arms according to real disposition—based on the algorithm or on the standard approach.

between this group and the remaining Novum cohort or the Standard group (data not shown).

As for the primary endpoint, the mortality rate in the Novum group was 4.3% (95% CI 2.0–8.5%), as compared to the Standard group mortality of 6.2% (95%CI 3.5–10.6%), which was not significantly different (intention-to treat analysis, Figure 3). This was confirmed by the per-protocol analysis (mortality 4.0% [95% CI 1.5–9.6%] in the Novum group versus 5.9% [95%CI 3.5–9.5%] in the Standard group) as well as by sensitivity analysis (Online Appendix, Table 4, http://links.lww.com/MD/A589). The separate analysis showed the following mortality for the groups: Novum w/o Overruler 4.0%, Overruler 4.8%, Standard 6.2% (all differences n. s.).

Secondary outcomes

Following the intention-to-treat analysis, the transfer rate to tertiary care hospitals and geriatric hospitals, as well as the discharge rates were similar in both groups. Importantly, none of the patients who were discharged (both from Novum and Standard groups) died within the 30-day follow-up period. ED LOS, hospital LOS, and rehospitalization rates were not statistically different in the 2 groups. A comparison of per-protocol and intention-to-treat analysis for the secondary outcomes can be found in the Online Appendix Table 5 (uploaded to "Supplemental Digital Content," http://links.lww.com/MD/A589).

Analysis of the Overruler group revealed same baseline characteristics and similar mortality as the remaining Novum group, but a significantly higher admission rate. A separate analysis of the Novum group without Overrulers (new algorithm 100% followed) in comparison to the Standard group was performed, which revealed no significant differences in disposition, ED LOS, and rehospitalization rate (Table 2).

DISCUSSION

In this prospective multicenter interventional pilot study, we could show that biomarker-assisted disposition in patients with NSC is safe. However, the feasibility of transforming observational findings into clinical practice by assisting difficult disposition decisions could only partly be shown due to impediments such as an unexpectedly high overruling rate. This may well be the main reason for missing secondary objectives and rejecting some hypotheses: First, discharge rates did not increase, and second, inappropriate disposition to lower levels of care (such as geriatric community hospitals or discharge) did not decrease.

Our findings are therefore only partly in line with our previous studies showing that biomarkers might serve as a risk stratification tool for patients with NSC.[19,38] Although these studies have shown the potential of biomarkers to improve prediction of prognosis in patients with NSC, their observational design did not allow drawing conclusions about real-life situations, such as real disposition decisions. Unfortunately, reasons for overruling biomarker-assisted disposition by emergency physicians were only superficially recorded. As the major reason for overruling being "medical reasons," it may be hypothesized that safety concerns play an important role in this vulnerable population of elderly patients. Insecurity about the final diagnosis[43] and a substantial mortality may drive physicians to use overruling towards a higher level of care as observed in our study, which may surprise considering the high pressure on resources and the shortage of available beds.[20]

Similar trends were observed in a previous study[20] on patients with NSC in which a 30% change towards higher level-of-care disposition (overruling primary disposition decisions) on purely clinical grounds was shown during observation. Similarly, as observed in the present study, the shift occurred toward acute ward of tertiary care. It might be concluded that the physicians' safety concerns drive the trend towards higher levels of care in this group of vulnerable patients. Obviously, even a biomarker-assisted disposition cannot counteract this trend.

TABLE 2. Secondary Endpoints

Secondary Endpoints		Novum (n = 125)	Overruler (N = 63)	Standard (N = 207)	*P* Value Novum vs STD	*P* Value Novum vs Overruler	*P* Value Standard vs Overruler
Patient disposition, n (%)	Discharged	45 (36.0%)	9 (14.3%)	65 (31.4%)	0.610	0.005	0.013
	Geriatric hospital	18 (14.4%)	14 (22.2%)	28 (13.5%)			
	Acute (ward/ICU)	62 (49.6%)	40 (63.5%)	114 (55.1%)			
All-cause mortality within 30 days FU by disposition, n	Discharged	0	0	0	n. a.	n. a.	n. a.
	Geriatric hospital	1	2	2	1.000	0.568	0.590
	Acute (ward/ICU)	4	1	11	0.579	0.646	0.187
Re-hosp within 30 days FU, n (%)		4 (3.2%)	2 (3.2%)	9 (4.3%)	0.774	1.000	1.000
ED LOS in minutes, median (IQR)		297 (175–491)	312 (177–488)	316 (218–507)	0.511	0.930	0.592
Hospital LOS in days, median (IQR)		8 (0–24)	7 (2–14)	9 (0–23)	0.689	0.986	0.474
Days to rehospitalization, median (IQR)		17 (9–25)	16 (10–21)	17 (8–25)	1.000	1.000	0.906
Hospital LOS during re-hosp. within 30 days FU, median (IQR)		1 (1–4)	22 (13–30)	7 (5–19)	0.078	0.374	1.000

P values from Fisher's or chi-square test for categorical variables (%), *P* values from the Wilcoxon test for numerical variables (median [IQR]). For 3 Standard patients, the information on final disposition is missing.
ET = effective transfer, FU = follow-up, re-hosp = re-hospitalization, ICU = intensive care unit, IQR = interquartile ranges, LOS = length of stay, STD = standard deviation.

Comparable concepts have been applied in patients with lower respiratory tract infections (LRTI): a study investigating disposition decisions showed that risk score-assisted decisions are less effective than biomarker-assisted decisions. Interestingly, the overruling rate was ~40%. As in our study, there were no differences in adverse outcomes.[33] A second study on patients with LRTIs comparing biomarker-assisted versus guideline-assisted decisions resulted in similar rates of adverse outcomes, as well as comparable overruling rates as in our study.[44] The largest randomized trial on nonsurgical intensive care patients showed that a biomarker-assisted strategy to treat suspected bacterial infections could reduce antibiotic exposure with no increase in adverse outcomes. However, the overruling rates in that trial were >50%.[45]

Another contributing factor might be higher discharge rates of this study (31.4% in Standard group) compared to our former studies (12.3% and 13%).[19,38] This might be due to a Hawthorne effect and might have mitigated the effect of our intervention, which was also observed in other biomarker studies.[33]

Taken together, this novel approach to use biomarker-assisted disposition in a high-risk population was shown to be safe, but due to high overruling rates toward the higher level of care the hypothesized benefits—especially in terms of higher discharge rates—could not be shown. Future studies should analyze the reasons for overruling in more detail. They should be powered to detect statistical differences in discharge rates and ED LOS. Multicenter studies involving larger numbers of patients, ideally in different countries should be conducted to validate the proposed algorithm.

LIMITATIONS

The most important limitation is the high overruling rate. However, this rate compares to previous studies and might reflect physicians' safety concerns about the new algorithm. Second, the diverse clinical characteristics and reasons for overruling were not documented in much detail because no formal criteria for "medical reasons" of overruling for physicians in charge were defined by the study protocol. Third, the time for obtaining the result of biomarker levels exceeded the usual lab turnaround time in some cases, which led to application of the Standard procedure (overruling).

Furthermore, we focused on patients presenting to the ED with nonspecific complaints because they are among the most challenging regarding the diagnostic process and also in terms of disposition. Therefore, the proposed concept cannot be applied to other populations, even though in LRTI and other conditions similar concepts were shown to be beneficial.

Our results can only be applied to certain settings, as not all health care systems offer geriatric community hospitals for intermediate risk patients. Therefore, the disposition process may be unique to the Swiss health care system.

The effect size was not easy to estimate as there were no previous similar interventional studies. Our considerations for the sample size were based on observations from own previous studies and expert opinion and would need to be adjusted in regard to the secondary endpoints for larger interventional studies.

Lastly, no formal cost-effectiveness evaluation was done comparing the cost of the biomarker-assisted algorithm with standard of care.

CONCLUSIONS

In this interventional multicenter feasibility study, we show that the application of an algorithm for disposition of

patients, combining clinical assessment and a stress biomarker, is safe in the heterogeneous group of patients with nonspecific complaints presenting to the ED. However, feasibility could only partly be shown due to an unexpectedly high overruling rate. Discharge rates did not increase. Inappropriate disposition to lower levels of care did not change.

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