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The value of biomarkers in predicting mortality in older medical emergency department patients

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Abstract

Objective: Older emergency department (ED) patients are at high risk of mortality and it is important to predict which patients are at highest risk. Biomarkers lactate, high-sensitivity cardiac Troponin T (hs-cTnT), N-terminal pro-B-type natriuretic peptide (NT-proBNP), D-dimer and procalcitonin may be able to identify those at risk. We aimed to assess the discriminatory value of these biomarkers for 30-day mortality and other adverse outcomes.

Design: Prospective cohort study. Upon arrival of patients, five biomarkes were measured. Area under the curves (AUCs) and interval likelihood ratios were calculated to investigate the discriminatory value of the biomarkers.

Setting: Emergency department (ED) in The Netherlands.

Participants: Older (≥65 years) medical ED patients, referred for internal medicine or gastroenterology.

Primary and secondary outcome measures: 30-day mortality was the primary outcome measure, while other adverse outcomes (intensive care unit/medium care unit admission, prolonged length of hospital stay loss of independent living and unplanned readmission) was the secondary outcome measure.

Results: The median age of the 450 included patients was 79 years (IQR 73-85). In total, 51 (11.3%) patients died within 30 days. The AUCs of all biomarkers for prediction of mortality were sufficient to good, with the highest AUC of 0.73 for hs-cTnT and NT-proBNP. Only for the highest lactate values, the LR was high enough (29.0) to be applicable for clinical decision making, but this applied to a minority of patients. The AUC for the composite secondary outcome (intensive and medium care admission, length of hospital stay >7 days, loss of independent living and unplanned readmission within 30 days) was lower, ranging between 0.58-0.67.

Conclusions: Although all 5 biomarkers predict 30-day mortality in older medical ED patients, their discriminatory value was not good enough to contribute to clinical decision making.

Strengths and limitations of this study

This was a prospective study in which biomarkers were measured in all older patients, irrespective of the problem they presented with.

The results of these tests were not reported back, except for lactate, and therefore did not influence the doctors.

We calculated not only the total predictive ability of the biomarkers, but also interval likelihood ratio's, as we hypothesized that extreme values do not add to decisionmaking in the same way as values that are intermediate.

The limitations of the study are, besides the single centre design, that not all consecutive patients were included because physicians priorited to providing care at busy moments.

Methods:

- Prospective single centre study
- Inclusion of older (>65 y) medical patients
- Five biomarkes were measured upon arrival, irrespective of the complaint of the patient, and these were not reported back to the physicians, except for lactate.
- Discriminatory value with respect to 30-day mortality was calculated as were interval likelihood ratios

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Introduction

Background

Biomarkers such as lactate, high-sensitivity cardiac Troponin T (hs-cTnT), N-terminal pro-B-type natriuretic peptide (NT-proBNP), D-dimer and procalcitonin (PCT) are frequently used to estimate the severity of specific diseases. They are able to detect underlying conditions or diseases that are often present in the older ED population including tissue hypoperfusion, myocardial injury, heart failure, thromboembolism and infections. Although several studies report that these markers are associated with adverse outcomes and predict short-term mortality [5-15], most of these were performed in relatively young ED patients [5-8, 10, 11, 14-16], in selected ED patients with infection or sepsis [10, 14-16] or in patients with non-specific complaints [12]. It is also noteworthy that in these studies biomarkers were only measured when the ED physician deemed this to be indicated, because they were not routinely measured [5-8, 10-12]. Consequently, the true discriminatory value of these biomarkers for prediction of adverse outcomes in ED patients remains unknown.

Importance

Older patients (≥65 years) who visit the emergency department (ED) are at a substantial risk of adverse outcomes including short-term mortality, intensive or medium care unit (ICU/MCU) admission, functional decline and readmissions [1-3]. During the ED visit, it is crucial to establish which patients are at highest risk, but this remains a challenging task [4]. It is possible that biomarkers are helpful in establishing this risk.

Goals of this investigation

The aim of this prospective study was to assess the discriminatory value of arterial lactate, hs-cTnT, NT-proBNP, D-dimer and PCT for 30-day mortality and other adverse outcomes (intensive care unit (ICU)/medium care unit (MCU) admission, prolonged length of hospital stay (LOS), loss of

independent living and unplanned readmission) when measured routinely in older medical ED patients.

Methods

Study design, setting and selection of participants

This study is part of the RISE UP study, a prospective multicentre study conducted at two EDs in The Netherlands [18]. This part of the study took place only in Zuyderland MC, a large teaching hospital in the south of the Netherlands. In all patients, we routinely measured biomarkers at presentation in the ED. Patients were included if they visited the ED between July 2016 and February 2017, were 65 years or older, examined and treated by an internist or gastroenterologist and if they provided written informed consent. Exclusion criteria were earlier participation in the study and inability to speak Dutch, German or English. This study was approved by the medical ethics committee of Zuyderland MC (NL55867.096.15) and registered on clinicaltrials.gov (NCT02946398).

Measurements

At the moment of routine blood sampling at the ED, an additional arterial blood gas sample and two venous blood samples were drawn. Lactate levels were measured immediately in arterial blood samples on the RAPIDPoint® 5000 system and were available for the attending physician. Venous blood samples were centrifuged at 1800g for 10 minutes and plasma was stored in a freezer at -20 °C. D-dimer levels were measured within 4 weeks after presentation using the Sysmex® CS-2100i system. Plasma was analysed for hs-cTnT, NT-proBNP and PCT levels within 3-4 months by the Cobas® 8000 modular analyser. Results of all biomarkers, except those for lactate, were blinded for all health care providers and only available to the investigators. If one of these four biomarkers were

ordered by the attending physician as part of normal clinical practice, a different blood sample was analysed, and the results were reported as usual.

Data were collected from electronical medical records. Age, sex and living situation were recorded. In addition, we retrieved data on comorbidity according to the Charlson Comorbidity Index (CCI)[19] and triage category (using the Manchester Triage System (MTS)[20]. The abovementioned five biomarkers were retrieved as well.

Outcomes

Thirty-day all-cause mortality, was used as primary endpoint for the discriminatory value of the biomarkers. The secondary endpoint was a composite endpoint of ICU/MCU admission, prolonged LOS (>7 days), loss of independent living and unplanned readmission within 30 days after discharge.

Patient and public involvement

No patient involved.

Analysis

We performed descriptive analyses of baseline characteristics, biomarker levels and outcomes on the observed data without imputation of missing values. Continuous variables are reported as means with standard deviations or medians with interquartile ranges (IQRs) and categorical variables as proportions. Comparisons between the survivor and non-survivor groups were made using unpaired-t-tests for continuous variables with Gaussian distribution, Mann-Whitney tests for continuous non-Gaussian data and Pearson's chi-square or Fisher's exact test for categorical data.

We calculated the discriminatory value of the biomarkers for the primary and secondary outcome by constructing the area under the curves (AUCs) of receiver operating characteristics (ROCs) with 95% confidence intervals (CIs) on the available data. Accuracy of the AUCs was considered excellent if

between 0.9-1.0, very good if 0.8-0.9, good if 0.7-0.8, sufficient if 0.6-0.7 and bad if between 0.5-0.6 [21].

We divided the biomarkers into 5 groups ranging from lowest through highest values. Next, interval likelihood ratios (LRs) and mortality percentages were calculated within these groups. We considered high LRs (>10) and low LR (<0.1) as being of additional value to clinical decision making [22].
We used univariable logistic regression to compute the Odds Ratios (ORs) with 95% CIs for the biomarkers with respect to 30-day mortality. Logistic regression analyses were performed on data after imputation of missing values to allow for the inclusion of all patients. Missing values of biomarkers were imputed using stochastic regression imputation with predictive mean matching (Supplemental Table S1). All biomarkers were tested for collinearity using Pearson's correlation coefficient and for influential outliers using Cook's distance. Linearity was visually checked for all biomarkers and log transformed or dichotomised depending on the relationship with the outcome. For dichotomisation, the optimum cut-off value was chosen based on the values being closest to the upper left corner of the AUC. If two values were equally distanced, the Youden's Index was used.

All data were analysed using IBM SPSS Statistics for Windows, Version 24.0, IBM Corp., Armonk, N.Y., USA and p-values ≤0.05 were considered statistically significant.

Results

Characteristics of study subjects

For all 450 patients included during the study period follow up was complete (See Supplemental Figure S1 for flow chart of inclusion). The median age was 79 years (interquartile range 73-85) and 52% were male. In total, 51 (11.3%) patients died within 30 days after the ED visit and 201 (44.7%) met the composite endpoint. The patients who died were older than those who survived (p-value

<0.001, Table 1). Non-survivors more frequently experienced the composite endpoint (72.5%) compared to the survivors (41.1%).

Main results

Biomarkers

Four biomarkers hs-cTnT, NT-proBNP, D-dimer and PCT were above the reference range in most patients (66.4, 86.0, 78.0 and 79.8% , resp.), whereas for lactate, this was true in 25.6% of patients. The highest values of the biomarkers were more often present in non-survivors whereas the lowest values were more often present in survivors, but there was a large overlap between the non-survivors and survivors (Fig 1).

Diagnostic accuracy of the biomarkers

The AUCs for prediction of 30-day mortality were sufficient for lactate and PCT with values of 0.68 (95% CI: 0.59-0.77) and 0.67 (95% CI: 0.60-0.75) resp. (Table 2). The AUCs of the other biomarkers were good with the highest AUCs for hs-cTnT and NT-proBNP with a value of 0.73 (95% CI 0.66 to 0.80) for both. The AUCs of the biomarkers for the composite endpoint were mostly sufficient, but lower than for mortality (ranging between 0.58 and 0.67).

LRs increased with higher biomarker values, except PCT (Table 3). Most of the biomarkers had maximum LRs between 3.2 (PCT) and 4.7 (NT-proBNP), except lactate. We retrieved a maximum LR of 29.0 when lactate was between 6.0 and 10.0 mmol/L with a mortality percentage of 80.0%. The maximum LRs were, however, only applicable to a limited number of patients (n=5). The lowest LRs for all biomarkers were less variable but ranging between 0.3 (NT-proBNP) and 0.6 (lactate).

Univariable logistic regression analysis

Lactate and D-dimer were dichotomised, and hs-cTnT, NT-proBNP and PCT were logarithmically transformed because they were not linearly associated with 30-day mortality. The optimum cut-off

value was >1.5 mmol/L for lactate and >3000 µg/L for D-dimer. None of the biomarkers were highly correlated. In the univariable logistic regression analysis, all biomarkers were strong predictors of 30-day mortality with p-values of <0.001 (Table 4).

Discussion

To the best of our knowledge, this is the first study evaluating the discriminatory value of lactate, hs-cTnT, NT-proBNP, D-dimer and PCT, when measured routinely, for predicting clinical outcome in older (≥65 years) medical ED patients. We conclude that these 5 biomarkers are predictive of 30-day mortality with the best discriminatory values for hs-cTnT and NT-proBNP (AUCs of 0.73). However, we observed a large overlap in biomarker values between the survivor and non-survivor group, resulting in suboptimal LRs. Overall, the predictive ability of the biomarkers for the composite endpoint turned out to be lower than for the primary endpoint.

We showed that lactate, hs-cTnT, NT-proBNP, D-dimer and PCT are sufficient to good predictors of 30-day mortality (AUCs ranging from 0.67 to 0.73) and sufficient predictors of the composite endpoint (AUCs ranging from 0.58 to 0.67) in older medical ED patients. Other studies showed the same results [10-12, 14, 15, 23-29]. However, in most of these studies, biomarkers were not measured routinely. Moreover, two studies showed that mortality was lowest in patients in whom biomarkers were not ordered during normal clinical practice [8, 11]. These findings show that the predictive value of biomarkers measured in all patients differs from that measured only when indicated by the physician. We think that the predictive values we found for the biomarkers are more reflective of their true prognostic ability than when measured on indication.

Despite the fact that the 5 biomarkers were overall predictive of 30-day mortality, on an individual level, we found a large overlap in biomarker values between survivors and non-survivors. The overlap in biomarker values was most prominent in patients with non-extreme values. Especially in this group of patients, it is likely that the prognosis of the patient is less evident to the treating physician. Therefore, an estimation of prognosis provided by a biomarker is highly important. However, the discriminatory value of biomarker values in these patients was low as illustrated by the moderate LRs. In an US study in trauma patients, clinically meaningful contribution to decision making only occurred at lactate levels of >9 mmol/L [30], which was only present in a minority of patients. In our study, lactate had an important LR of 29 when between 6-10 mmol/l, which was only applicable to five patients. For the secondary composite endpoint, the discriminatory value of the biomarkers was even lower (ranging between 0.58 and 0.67). Therefore, we conclude that the five biomarkers do not contribute to clinical decision making.

Besides their discriminatory ability, the extra costs for determining the biomarkers should be taken into account. In more than 90% of patients (75% for lactate), biomarkers were not ordered by the physician (Supplemental Table S2). Measuring these biomarkers on a routine basis will therefore lead to direct and indirect costs because abnormal test results (26-86% of results were outside reference range in our study) will undoubtedly lead to additional diagnostic tests, like CT scans. The relative limited discriminatory value and the expected extra costs support our conclusion that routinely determined biomarkers are not beneficial for the care of older ED patients.

While we showed that biomarkers, measured at the ED visit, predicts 30-day mortality, it is unknown whether assessment of these parameters will influence clinical decision making, outcome, well-being, and medical costs. For this reason, the impact of biomarkers on clinical practice and patient related outcome measures may be an interesting subject for future studies.

Our study has some limitations. First, due to moments of crowding of the ED, it was not possible to include every possible candidate, as physicians had to give priority to providing emergency care. We detected no evidence for selection bias but cannot exclude it either [17]. In addition, we only measured biomarker values immediately after arrival at the ED. It is possible that serial biomarker measurement may have yielded different information and a different predictive ability.

In conclusion, the biomarkers lactate, hs-cTnT, NT-proBNP, D-dimer and PCT, when measured routinely, have predictive value with regard to short-term mortality and other adverse outcomes in older medical ED patients, but, given the large overlap in values between those with and without adverse outcomes, they are unlikely to contribute to clinical decision making. Therefore, we conclude that routine measurement of these parameters is not recommended.

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Author contributions

NZ, JB, PWL and PMS are responsible for developing the research question and study design. NZ and RH collected all data. NZ and PMS are responsible for study management and data collection. NZ and SMJK performed the statistical analysis. Data was interpreted by all authors and NZ drafted the first version of the manuscript. MR performed all laboratary tests. RH, JB, PWL, MR, SMJK and PMS critically revised the manuscript. All authors have read and approved the final version of the manuscript.

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Data sharing: All data are available upon reasonable request

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Table 1. *Baseline characteristics of study participants*

	Reference Values	Total N=450	Non-survivors N=51	Survivors N=399	[a]
Age, median (IQR), years		450	83 (77-87)	79 (73-85)	***
Male sex, n %		450	26 (51.0)	208 (52.1)	
Community-dwelling, n %		450	36 (70.6)	353 (88.5)	***
CCI score, median (IQR)		450	3 (2-5)	2 (1-3)	**
MTS category, n %		447			*
Red			2 (3.9)	1 (0.3)	
Orange			10 (19.6)	46 (11.6)	
Yellow			28 (54.9)	226 (57.1)	
Green			11 (21.6)	122 (30.8)	
Blue			-	1 (0.3)	
Biomarkers					
lactate, median (IQR), mmol/L	0.6-1.8	378	2.0 (1.5-2.8)	1.4 (1.0-1.9)	***
hs-cTnT, median (IQR), ng/L	<14	425	42 (26-84)	21 (12–39)	***
NT-proBNP, median (IQR), ng/L	<125	424	2766 (943-11597)	759 (266-2377)	***
D-dimer, median (IQR), µg/L	<500	407	3445 (1281-6497)	1251 (660-2804)	***
PCT, median (IQR), ng/mL	<0.05	424	0.32 (0.13-1.40)	0.12 (0.06-0.31)	***

CCI=Charlson Comorbidity Index; hs-cTnT=high-senstivity cardiac Troponin T; IQR=interquartile range; MTS=Manchester Triage System; NT-proBNP=N-terminal pro-B-type natriuretic peptide; PCT=procalcitonin; SD=standard deviation

Analysis in this table made using non-imputed data

[a] Significant difference between non-survivors and survivors with a p-value of 0.01- <0.05 (*), 0.001- <0.01 (**) or <0.001 (***)

Table 2. *AUCs for the biomarkers with respect to mortality and the composite endpoint*

		AUC (95 % CI)	
Biomarker	**n**	**30-day mortality**	**Composite endpoint**
lactate	378	0.68 (0.59 – 0.77)	0.62 (0.56 – 0.67)
hs-cTnT	425	0.73 (0.66 – 0.80)	0.67 (0.61 – 0.72)
NT-proBNP	424	0.73 (0.66 – 0.80)	0.65 (0.60 – 0.71)
D-dimer	407	0.70 (0.62 – 0.77)	0.58 (0.52 – 0.64)
PCT	424	0.67 (0.60 – 0.75)	0.65 (0.60 – 0.70)

AUC=area under the curve; CI=confidence interval; hs-cTnT=high-senstivity cardiac Troponin T; NT-proBNP=N-terminal pro-B-type natriuretic peptide; PCT=procalcitonin

Analysis in this table made using non-imputed data

Table 3. *Interval likelihood ratios for the biomarkers*

Biomarker	Mortality				N	LR	Observed Mortality (%)
	Yes (n %)		No (n %)				
lactate (mmol/L)							
0 – 1.0	5	(10.9)	62	(18.7)	67	0.6	7.5
>1.0 – 2.0	20	(43.5)	197	(59.3)	217	0.7	9.2
>2.0 – 4.0	14	(30.4)	65	(19.6)	79	1.6	17.7
>4.0 – 6.0	3	(6.5)	7	(2.1)	10	3.1	30.0
>6.0 – 10.0	4	(8.7)	1	(0.3)	5	29.0	80.0
hs-cTnT (ng/L)							
0 – 20	9	(18.4)	184	(48.9)	193	0.4	4.7
>20 – 40	13	(26.5)	102	(27.1)	115	1.0	11.3
>40 – 60	11	(22.4)	44	(11.7)	55	1.9	20.0
>60 – 100	8	(16.3)	28	(7.4)	36	2.2	22.2
>100	8	(16.3)	18	(4.8)	26	3.4	30.8
NT-proBNP (ng/L)							
0 – 500	6	(12.2)	150	(40.0)	156	0.3	3.8
>500 – 1000	7	(14.3)	69	(18.4)	76	0.8	9.2
>1000 – 2500	9	(18.4)	67	(17.9)	76	1.0	11.8
>2500 – 10,000	14	(28.6)	68	(18.1)	82	1.6	17.1
>10,000	13	(26.5)	21	(5.6)	34	4.7	38.2
D-dimer (µg/L)							
0 – 1000	8	(17.0)	149	(41.1)	157	0.4	5.1
>1000 – 2500	12	(25.5)	112	(31.1)	124	0.8	9.7
>2500 – 5000	12	(25.5)	56	(15.6)	68	1.6	17.6
>5000 – 10,000	9	(19.1)	30	(8.3)	39	2.3	23.1
>10,000	6	(12.8)	13	(3.6)	19	3.6	31.6
PCT (ng/L)							
0 – 0.1	10	(20.4)	166	(44.3)	176	0.5	5.7
>0.1 – 0.5	16	(32.7)	137	(36.5)	153	0.9	10.5
>0.5 – 1.0	6	(12.2)	21	(5.6)	27	2.2	22.2
>1.0 – 5.0	12	(24.5)	29	(7.7)	41	3.2	29.3
>5.0	5	(10.2)	22	(5.9)	27	1.7	18.5

hs-cTnT=high-senstivity cardiac Troponin T; LR=likelihood ratio; NT-proBNP=N-terminal pro-B-type natriuretic peptide; PCT=procalcitonin

Table 4. *Univariable logistic regression analysis for 30-day mortality*

Predictors	Univariable analysis	
	Odds Ratio (95% CI)	P-value
lactate >1.5 mmol/L	4.29 (2.18-8.44)	<0.001
hs-cTnT – per log ng/L increase	2.36 (1.70-3.27)	<0.001
NT-proBNP – per log ng/L increase	1.78 (1.45-2.18)	<0.001
D-dimer >3000 µg/L	2.91 (1.61-5.28)	<0.001
PCT – per log ng/mL increase	1.34 (1.15-1.56)	<0.001

CI=confidence interval; hs-cTnT=high-senstivity cardiac Troponin T; log=logarithm; NT-proBNP=N-terminal pro-B-type natriuretic peptide; PCT=procalcitonin

Analysis in this table made using imputed data

Legends of figures

Figure 1. Distribution of the five biomarkers among survivors and non-survivors. Bars represent the proportion of patients with the according biomarker value within the survivor and non-survivor group.

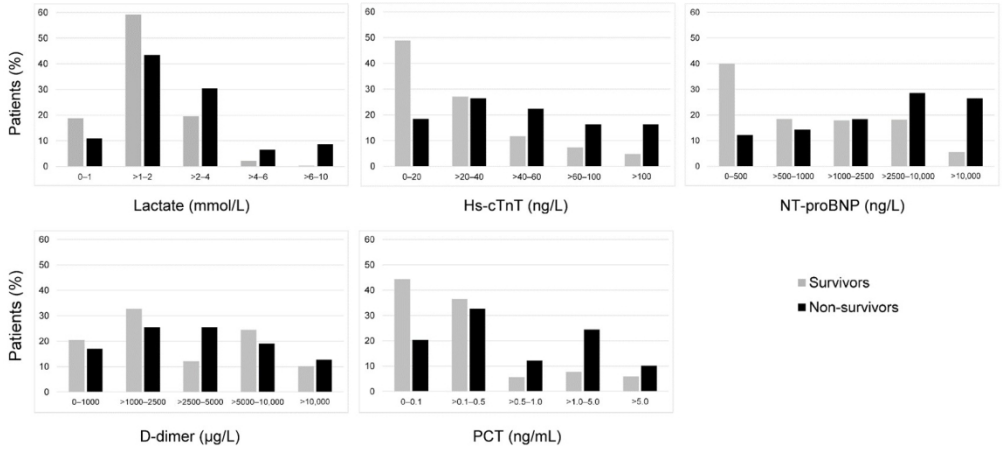


Figure 1. Distribution of the five biomarkers among survivors and non-survivors. Bars represent the proportion of patients with the according biomarker value within the survivor and non-survivor group.

284x129mm (150 x 150 DPI)

Supplemental File

Supplementary tables

Supplemental Table S1. *Overview imputed values*

Imputed variable	Total (n=450) n (%)
Lactate	72 (16.0)
Hs-cTnT	25 (5.6)
NT-proBNP	26 (5.8)
D-dimer	43 (9.6)
PCT	26 (5.8)

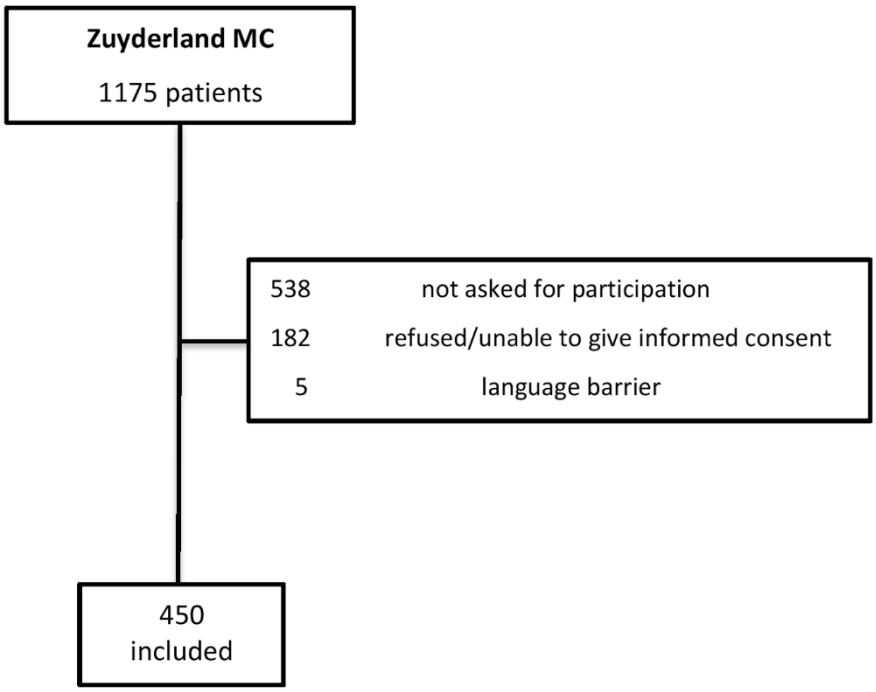
Hs-cTnT, high-sensitivity cardiac Troponin T; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PCT, procalcitonin

Supplemental Table S2. *Biomarkers ordered by the physician*

Biomarker	**% of patients[a]**
Lactate	25.8
Hs-cTnT	7.6
NT-proBNP	8.7
D-dimer	5.1
PCT	0.0

Hs-cTnT, high-senstivity cardiac Troponin T; NT-pro-BNP, N-terminal pro-B-type natriuretic peptide; PCT, procalcitonin

[a]Represents the proportion of patients for whom the biomarker was ordered by the physician



Supplementary Figure S1. Flowchart of patient selection in Zuyderland MC.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4-5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	n.a.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	6-7
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	n.a.
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, explain how loss to follow-up was addressed	n.a.
		(*e*) Describe any sensitivity analyses	n.a.
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7 and suppl fig 1
		(c) Consider use of a flow diagram	suppl fig 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	suppl table 1
		(c) Summarise follow-up time (eg, average and total amount)	7
Outcome data	15*	Report numbers of outcome events or summary measures over time	7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8 and tables
		(*b*) Report category boundaries when continuous variables were categorized	8 and table 3
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	table 3 and 8
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n.a.
Discussion			
Key results	18	Summarise key results with reference to study objectives	9-11
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	9
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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The value of biomarkers in predicting mortality in older medical emergency department patients: a Dutch prospective study

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Abstract

Objective: Older emergency department (ED) patients are at high risk of mortality and it is important to predict which patients are at highest risk. Biomarkers lactate, high-sensitivity cardiac Troponin T (hs-cTnT), N-terminal pro-B-type natriuretic peptide (NT-proBNP), D-dimer and procalcitonin may be able to identify those at risk. We aimed to assess the discriminatory value of these biomarkers for 30-day mortality and other adverse outcomes.

Design: Prospective cohort study. Upon arrival of patients, five biomarkes were measured. Area under the curves (AUCs) and interval likelihood ratios were calculated to investigate the discriminatory value of the biomarkers.

Setting: Emergency department (ED) in The Netherlands.

Participants: Older (≥65 years) medical ED patients, referred for internal medicine or gastroenterology.

Primary and secondary outcome measures: 30-day mortality was the primary outcome measure, while other adverse outcomes (intensive care unit/medium care unit admission, prolonged length of hospital stay, loss of independent living and unplanned readmission) was the composite secondary outcome measure.

Results: The median age of the 450 included patients was 79 years (IQR 73-85). In total, 51 (11.3%) patients died within 30 days. The AUCs of all biomarkers for prediction of mortality were sufficient to good, with the highest AUC of 0.73 for hs-cTnT and NT-proBNP. Only for the highest lactate values, the LR was high enough (29.0) to be applicable for clinical decision making, but this applied to a

minority of patients. The AUC for the composite secondary outcome (intensive and medium care admission, length of hospital stay >7 days, loss of independent living and unplanned readmission within 30 days) was lower, ranging between 0.58-0.67.

Conclusions: Although all 5 biomarkers predict 30-day mortality in older medical ED patients, their individual discriminatory value was not high enough to contribute to clinical decision making.

Strengths and limitations of this study

This was a prospective study in which biomarkers were measured in all older patients, irrespective of the problem they presented with.

The results of these tests were not reported back, except for lactate, and therefore did not influence the doctors.

We calculated not only the total predictive ability of the biomarkers, but also interval likelihood ratio's, as we hypothesised that extreme values do not add to decision making in the same way as values that are intermediate.

The limitations of the study are, besides the single centre design, that not all consecutive patients were included because physicians prioritised to providing care at busy moments.

Introduction

Background

Biomarkers such as lactate, high-sensitivity cardiac Troponin T (hs-cTnT), N-terminal pro-B-type natriuretic peptide (NT-proBNP), D-dimer and procalcitonin (PCT) are frequently used to diagnose and estimate the severity of specific diseases. They are able to detect underlying conditions or diseases that are often present in older patients (≥65 years) who visit the emergency department (ED). These include tissue hypoperfusion, myocardial injury, heart failure, thromboembolism and infections. Although several studies report that these markers are associated with adverse outcomes and predict short-term mortality [1-11], most of these were performed in relatively young ED patients [1-4 6 7 10-12], in selected ED patients with infection or sepsis [6 10-12] or in patients with non-specific complaints [8]. It is also noteworthy that in these studies biomarkers were only measured when the ED physician deemed this to be indicated, because they were not routinely measured [1-4 6-8]. Consequently, the true discriminatory value of these biomarkers for prediction of adverse outcomes in ED patients remains unknown.

Importance

Older patients who visit the ED are at a substantial risk of adverse outcomes including short-term mortality, intensive or medium care unit (ICU/MCU) admission, functional decline and readmissions [13-15]. During the ED visit, it is crucial to establish which older patients are at highest risk, but this remains a challenging task [16]. It is possible that biomarkers are helpful in establishing this risk.

Goals of this investigation

The aim of this prospective study was to assess the discriminatory value of arterial lactate, hs-cTnT, NT-proBNP, D-dimer and PCT for 30-day mortality and other adverse outcomes (intensive care unit (ICU)/medium care unit (MCU) admission, prolonged length of hospital stay (LOS), loss of

independent living and unplanned readmission) when measured routinely in older medical ED patients.

Methods

Study design, setting and selection of participants

This study is part of the RISE UP study, a prospective multicentre study conducted at two EDs in The Netherlands. The study protocol of this study was published online [17]. This part of the study took place in Zuyderland MC, a large teaching hospital in the south of the Netherlands, because biomarkers were measured in patients included in this site only. Patients were included if they visited the ED between July 2016 and February 2017, were 65 years or older, examined and treated by an internist or gastroenterologist and if they provided written informed consent. Exclusion criteria were earlier participation in the study and inability to speak Dutch, German or English. This study was approved by the medical ethics committee of Zuyderland MC (NL55867.096.15) and registered on clinicaltrials.gov (NCT02946398).

Measurements

At the moment of routine blood sampling at the ED, an additional arterial blood gas sample and two venous blood samples were drawn. Lactate levels were measured immediately in arterial blood samples on the RAPIDPoint® 5000 system and were available for the attending physician. Venous blood samples were centrifuged at 1800g for 10 minutes and plasma was stored in a freezer at -20 °C. D-dimer levels were measured within 4 weeks after presentation using the Sysmex® CS-2100i system. Plasma was analysed for hs-cTnT, NT-proBNP and PCT levels within 3-4 months by the Cobas® 8000 modular analyser. Results of all biomarkers, except those for lactate, were blinded for all health care providers and only available to the investigators. If one of these four biomarkers were

ordered by the attending physician as part of normal clinical practice, a different blood sample was analysed, and the results were reported as usual.

All data were collected from electronical medical records. The following data were retrieved upon arrival at the ED visit: age, sex and living situation, data on comorbidity according to the Charlson Comorbidity Index (CCI)[18] and triage category (using the Manchester Triage System (MTS)[19]. The abovementioned five biomarkers were retrieved as well.

Outcomes

Thirty-day all-cause mortality, was used as primary endpoint for the discriminatory value of the biomarkers. The secondary endpoint was a composite endpoint of ICU/MCU admission, prolonged LOS (>7 days), loss of independent living and unplanned readmission within 30 days after discharge. Length of hospital stay was retrieved for patients who were admitted immediately following the ED visit. Loss of independent living was defined as discharge to a nursing home/hospice or with palliative care in previously community dwelling patients.

Data regarding the outcomes was collected by checking the electronical medical files, which are connected to the municipal administration and by contacting the general practitioner if necessary.

Patient and public involvement

No patient involved.

Analysis

The sample size available for this study depended on a prospective cohort study, the RISE-UP study, which provided data on 450 patients[17]. For logistic regression analysis, at least 10 event per candidate predictor are needed, according to prediction modelling guidelines. We assumed that the

mortality rate would be around 11%. Therefore, the inclusion of 450 patients provided more than sufficient observations for our primary objective.

We performed descriptive analyses of baseline characteristics, biomarker levels and outcomes on the observed data without imputation of missing values. Continuous variables are reported as means with standard deviations or medians with interquartile ranges (IQRs) and categorical variables as proportions. Comparisons between the survivor and non-survivor groups were made using unpaired-t-tests for continuous variables with Gaussian distribution, Mann-Whitney tests for continuous non-Gaussian data and Pearson's chi-square or Fisher's exact test for categorical data.

We calculated the discriminatory value of the biomarkers for the primary and secondary outcome by constructing the area under the curves (AUCs) of receiver operating characteristics (ROCs) with 95% confidence intervals (CIs) on the available data. Accuracy of the AUCs was considered excellent if between 0.9-1.0, very good if 0.8-0.9, good if 0.7-0.8, sufficient if 0.6-0.7 and bad if between 0.5-0.6 [20].

We divided the biomarkers into 5 groups ranging from lowest through highest values. Next, interval likelihood ratios (LRs) and mortality percentages were calculated within these groups. We considered high LRs (>10) and low LR (<0.1) as being of additional value to clinical decision making [21].

We used univariable logistic regression to compute the Odds Ratios (ORs) with 95% CIs for the biomarkers with respect to 30-day mortality.

As a subanalysis, we evaluated the discriminatory ability of a combination of biomarkers. For this purpose, we used logistic regression with backwards elimination using a p-value of 0.10 for removal and determined the discriminatory ability of this new model by calculating the AUC with 95% CI.

Logistic regression analyses were performed on data after imputation of missing values to allow for the inclusion of all patients. Sensitivity analyses were performed to assess the impact of missing data

on our results by comparing the results after imputation to complete case analysis. Missing values of biomarkers were imputed using stochastic regression imputation with predictive mean matching (Supplemental Table S1). All biomarkers were tested for collinearity using Pearson's correlation coefficient and for influential outliers using Cook's distance. Linearity was visually checked for all biomarkers and log transformed or dichotomised depending on the relationship with the outcome. For dichotomisation, the optimum cut-off value was chosen based on the values being closest to the upper left corner of the AUC. If two values were equally distanced, the Youden's Index was used. All data were analysed using IBM SPSS Statistics for Windows, Version 24.0, IBM Corp., Armonk, N.Y., USA and p-values <0.05 were considered statistically significant.

Results

Characteristics of study subjects

For all 450 patients included during the study period follow up was complete (Figure 1).The median age was 79 years (interquartile range 73-85) and 52% were male. In total, 51 (11.3%) patients died within 30 days after the ED visit and 201 (44.7%) met the composite endpoint. The patients who died were older than those who survived (p-value <0.001, Table 1). Non-survivors more frequently experienced the composite endpoint (n=37, 72.5%) compared to the survivors (n=164, 41.1%, p-value <0.001).

Main results

Biomarkers

Four biomarkers hs-cTnT, NT-proBNP, D-dimer and PCT were above the reference range in most patients (66.4, 86.0, 78.0 and 79.8% , resp.), whereas for lactate, this was true in 25.6% of patients. The highest values of the biomarkers were more often present in non-survivors whereas the lowest

values were more often present in survivors, but there was a large overlap between the non-survivors and survivors (Table 1, Figure 2).

Diagnostic accuracy of the biomarkers

The AUCs for prediction of 30-day mortality were sufficient for lactate and PCT with values of 0.68 (95% CI: 0.59-0.77) and 0.67 (95% CI: 0.60-0.75) resp. (Table 2). The AUCs of the other biomarkers were good with the highest AUCs for hs-cTnT and NT-proBNP with a value of 0.73 (95% CI 0.66 to 0.80) for both. The AUCs of the biomarkers for the composite endpoint were mostly sufficient, but lower than for mortality (ranging between 0.58 and 0.67).

LRs increased with higher biomarker values, except PCT (Table 3). Most of the biomarkers had maximum LRs between 3.2 (PCT) and 4.7 (NT-proBNP), except lactate. We retrieved a maximum LR of 29.0 when lactate was between 6.0 and 10.0 mmol/L with a mortality percentage of 80.0%. The maximum LRs were, however, only applicable to a limited number of patients (n=5). The lowest LRs for all biomarkers were less variable but ranging between 0.3 (NT-proBNP) and 0.6 (lactate).

Univariable logistic regression analysis

Lactate and D-dimer were dichotomised, and hs-cTnT, NT-proBNP and PCT were logarithmically transformed because they were not linearly associated with 30-day mortality. The optimum cut-off value was >1.5 mmol/L for lactate and >3000 µg/L for D-dimer. None of the biomarkers were highly correlated. In the univariable logistic regression analysis, all biomarkers were strong predictors of 30-day mortality with p-values of <0.001 (Table 4).

Subanalysis of combining biomarkers

In order to assess the discriminatory value of multiple biomarkers, we developed a model through backwards elimination in the multiple logistic regression analysis. PCT did not contribute significantly

to the model (p-value 0.51) and was therefore removed (Table 4). This resulted in a model consisting of lactate, hs-cTnT, NT-proBNP and D-dimer. The AUC for prediction of 30-day mortality of these four biomarkers combined was 0.82 (95% CI: 0.76 – 0.87).

Discussion

To the best of our knowledge, this is the first study evaluating the discriminatory value of lactate, hs-cTnT, NT-proBNP, D-dimer and PCT, when measured routinely, for predicting clinical outcome in older (≥65 years) medical ED patients. We conclude that these 5 biomarkers are predictive of 30-day mortality with the best discriminatory values for hs-cTnT and NT-proBNP (AUCs of 0.73). However, we observed a large overlap in biomarker values between the survivor and non-survivor group, resulting in suboptimal LRs. Overall, the predictive ability of the biomarkers for the composite endpoint turned out to be lower than for the primary endpoint.

We showed that lactate, hs-cTnT, NT-proBNP, D-dimer and PCT are sufficient to good predictors of 30-day mortality (AUCs ranging from 0.67 to 0.73) and sufficient predictors of the composite endpoint (AUCs ranging from 0.58 to 0.67) in older medical ED patients. Other studies showed the same results [6-8 10 11 22-28]. However, in most of these studies, biomarkers were not measured routinely. Moreover, two studies showed that mortality was lowest in patients in whom biomarkers were not ordered during normal clinical practice [4 7]. These findings show that the predictive value of biomarkers measured in all older ED patients differs from that measured only when indicated by the physician. We think that the predictive values we found for the biomarkers are more reflective of their true prognostic ability than when measured on indication.

Despite the fact that the 5 biomarkers were overall predictive of 30-day mortality, on an individual level, we found a large overlap in biomarker values between survivors and non-survivors. The overlap in biomarker values was most prominent in patients with non-extreme values. Especially in this group of patients, it is likely that the prognosis of the patient is less evident to the treating physician. Therefore, an estimation of prognosis provided by a biomarker is highly important. However, the discriminatory value of biomarker values in these patients was low as illustrated by the moderate LRs. In an US study in trauma patients, clinically meaningful contribution to decision making only occurred at lactate levels of >9 mmol/L [29], which was only present in a minority of patients. In our study, lactate had an important LR of 29 when between 6-10 mmol/l, which was only applicable to five patients. For the secondary composite endpoint, the discriminatory value of the biomarkers was even lower (ranging between 0.58 and 0.67). Therefore, we conclude that the five biomarkers do not contribute to clinical decision making.

Besides their discriminatory ability, the extra costs for determining the biomarkers should be taken into account. In more than 90% of patients (75% for lactate), biomarkers were not ordered by the physician (Supplemental Table S2). Measuring these biomarkers on a routine basis will therefore lead to direct and indirect costs because abnormal test results (26-86% of results were outside reference range in our study) will undoubtedly lead to additional diagnostic tests, like CT scans.

In the multivariable analysis, stepwise elimination resulted in a new model consisting of four biomarkers, lactate, hs-cTnT, NT-proBNP and D-dimer, which yielded an AUC of 0.82. This discriminatory ability was, however, not better than that of the recently developed RISE UP score (AUC 0.83), which consists of age, vital signs and four routine laboratory tests albumin, blood urea nitrogen, lactate dehydrogenase, and bilirubin [30]. The RISE UP score was developed in the same patient sample and has the advantage of using inexpensive variables, which are collected in routine ED care making the score feasible for use in older ED patients. In addition, we recently showed that adding these biomarkers to the RISE UP model only minimally improved the AUC of the model by

0.03 [31].The limited added discriminatory ability and the expected extra costs support our conclusion that routinely determined biomarkers are not beneficial for prediction of mortality in older ED patients.

While we showed that biomarkers, measured at the ED visit, predicts 30-day mortality, it is unknown whether assessment of these parameters will influence clinical decision making, outcome, well-being, and medical costs. For this reason, the impact of biomarkers on clinical practice and patient related outcome measures may be an interesting subject for future studies.

Our study has some limitations. First, due to moments of crowding of the ED, it was not possible to include every possible candidate, as physicians had to give priority to providing emergency care. We detected no evidence for selection bias but cannot exclude it either [17]. In addition, we only measured biomarker values immediately after arrival at the ED. It is possible that serial biomarker measurement may have yielded different information and a different predictive ability.

In conclusion, the biomarkers lactate, hs-cTnT, NT-proBNP, D-dimer and PCT, when measured routinely, have predictive value with regard to short-term mortality and other adverse outcomes in older medical ED patients, but, given the large overlap in values between those with and without adverse outcomes, they are unlikely to individually contribute to clinical decision making. Therefore, we conclude that routine measurement of these parameters is not recommended.

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Author contributions

NZ, JB, PWL and PMS are responsible for developing the research question and study design. NZ and RH collected all data. NZ and PMS are responsible for study management and data collection. NZ and SMJK performed the statistical analysis. Data was interpreted by all authors and NZ drafted the first version of the manuscript. MR performed all laboratary tests. RH, JB, PWL, MR, SMJK and PMS critically revised the manuscript. All authors have read and approved the final version of the manuscript.

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Conflicts of interest statement: None of the authors have any conflicts of interest to disclose.

Data sharing: All data are available upon reasonable request

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Table 1. *Baseline characteristics of study participants*

	Reference Values	Missing values	Non-survivors N=51	Survivors N=399	[a]
Age, median (IQR), years		-	83 (77-87)	79 (73-85)	***
Male sex, n (%)		-	26 (51.0)	208 (52.1)	
Community-dwelling, n (%)		-	36 (70.6)	353 (88.5)	***
CCI score, median (IQR)		-	3 (2-5)	2 (1-3)	**
MTS category, n (%)		3 (0.7)			*
Red			2 (3.9)	1 (0.3)	
Orange			10 (19.6)	46 (11.6)	
Yellow			28 (54.9)	226 (57.1)	
Green			11 (21.6)	122 (30.8)	
Blue			-	1 (0.3)	
Biomarkers					
lactate, median (IQR), mmol/L	0.6-1.8	72 (16.0)	2.0 (1.5-2.8)	1.4 (1.0-1.9)	***
hs-cTnT, median (IQR), ng/L	<14	25 (5.6)	42 (26-84)	21 (12–39)	***
NT-proBNP, median (IQR), ng/L	<125	26 (5.8)	2766 (943-11597)	759 (266-2377)	***
D-dimer, median (IQR), µg/L	<500	43 (9.6)	3445 (1281-6497)	1251 (660-2804)	***
PCT, median (IQR), ng/mL	<0.05	26 (5.8)	0.32 (0.13-1.40)	0.12 (0.06-0.31)	***
Outcome					
Composite endpoint[b], n (%)		-	37 (72.5)	164 (41.1)	***

CCI=Charlson Comorbidity Index; hs-cTnT=high-senstivity cardiac Troponin T; IQR=interquartile range; MTS=Manchester Triage System; NT-proBNP=N-terminal pro-B-type natriuretic peptide; PCT=procalcitonin; SD=standard deviation

Analysis in this table made using non-imputed data

[a] Significant difference between non-survivors and survivors with a p-value of 0.01- <0.05 (*), 0.001- <0.01 (**) or <0.001 (***)

[b]Composite endpoint consisting of ICU/MCU admission, prolonged LOS (>7 days), loss of independent living and unplanned readmission within 30 days after discharge

Table 2. *AUCs for the biomarkers with respect to mortality and the composite endpoint*

		AUC (95 % CI)	
Biomarker	**n**	**30-day mortality**	**Composite endpoint**
lactate	378	0.68 (0.59 – 0.77)	0.62 (0.56 – 0.67)
hs-cTnT	425	0.73 (0.66 – 0.80)	0.67 (0.61 – 0.72)
NT-proBNP	424	0.73 (0.66 – 0.80)	0.65 (0.60 – 0.71)
D-dimer	407	0.70 (0.62 – 0.77)	0.58 (0.52 – 0.64)
PCT	424	0.67 (0.60 – 0.75)	0.65 (0.60 – 0.70)

AUC=area under the curve; CI=confidence interval; hs-cTnT=high-senstivity cardiac Troponin T; NT-proBNP=N-terminal pro-B-type natriuretic peptide; PCT=procalcitonin

Analysis in this table made using non-imputed data

Table 3. *Interval likelihood ratios for the biomarkers*

Biomarker	Mortality				N	LR	Observed Mortality (%)
	Yes (n %)		No (n %)				
lactate (mmol/L)							
0 – 1.0	5	(10.9)	62	(18.7)	67	0.6	7.5
>1.0 – 2.0	20	(43.5)	197	(59.3)	217	0.7	9.2
>2.0 – 4.0	14	(30.4)	65	(19.6)	79	1.6	17.7
>4.0 – 6.0	3	(6.5)	7	(2.1)	10	3.1	30.0
>6.0 – 10.0	4	(8.7)	1	(0.3)	5	29.0	80.0
hs-cTnT (ng/L)							
0 – 20	9	(18.4)	184	(48.9)	193	0.4	4.7
>20 – 40	13	(26.5)	102	(27.1)	115	1.0	11.3
>40 – 60	11	(22.4)	44	(11.7)	55	1.9	20.0
>60 – 100	8	(16.3)	28	(7.4)	36	2.2	22.2
>100	8	(16.3)	18	(4.8)	26	3.4	30.8
NT-proBNP (ng/L)							
0 – 500	6	(12.2)	150	(40.0)	156	0.3	3.8
>500 – 1000	7	(14.3)	69	(18.4)	76	0.8	9.2
>1000 – 2500	9	(18.4)	67	(17.9)	76	1.0	11.8
>2500 – 10,000	14	(28.6)	68	(18.1)	82	1.6	17.1
>10,000	13	(26.5)	21	(5.6)	34	4.7	38.2
D-dimer (µg/L)							
0 – 1000	8	(17.0)	149	(41.1)	157	0.4	5.1
>1000 – 2500	12	(25.5)	112	(31.1)	124	0.8	9.7
>2500 – 5000	12	(25.5)	56	(15.6)	68	1.6	17.6
>5000 – 10,000	9	(19.1)	30	(8.3)	39	2.3	23.1
>10,000	6	(12.8)	13	(3.6)	19	3.6	31.6
PCT (ng/L)							
0 – 0.1	10	(20.4)	166	(44.3)	176	0.5	5.7
>0.1 – 0.5	16	(32.7)	137	(36.5)	153	0.9	10.5
>0.5 – 1.0	6	(12.2)	21	(5.6)	27	2.2	22.2
>1.0 – 5.0	12	(24.5)	29	(7.7)	41	3.2	29.3
>5.0	5	(10.2)	22	(5.9)	27	1.7	18.5

hs-cTnT=high-senstivity cardiac Troponin T; LR=likelihood ratio; NT-proBNP=N-terminal pro-B-type natriuretic peptide; PCT=procalcitonin

Table 4. *Univariable and multivariable logistic regression analysis for 30-day mortality*

Predictors	Univariable analysis		Multivariable analysis[a]	
	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value
lactate >1.5 mmol/L	4.29 (2.18 – 8.44)	<0.001	2.98 (1.46 – 6.09)	0.003
hs-cTnT – per log ng/L increase	2.36 (1.70 – 3.27)	<0.001	1.53 (1.01 – 2.32)	0.002
NT-proBNP – per log ng/L increase	1.78 (1.45 – 2.18)	<0.001	1.49 (1.15 – 1.92)	0.002
D-dimer >3000 µg/L	2.91 (1.61 – 5.28)	<0.001	2.77 (1.44 – 5.33)	0.045
PCT – per log ng/mL increase	1.34 (1.15 – 1.56)	<0.001	-	-
			AUC (95% CI)	
			0.82 (0.76- 0.87)	

CI=confidence interval; hs-cTnT=high-senstivity cardiac Troponin T; log=logarithm; NT-proBNP=N-terminal pro-B-type natriuretic peptide; PCT=procalcitonin

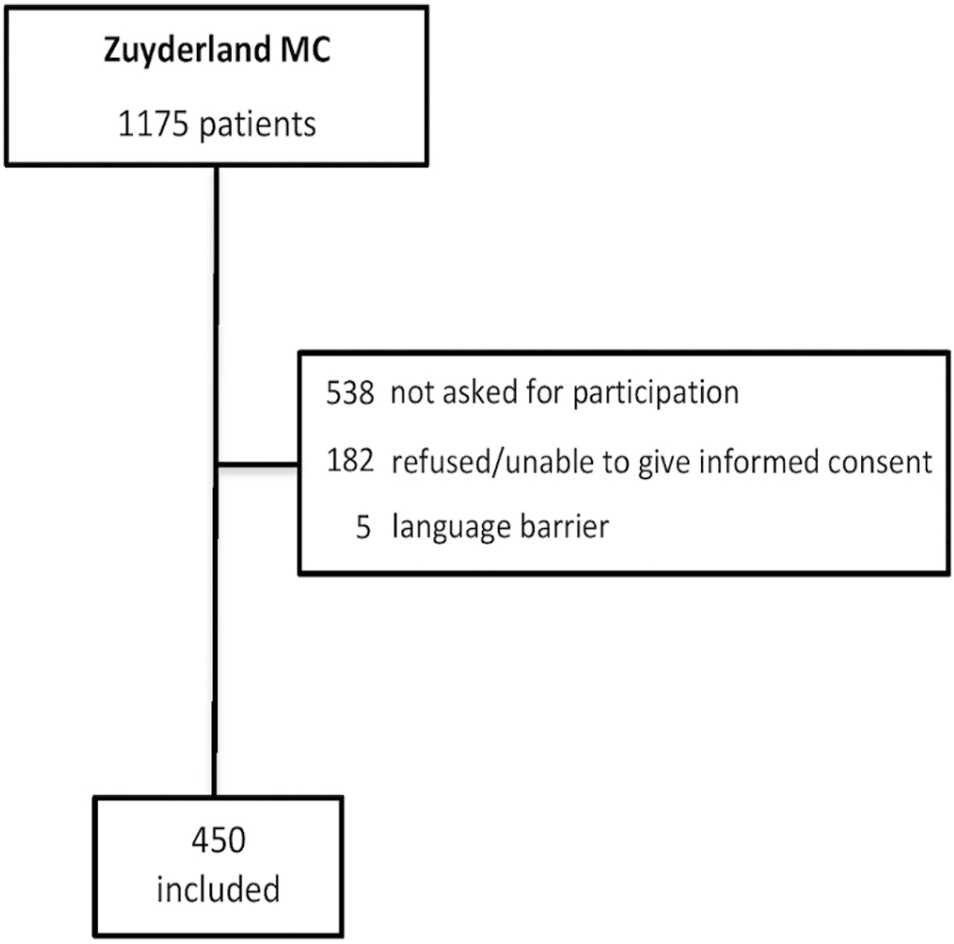
Analysis in this table made using imputed data

[a] Model of biomarkers selected through backwards stepwise elimination using multivariable logistic regression analysis.

Legends of figures

Figure 1. **Flowchart of patient selection**

Figure 2. Distribution of the five biomarkers among survivors and non-survivors. Bars represent the proportion of patients with the according biomarker value within the survivor and non-survivor group.



Flowchart of patient inclusion

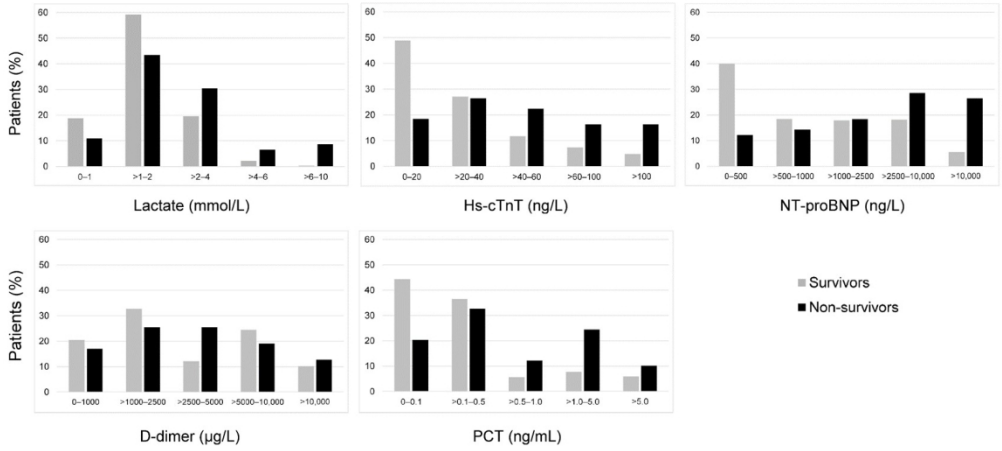


Figure 2. Distribution of the five biomarkers among survivors and non-survivors. Bars represent the proportion of patients with the according biomarker value within the survivor and non-survivor group.

284x129mm (150 x 150 DPI)

Supplemental File

Supplementary tables

Supplemental Table S1. *Overview imputed values*	
Imputed variable	Total (n=450) n (%)
Lactate	72 (16.0)
Hs-cTnT	25 (5.6)
NT-proBNP	26 (5.8)
D-dimer	43 (9.6)
PCT	26 (5.8)

Hs-cTnT, high-sensitivity cardiac Troponin T; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PCT, procalcitonin

Supplemental Table S2. *Biomarkers ordered by the physician*	
Biomarker	**% of patients[a]**
Lactate	25.8
Hs-cTnT	7.6
NT-proBNP	8.7
D-dimer	5.1
PCT	0.0

Hs-cTnT, high-senstivity cardiac Troponin T; NT-pro-BNP, N-terminal pro-B-type natriuretic peptide; PCT, procalcitonin

[a]Represents the proportion of patients for whom the biomarker was ordered by the physician

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4-5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	n.a.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	6-7
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	n.a.
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, explain how loss to follow-up was addressed	n.a.
		(*e*) Describe any sensitivity analyses	n.a.
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7 and suppl fig 1
		(c) Consider use of a flow diagram	suppl fig 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	suppl table 1
		(c) Summarise follow-up time (eg, average and total amount)	7
Outcome data	15*	Report numbers of outcome events or summary measures over time	7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8 and tables
		(*b*) Report category boundaries when continuous variables were categorized	8 and table 3
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	table 3 and 8
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n.a.
Discussion			
Key results	18	Summarise key results with reference to study objectives	9-11
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	9
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.