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Independent predictors of major adverse cardiovascular events in emergency department patients who are hospitalised with a suspected infection: a retrospective cohort study

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ABSTRACT

Objective: Emergency department (ED) patients hospitalised with a suspected infection have an increased risk for major adverse cardiovascular events (MACE). This study aims to identify independent predictors of MACE after hospital admission which could be used for identification of high-risk patients who may benefit from preventive strategies.

Setting: Dutch tertiary care centre and urban hospital.

Participants: Consecutive, hospitalised, ED patients with a suspected infection.

Design: This was a secondary analysis using an existing database in which consecutive, hospitalised, ED patients with a suspected infection were prospectively enrolled. Potential independent predictors, including illness severity, as assessed by the Predisposition, Infection, Response, Organ failure (PIRO) score, and classic cardiac risk factors were analysed by multivariable binary logistic regression. Prognostic and discriminative performance of the model was quantified by the Hosmer-Lemeshow test and receiver operator characteristics with area under the curve (AUC) analyses, respectively. Maximum sensitivity and specificity for identification of MACE were calculated.

Primary outcome: MACE within 90 days after hospital admission.

Results: 36 (2.1%) of the 1728 included patients developed MACE <90 days after ED presentation. Independent predictors of MACE were the RO components of the PIRO score, reflecting acute organ failure, with a corrected OR (OR (95% CI) 1.1 (1.0 to 1.3) per point increase), presence of atrial fibrillation/flutter; OR 3.9 (2.0 to 7.7) and >2 classic cardiovascular risk factors; 2.2 (1.1 to 4.3). The AUC was 0.773, and the goodness-of-fit test had a p value of 0.714. These predictors identified MACE with 75% sensitivity and 70% specificity.

Conclusions: Besides the classical cardiovascular risk factors, atrial fibrillation and signs of acute organ failure were independent risk factors of MACE in ED patients hospitalised with a suspected infection. Future studies should investigate whether preventive measures

Strengths and limitations of this study

- This is the first study that identified independent predictors (signs of acute onset organ failure, atrial fibrillation, and more than two classic cardiac risk factors) of major adverse cardiovascular events (MACE) in emergency department patients hospitalised with an infection.
- The predictors of MACE might be used to identify a subgroup of emergency department patients who may benefit from secondary prevention, such as antiplatelet therapy, during or after their hospitalisation with an infection.
- Despite acceptable interobserver agreement and thorough follow-up, some information bias cannot be excluded due to the retrospective nature of the study.
- There were 36 (2.1%) cases of MACE in this study, limiting the number of variables in our prediction model.

like antiplatelet therapy should be initialised in hospitalised ED patients with suspected infection and high risk for MACE.

INTRODUCTION
Background

Ischaemic heart disease and cerebrovascular disease are still the major causes of death and morbidity worldwide.[1] Previous studies have shown an increased risk for major adverse cardiovascular events (MACE) after infections,[2–8] which was explained by endothelial dysfunction, procoagulant changes in the blood and proinflammatory changes in atherosclerotic plaques facilitating plaque rupture.[9] The highest risk was found in patients with acute organ failure in the first

week after infection.[4] Temporary prevention of MACE could be an important strategy for patients hospitalised with an infection. One prospective observational study showed that aspirin use lowered 30-day mortality after hospitalisation with a community-acquired pneumonia.[10] The positive effect of aspirin may be explained by the anti-inflammatory and anticoagulant effects of aspirin. Early recognition and management of cardiovascular disease may, therefore, have a large impact on patient outcome.

Importance
Prevention or at least early detection of MACE after hospitalisation with a severe infection might be possible if we can predict which patients will experience an MACE. Since the majority of patients will be hospitalised with a severe infection via the emergency department (ED), ED physicians, cardiologists and neurologists should be able to identify which patients are at highest risk.

Goals of this investigation
The aim of the present study was, therefore, twofold: first, to identify independent predictors of MACE in ED patients hospitalised with a suspected infection. Second, to investigate if a subset of ED patients can be identified with sufficient diagnostic accuracy to justify close monitoring or even initiation of secondary prevention.

METHODS
Study design and setting
This was a secondary analysis using an existing database in which consecutive hospitalised ED patients with a suspected infection were prospectively enrolled and the incidence of an MACE 90 days after hospital admission was retrospectively recorded. Patients were enrolled at the ED of the Leiden University Medical Centre (LUMC), a tertiary care university hospital with approximately 30 000 annual visits and the Rijnstate Hospital (RH, Arnhem, The Netherlands), an urban hospital with approximately 30 000 visits per year. Inclusion took place from 1 June 2011 to 1 June 2014 (LUMC), and from 1 March 2012 to 1 April 2013 (RH). The study was approved by the medical ethics committee of the LUMC who waived the need for individual consent because of the purely observational character of the study. Patients who appeared to have no infection, according to their final hospital discharge letter, were excluded (eg, those with pulmonary embolus or autoimmune and haematological disorders presenting with fever).

Selection of participants
An existing database was used in which all consecutive ED patients ≥17 years with suspected infection and triage category yellow, orange or red were prospectively included by the triage nurse or the nurse/physician who took care of the patient.[11] Only patients admitted to hospital with intravenous antibiotics were included. Triage categories blue and green were excluded in this database because most of these patients were expected to be at very low risk (ie, patients with a simple pharyngitis). Any sign that triggered the triage nurse and treating physician to suspect an infection was suitable to start the screening algorithm (ie, fever, coughing, erythema, etc).

Data collection and measurements
Demographics, comorbidities, use of medication, clinical data, laboratory data and outcomes were already prospectively recorded in the digital hospital information system (Chipsoft, Amsterdam) by the triage nurse or treating nurse/physician and then collected in a SPSS file (SPSS V.20.0, IBM) by a medical student. This included a score that quantifies illness severity, the so-called Predisposition, Infection, Response and Organ-failure (PIRO) score, which has been described previously, and has been validated in our ED.[12] [13] This score consists of four components of which the PI components mainly reflect non-modifiable patient characteristics like age and comorbidities, and the RO components reflect the modifiable and potentially reversible patient factors, such as signs of acute onset organ dysfunction.

Atherosclerotic heart disease, including previous myocardial infarction and (unstable) angina pectoris, was recorded as one of the comorbidities. Use of antihypertensive medication and use of statins were chosen as indicators of hypertension and hypercholesterolaemia, respectively. All other risks for cardiovascular disease were later collected as new data from the digital hospital information system and transferred to a SPSS data file by medical students. These additional variables were: a medical history of diabetes mellitus (type 1 or 2), smoking (currently smoking or any smoking in the past), positive family history of cardiovascular disease (at least one first-degree relative with acute coronary syndrome (ACS) or stroke before 65 years of age), history of cerebral vascular accident (CVA) or transient ischaemic attack (TIA), history of peripheral ischaemia and history of atrial fibrillation/flutter (first detected, paroxysmal, persistent and permanent).

Correspondent to the thrombolysis in myocardial infarction (TIMI) risk score,[14] a composite variable was constructed representing the baseline cardiovascular risk for each included patient in which 0–3 risk factors were scored as 0, and 3 or more risk factors were scored as 1. The risk factors included in this score were male gender, history of cardiovascular disease (atherosclerotic heart disease, CVA, TIA or peripheral ischaemia), history of diabetes mellitus, hypertension, hypercholesterolaemia, smoking and positive family history of cardiovascular disease. If data of cardiovascular risk factors were missing, they were assumed to be absent and scored as 0, as has been done in previous studies.[15]

In addition, the use of antiplatelet therapy (aspirin or clopidogrel), and the use of oral anticoagulants (fenprocoumon or acenocoumarol) before ED presentation

were obtained from the patients who had an MACE within 90 days after hospital admission.

Primary outcome

The primary outcome was the occurrence of MACE within 90 days after hospital admission with a suspected infection. MACE was defined as follows: ACS, a resuscitation setting with ventricular tachycardia or fibrillation as first rhythm or a (sudden) death presumed to be of cardiac origin according to the medical file, stroke (ischaemic and haemorrhagic), TIA and acute peripheral ischaemia of the legs.

ACS, including (non)-ST-elevation myocardial infarction and unstable angina pectoris, was defined according to the third universal definition of myocardial infarction.[16] The diagnosis of stroke and TIA were based on clinical presentation and had to be confirmed by a neurologist, preferably with radiological imaging. Acute peripheral ischaemia was defined as a sudden decrease in limb perfusion that causes a potential threat to limb viability. Patients who presented later than 2 weeks after the acute event were not considered to have acute ischaemia.[17]

The occurrence of an MACE was collected from the hospital information system by the medical students based on discharge letters, notes of the nurses and treating physicians in the medical file during admission, consultations of other specialists and laboratory and radiological results.

The certainty of MACE was scored as definite, probable or possible. MACE was labelled as definite if the above definitions were unequivocally met and confirmed by a cardiologist or neurologist. MACE was scored as probable if there were clear clinical signs of the aforementioned MACE which were confirmed by a cardiologist or neurologist, but limited radiological evidence was available. For example, because no further diagnostic testing was pursued, that is, in case of Do Not Resuscitate status and explicit wish of the patient to stop further diagnostic testing. Possible MACE was defined as no clear clinical sign and without diagnostics but with strong suspicion. Elevated high-sensitivity troponin-T levels with no other clinical symptoms were presumed to be secondary to the sepsis and grouped apart from the MACE cases as 'demand ischaemia'. For this study, we only used the definite and probable cases of MACE. A synopsis of all-found cases is available in the web-appendix (see online supplementary file 1).

Patients who had insufficient medical information about the 90 days after hospital admission in their file were contacted by telephone and asked if they had an MACE after their stay in the hospital. If these patients could not be contacted (wrong telephone number, emigrated, etc) they were treated as lost to follow-up.

Data analysis

Continuous data were presented as mean (SD) if normally distributed, and as median (IQR) if right skewed.

Categorical data were presented as number (%). Continuous data were compared using the Student t test or Mann-Whitney test, as appropriate. Categorical data were compared using the χ^2 test.

The prediction model was constructed using multivariable logistic regression analysis. In the regression analysis, the composite variable of classic cardiovascular risk factors and the RO score were forced into the model because organ dysfunction and the TIMI score are associated with MACE in previous studies, and we wanted to evaluate these predictors in our model.[4 14 18]

In addition, forward entry of variables with p<0.2 in the univariate analysis was used to identify potential independent predictors of MACE within 90 days. To prevent collinearity, individual components of the RO score were not included, even if they had a p<0.2 in the univariate analysis. High-sensitivity cardiac troponin T was considered to be an outcome measure, and therefore, not included in the model. Finally, the predictor variables with p<0.05 were selected to form the final prediction model.

To prevent overfitting, the rule of thumb that number of events divided by 10 was the number of predictor variables was used in the model. Prognostic and discriminative performance of the model was quantified by the Hosmer-Lemeshow test and receiver operator characteristics with AUC analysis, respectively. The ORs with 95% CIs were reported. p Value <0.05 was considered to be significant.

The 3 ORs of the independent predictors were subsequently used to calculate the maximum diagnostic accuracy. For the presence of each independent predictor, a number of points were assigned correspondent to the magnitude of the OR. Using receiver operator characteristics with AUC analysis, the cut-off point with a maximum combined sensitivity and specificity was selected.

Furthermore, interobserver agreement was assessed in a random subset of 200 patients (with 400 comparisons of MACE before and after hospital admission) using the Cohen's κ and the number of agreements for the outcome and certainty of MACE.

All data were analysed using SPSS statistics (SPSS, V.20.0, IBM).

Sensitivity analysis

To investigate the impact of the patients who were lost to follow-up on results of the model, two sensitivity analyses were performed. In the first sensitivity analysis, patients who were lost to follow-up were considered to have had no MACE and were subsequently included in the analysis. In the second sensitivity analysis, 2% (the incidence of MACE in the included patients) of the patients lost to follow-up were considered to have had an MACE. These 2% were selected randomly by SPSS, and the others were scored automatically as 'no MACE.'

RESULTS
Patient characteristics

A total of 1728 patients were included, of whom 36 patients (2.1%) developed MACE within 90 days after hospital admission (2.2% if the missing patients were left out of the denominator). Because 125 (7.2%) patients were lost in follow-up, 1603 were included in the multivariable logistic regression analysis (figure 1). Patient characteristics of missing patients are shown in online supplementary file 2. From six patients (0.3%), no records were retrieved, and they were treated as loss to follow-up. In 119 patients, there was a lack of information in the medical file after inclusion, which gives a total of 125 patients (7.2%) treated as loss to follow-up after inclusion.

Patient characteristics and outcomes are shown in table 1. Patients with MACE had a longer hospital stay (10 vs 6 days, p=0.001) and a higher mortality rate within 90 days (38% vs 14%, p<0.001). Of the 36 patients with an MACE, most patients had pneumonia as suspected site of infection (49%), followed by urine tract infection (24%). In 198 (99%) of 200 comparisons, data abstractors had agreement. In one patient, one data abstractor scored 'no MACE' while the other scored 'possible MACE' (This had no effect on the analysis since 'no' and 'possible' MACE were not counted as an MACE). In the second patient without agreement, one data abstractor scored 'possible MACE' while the other scored 'probable MACE.' In this case, the principal investigator (BdG) decided not to include this patient in the analysis, and the patient was scored as possible). In all other cases there was agreement. The interobserver variability for assessment of MACE was substantial with a Cohen's κ coefficient of 0.71.

Independent predictors of MACE

The p values of the univariate analysis are shown in table 1. Table 2 contains the included predictors from the first and final prediction models after multivariable

binary logistic regression analysis. The independent predictors of MACE within 90 days after ED presentation were the presence of atrial fibrillation/flutter (corrected OR (95% CI) of 3.9 (2.0 to 7.7)), more than two classic cardiac risk factors (2.2 (1.1 to 4.3)) and the RO score (1.1 (1.0 to 1.3), meaning that with every point increase in the OR score of the PIRO classification, the odds for MACE increases with 1.1). The Hosmer-Lemeshow goodness-of-fit test had a p value of 0.714. In figure 2, the ROC curve is shown. The model had an AUC of 0.773 (95% CI 0.698 to 0.849).

Sensitivity analyses

If it was assumed that all the 125 patients with loss to follow-up had no MACE, the independent predictors would also be the presence of atrial fibrillation/flutter with a corrected OR of 3.9 (2.0 to 7.7), presence of >2 risk factors (2.3 (1.1 to 4.5)) and the RO score (1.1 (1.0 to 1.3) per point). The Hosmer-Lemeshow goodness-of-fit test had a p value of 0.367, and the AUC of 0.778 (0.704 to 0.851) (see online supplementary file 3a).

In addition, if it was assumed that a random 2% of the patients with loss to follow-up had an MACE there were still three independent predictors. The presence of atrial fibrillation (3.2 (1.7 to 6.1)), presence of more than two classical risk factors (1.9 (1.0 to 3.6)), and the RO score (1.1 (1.0 to 1.2) per point increase. The Hosmer-Lemeshow goodness-of-fit test had a p value of 0.936, and the AUC of 0.736 (0.659 to 0.813) (see online supplementary file 3b).

Diagnostic accuracy of presence of independent predictors

The 3 ORs of the independent predictors were subsequently used to calculate the maximum diagnostic accuracy by assigning points correspondent to the value of the OR; atrial fibrillation 4 points, more than two risk factors 2 points, and RO score categorised as score >6 with 2 points.

Figure 1 Patient flow through study. ED, emergency department; MACE, major adverse cardiovascular events.
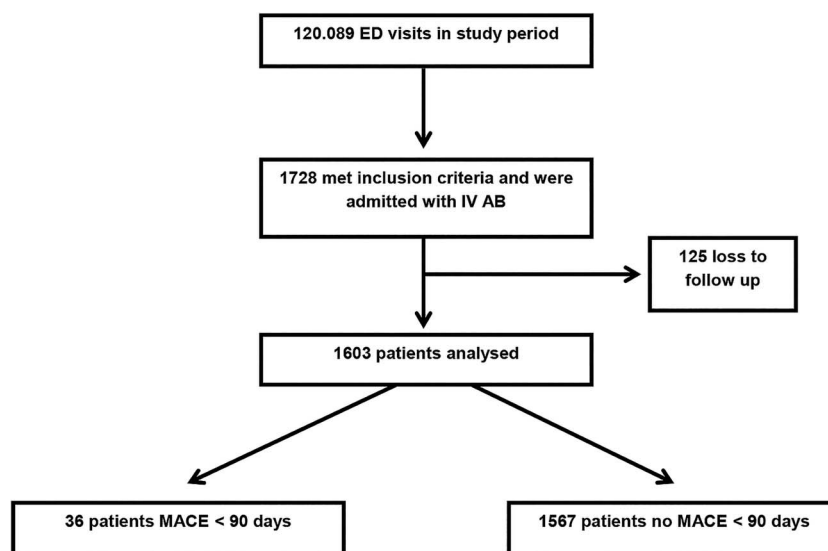
Table 1 Patient characteristics

	Total	MACE <90 days after sepsis	No MACE <90 days after sepsis	p Value
N (125 missing due to lost in follow-up*)	1728	36	1567	
Demographics				
Age, mean (SD)	61 (17)	75 (12)	61 (17)	<0.001
Gender, (male, %)	975 (56)	25 (68)	877 (56)	0.161
Comorbidities, n (%)				
Atherosclerotic heart disease	333 (19)	15 (41)	295 (19)	0.001
CVA/TIA (6)	196 (11)	11 (30)	170 (11)	<0.001
Peripheral ischaemia (6)	108 (6)	5 (14)	99 (6)	0.079
Any history of CVD (5)†	509 (30)	22 (60)	453 (29)	<0.001
Diabetes mellitus (6)	371 (22)	16 (43)	336 (22)	0.002
Atrial fibrillation (6)	272 (16)	18 (49)	238 (15)	<0.001
COPD	280 (16)	7 (19)	253 (16)	0.652
Liver disease	83 (5)	1 (3)	76 (5)	0.545
Renal disease	298 (17)	8 (22)	275 (18)	0.522
Immunocompromised	685 (40)	8 (22)	662 (42)	0.012
Malignancy –	204 (12)	9 (24)	191 (12)	0.027
Malignancy +	210 (12)	1 (3)	204 (13)	0.063
Nursing home resident	111 (6)	6 (16)	84 (5)	0.005
Risk factors, n (%)				
Smoking (257)	847 (49)	25 (68)	772 (49)	0.056
Positive family history CVD (998)	230 (13)	9 (24)	213 (14)	0.431
Hypertension (10)	735 (43)	24 (65)	661 (42)	0.007
Hypercholesterolaemia (9)	433 (25)	16 (43)	396 (25)	0.014
Total number of risk factors >2	619 (36)	23 (62)	569 (36)	<0.001
Suspected site of infection, n (%)‡				
Pneumonia	827 (48)	18 (49)	737 (47)	0.848
Urinary tract	490 (28)	9 (24)	442 (28)	0.602
Abdomen	291 (17)	8 (22)	270 (17)	0.487
Skin	150 (9)	5 (14)	136 (9)	0.305
Neurological	42 (2)	2 (5)	36 (2)	0.220
Other	334 (19)	8 (22)	310 (20)	0.783
Clinical presentation on admission				
Systolic blood pressure, mean (SD) (236)	133 (26)	136 (28)	132 (26)	0.473
Heart rate, mean (SD) (43)	108 (20)	110 (21)	109 (20)	0.763
Respiratory rate, median (IQR) (513)	24 (19–30)	27 (21–33)	24 (19–30)	0.080
Oxygen saturation, mean (SD) (67)	95 (5)	94 (5)	95 (5)	0.105
Temperature (°C), mean (SD) (41)	38.7 (2.0)	38.2 (2.0)	38.7 (1.6)	0.080
Altered mental status n (%) (206)	287 (17)	12 (32)	245 (16)	0.006
Laboratory analysis on admission				
White cell counts (10^9/L), median (IQR) (7)	12.0 (7.8–16.7)	12.8 (8.6–16.3)	11.9 (7.5–16.6)	0.503
Creatinine (µg/L), median (IQR) (14)	87 (67–120)	95 (77–133)	87 (67–120)	0.075
Urea (mmol/L), median (IQR) (15)	7.0 (5.1–10.3)	8.8 (6.6–14.7)	7.0 (5.1–10.3)	0.002
Lactate (mmol/L), median (IQR) (227)§	1.8 (1.3–2.5)	2.3 (1.5–3.4)	1.8 (1.3–2.5)	0.057
Platelets (10^3/mm³), median (IQR) (37)	207 (150–276)	203 (144–268)	205 (150–275)	0.950
CRP (mg/L), median (IQR) (20)	87 (33–192)	144 (71–202)	86 (32–191)	0.048
Hs-TnT (ng/L), median (IQR) (884)	15 (6–39)	93 (13–460)	14 (6–37)	<0.001
INR, median (IQR) (687)	1.1 (1.0–1.5)	1.3 (1.0–1.8)	1.1 (1.0–1.4)	0.412
Organ dysfunction, n (%)				
Urea >7.14 mmol/L	825 (48)	25 (68)	740 (47)	0.014
Respiratory rate >20/min	917 (53)	28 (76)	817 (52)	0.005
Lactate >4.0 mmol/L	120 (7)	7 (19)	102 (7)	0.003
Bands > 5%, n (%)	103 (6)	5 (14)	90 (6)	0.048
Systolic blood pressure <70 mm Hg	11 (1)	0 (0)	11 (1)	0.609
Systolic blood pressure 70–90 mm Hg	85 (5)	3 (8)	78 (5)	0.391
Systolic blood pressure >90 mm Hg	1632 (94)	34 (92)	1477 (94)	0.531
Platelets <150×10^9/L	412 (24)	9 (24)	380 (24)	0.993

Continued

Table 1 Continued

	Total	MACE <90 days after sepsis	No MACE <90 days after sepsis	p Value
Illness severity				
Total PIRO score, median (IQR)	10 (6–14)	13 (10–16)	10 (6–13)	<0.001
Total PI score, median (IQR)	4 (3–6)	5 (4–7)	4 (3–6)	0.013
Total RO score, median (IQR)	6 (2–8)	8 (5–10)	6 (2–8)	<0.001
Acute onset organ failure n (%)	352 (20)	15 (41)	310 (20)	0.002
DNR status, n (%) (5)	359 (21)	14 (38)	308 (20)	0.007
Outcome				
Hospital stay (day), median (IQR) (52)	6 (3–10)	10 (6–17)	6 (3–10)	0.001
ICU admission, n (%) (4)	178 (10)	4 (11)	164 (11)	0.949
Mortality <90 days, n (%) (85)	249 (14)	14 (38)	224 (14)	<0.001

Numbers in brackets behind individual variables represent missing data.
*Of the 125 patients no information was available in the medical files after they had presented to the ED with a suspected infection and they could not be contacted by telephone.
†Any history of CVD (5): atherosclerotic heart disease and/or TIA/stroke and/or peripheral ischaemia or two or three of these comorbidities.
‡Multiple sites of infection are possible.
§From peripheral lines (in the Netherlands, central lines are generally only placed in the ICU).
COPD, chronic obstructive pulmonary disease; CRP, C reactive protein; CVA, cerebral vascular accident; CVD, cardiovascular disease, patients with arteriosclerotic heart disease, CVA/TIA and/or peripheral ischaemia of the legs; DNR status, do not resuscitate status; family history, at least one first-degree relative <65 years with atherosclerotic disease; ED, emergency department; Hs-TnT, high-sensitivity cardiac troponin T; ICU, intensive care unit; INR, international normalised ratio; MACE, major adverse cardiovascular events; PIRO, Predisposition, Infection, Response, Organ failure; PI score, Predisposition and Infection; RO score, Response and Organ failure; TIA, transient ischaemic attack; atrial fibrillation, atrial fibrillation or atrial flutter new onset, paroxysmal, persistent and permanent; immunocompromised, HIV/AIDS, hematologic malignancy, chemotherapy, use of immunosuppressive medication or oral corticosteroids; malignancy −, malignancy without metastases; malignancy +, malignancy with metastases or hematologic malignancy; family history, at least one first-degree relative <65 years with atherosclerotic disease; total of risk factors, includes diabetes, smoking, family history, use of antihypertensive, use of statins, missing risk factors are assumed to be absent.

The Response and Organ failure (RO) score of the PIRO classification can be 0 to 20 (figure 1 of ref [12]). The corrected OR of the RO score in the present study was 1.1, meaning that with every point increase in the RO score, the odds for MACE increases by a factor of 1.1. For an increase of 6 points in the RO score, this means that the odds for MACE increases by a factor 1.8 (ie, 1.1^6). We have rounded the 1.8 to 2 in the calculation and assigned 2 points for an RO score increase of 6 points. The cut-off of 6 points was based on the ROC curve.

Subsequently, using a cut-off value of 3, which had the largest possible sensitivity and specificity according to the ROC curve, the diagnostic accuracy to identify MACE was moderate, with 75% sensitivity and 70% specificity. Of the 36 patients with MACE, 27 had a score of ≥4 points (true positives) and nine patients had a score of 0–3 points (false negatives). Of the 1567 patients without MACE, 1097 had a score from 0 to 3 points (true negatives) and 470 had a score ≥4 points (false positives).

Of the 36 patients with MACE after infection, 16 already used antiplatelet therapy and 11 patients were on oral anticoagulants; 11 patients used none of them and 1 of the patients used both.

DISCUSSION

The main finding of the present study is that there are three in the ED readily available variables that can accurately predict the occurrence of MACE within 90 days after hospitalisation with an infection: presence of atrial fibrillation/flutter, more than two classical cardiovascular risk factors and signs of acute onset organ dysfunction.

Table 2 Multivariable binary logistic regression models: first and final prediction model

Variable	OR (95% CI)	p Value	Corrected OR (95% CI)	p Value
Altered mental status	1.5 (0.7 to 3.4)	0.298		
Presence of atrial fibrillation/flutter	3.9 (1.9 to 8.1)	<0.001	3.9 (2.0 to 7.7)	<0.001
C reactive protein (mg/L)	1.0 (1.0 to 1.0)	0.210		
Predisposition, Infection score	1.1 (0.9 to 1.3)	0.329		
Response, Organ failure score	1.1 (1.0 to 1.2)*	0.064	1.1 (1.0 to 1.3)	0.004
Risk factors total >2	2.6 (1.2 to 5.5)	0.016	2.2 (1.1 to 4.3)	0.029
Temperature (°C)	0.9 (0.8 to 1.0)	0.036		

*With every point increase in the OR score of the Predisposition, Infection, Response, Organ failure classification, the odds for major adverse cardiovascular events increases with 1.1. Hosmer and Lemeshow goodness of fit p=0.714, area under the curve (95% CI) 0.773 (0.698 to 0.849).
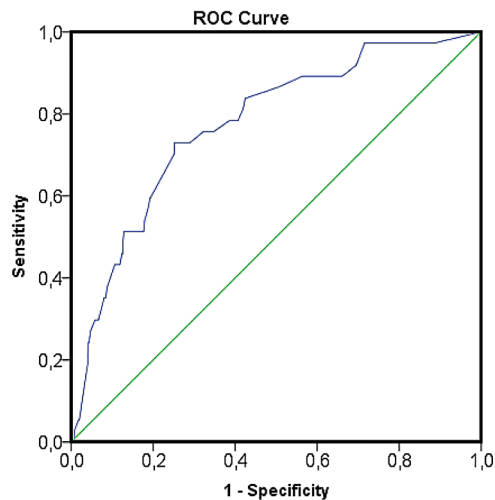
Figure 2 Receiver operator characteristics (ROC) with area under the curve (AUC) analysis. The AUC was 0.773 (95% CI 0.698 to 0.849).

The association between infections and MACE has been well established in previous studies.[2–8] In the present study, MACE within 90 days after hospitalisation with an infection occurred with a frequency of 2.1%. As suggested by a recent study by Corrales-Medina et al,[4] it is essential that we now focus on specific target strategies and prevention. To the best of our knowledge, this is the first study that identified independent predictors of MACE after hospitalisation with an infection, a first necessary step to prevent or at least detect cardiovascular events in an early stage. Correspondent to previous studies in patients presenting to the ED with chest pain suggestive of ACS, the presence of two or more classic cardiovascular risk factors increased the short-term risk for MACE in ED patients hospitalised with a suspected infection.[14 15 18–20]

Interestingly, a recent systematic review by Kuipers et al[21] showed that new-onset atrial fibrillation in critically ill patients is independently associated with a poor outcome, including mortality and longer hospital stay. This association has also been found for pre-existing atrial fibrillation.[22] It is possible that MACE is part of the pathophysiological path between atrial fibrillation and poor outcome, because atrial fibrillation/flutter was a strong independent predictor of MACE in the present study. If atrial fibrillation is a risk factor for MACE, this might be an argument for pharmacological treatment and prevention of atrial fibrillation in patients admitted with an infection. However, because cause and effect can hardly be separated in observational studies, this issue should first be investigated in randomised controlled trials.

In addition to the classic cardiovascular risk factors, the RO component of the PIRO score was found to be an independent predictor of MACE. The RO components of the PIRO classification largely reflect the presence of acute onset organ failure, similar to the acute physiology scores of the APACHE and MEDS scores.[23 24] This corresponds with the study by Corrales-Medina et al[4] who found that pneumonia patients with acute organ dysfunction had higher hazards for MACE than patients without organ dysfunction.

Clinical perspective

Importantly, the combination of the three predictors of the present study enabled identification of MACE with a sensitivity of 75% and specificity of 70%. Although this may be labelled as moderate diagnostic accuracy, in 27 of 36 patients, there would be the potential for early detection or even prevention of MACE if, for example, antiplatelet therapy would have been initiated at hospital admission. The relatively low specificity would result in unnecessary antiplatelet therapy in approximately one-third of the patients. However, the potential mortality and morbidity reduction by prevention of MACE might easily outweigh the morbidity caused by possible bleeding complications. In fact, a prospective study by Falcone et al[10] showed that 30-day mortality in elderly patients with community-onset pneumonia was lower in patients on aspirin before hospital admission. This indicates that these patients still benefit from antiplatelet therapy, even without an increased risk for MACE.

Besides the initiation of antiplatelet therapy, ED patients hospitalised with an infection and medical professionals taking care of these patients during or after hospital admission should be warned for signs of ACS or stroke if a patient has a high-risk profile, so that at least MACE is detected at an early stage.

Limitations

Although the present study is the first to identify independent predictors of MACE after hospitalisation with an infection via the ED, there are several limitations.

First, the retrospective nature made our study prone to information bias, especially for measurement of the cardiovascular risk factors and MACEs. However, interobserver agreement and Cohen's κ was high, indicating that the interobserver variability was low. Furthermore, besides careful assessment of all medical files, we also contacted patients to ask if they had had an MACE. In this way, MACEs were also detected if presented to another hospital. Nevertheless, some recall bias cannot be excluded. In addition, 7.2% of the patients were lost to follow-up. In the sensitivity analysis, however, the same predictor variables stood out, indicating that our model was robust and information bias did not change our main conclusion. Second, the many missing data on the presence of a family history positive for cardiovascular disease and smoking status were assumed to be absent. Since most of these missing data were in the 'no MACE' group, the effect of risk factors >2 could be overestimated. However, the effect of classic cardiovascular risk factors has already been well established in other studies. The presence of atrial fibrillation/flutter and the RO components of the PIRO score are new

outcomes in the present study, and those data were almost complete.

Finally, in the original study protocol, we anticipated more events than the 36 (2.1%) cases of MACE in this study, limiting the number of variables in our prediction model. We resolved this by creating composite variables, representing groups of separate factors. It cannot be excluded, however, that certain variables in these composite variables have more impact than others. This issue should be taken into account in future studies. Larger populations are needed to validate and improve our prediction model.

In summary, in addition to the classical cardiovascular risk factors, atrial fibrillation/flutter and signs of acute organ dysfunction are independent predictors of MACE within 90 days after hospitalisation with a suspected infection. Future studies are needed to validate and improve these predictors before they can be used in large experimental trials, and eventually, for preventive strategies in clinical practise.

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