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ORIGINAL RESEARCH ARTICLE

Prognostic factors for important clinical outcomes in patients with a severe infection

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Abstract
Background Patients who are admitted with a suspicion of a severe infection usually enter the hospital through the emergency department (ED). The recognition of prognostic factors in an early stage affects further treatment and might improve clinical outcomes.
Aims We examined possible prognostic factors for four important outcomes: intensive care unit (ICU) admission, positive blood cultures, mortality and re-admission.
Methods All adult patients arriving at the ED with a suspected infection for whom admittance and intravenous (iv) antibiotics were indicated were included between March and December 2006. Possible prognostic variables were obtained from medical history, physical examination and laboratory results during the ED presentation. Data were analysed using logistic regression analysis.
Results A total of 295 ED patients were evaluated, of whom 27 were referred to the ICU, 62 had a positive blood culture, 16 died and 48 were re-admitted. In multivariate analysis, patients with a respiration rate of >25/min were at higher risk for ICU admission. Patients with a positive blood culture had a higher heart rate and a higher percentage of segmented neutrophils. Patients who died during admission were more likely to be older, confused and had lower blood pressure. Patients who were re-admitted within 30 days were more likely to be male, younger and less likely to have a positive blood culture.
Conclusions Routine clinical and biochemical information can be used to predict ICU admission, the presence of bacteraemia, mortality and re-admission (within 30 days) and should be taken into consideration for treatment decisions.

Keywords Infection · Prognostic factors · ICU admission · Bacteraemia · Mortality · Re-admission

Introduction

Patients with a suspicion of a severe infection are frequently seen at the emergency department (ED). It has been estimated that in nearly 40% of all patients who presented at the ED, a severe infection was the main reason for admission at the Internal Medicine department in our hospital. The first 4 to 6 h in the treatment of these patients are of crucial importance to decrease not only the morbidity and mortality [1–5], but also other outcomes like the duration of hospital stay [2, 5, 6]. Recognition of prognostic factors in an early stage of the treatment will influence further treatment. Risk assessments can help physicians to improve the efficiency of treatment, with optimal monitoring of high-risk patients preventing unnecessary complications, ICU admissions or deaths [7]. Therefore it is important to identify these prognostic factors.

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In addition, little is known about factors related to readmission that occur soon after discharge in patients with severe infections. Identifying modifiable predictors may help reduce the burden of these readmissions.

As part of a health care innovation project aiming to decreasing the "door to needle" time in patients with the suspicion of a severe infection who presented at the ED, standardised collection of variables from medical history, physical examination and laboratory results during ED presentation took place. This provides a unique opportunity to investigate the relationship between these variables and ICU admission, the presence of bacteraemia, mortality and re-admission (within 30 days).

Methods

As part of the above-mentioned project, a prospective survey of medical records and prescription charts was performed at the department of Infectious Diseases of a tertiary teaching hospital. All consecutive adult patients arriving at the ED with a suspected infection for whom admittance and intravenous (iv) antibiotics were indicated were considered as having severe infections and were included between 1 March and 31 December 2006. Possible prognostic clinical and microbiological data were obtained on case record forms and extracted from medical charts.

The baseline variables included age, gender, medication and medical history. Vital functions were degrees of illness (severe, moderate, not sick), consciousness (normal, confused or comatose), body temperature (with or without chills), heart rate, blood pressure (BP), respiration rate and peripheral oxygen levels. The laboratory variables were haemoglobin, white blood cell count (WBC) (with differentiation), platelets, C-reactive protein (CRP), creatinine, blood gas analysis, glucose, creatinine phosphate kinase (CPK), albumin, aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), gamma-glutamyltransferase (yGT) and alkaline phosphatase. Cultures of blood, urine, sputum, ascites and fluids were collected when indicated. Door to needle time (DNT) was calculated and the final diagnosis at discharge was recorded. Blood cultures were taken at the ED before administration of antibiotic therapy. We determined that the most relevant clinical outcomes were: ICU admission, the presence of bacteraemia, mortality and re-admission within 30 days after discharge. Considering the analysis for the outcome re-admission, we excluded the patients who died during the first admission in these analyses. Furthermore, we excluded patients who were admitted with the diagnosis “neutropenic fever”, because these patients were often re-admitted for a planned chemotherapy treatment.

Definitions

A severe infection was defined as a suspected infection for which admittance and intravenous (iv) antibiotics were indicated. A high heart rate was defined as a heart rate >100 beats/minute. Fast respiration rate was defined as a respiration rate >25/min.

The door to needle time (DNT) was defined as the time between the arrival of the patient at the ED and the administration of antibiotics. Bacteraemia was defined as a positive blood culture at baseline. ICU admission was defined as admission to the ICU during the hospital stay of the patient. A new infection during admission was defined as the presence of a microorganism in the blood culture, which was not the causative microorganism of the suspected infection at the ED. Final diagnoses were defined as the diagnoses that were reported when patients were dismissed from the hospital.

Statistics

We compared groups with and without the outcome of interest. Differences in continuous data were tested with the Mann-Whitney test. Differences in categorical data between groups were tested with the chi-square test. We used a logistic regression analysis to examine potential risk factors for the four outcomes. Multivariate models were built using backstep stepwise techniques. Variables with a p-value<0.20 in univariate analysis were considered for entry in the multivariate model. P-values≤ 0.05 were considered statistically significant. Statistical analysis was performed by using SPSS 12.0.2 (SPSS Inc, Chicago, IL).

Results

Patient characteristics are summarized in Table 1. We included all patients (n=295) who arrived at the ED with a suspicion of a severe infection for whom iv antibiotics and hospital admission were indicated from March till December 2006. Only 13.4% of all included patients who were suspected to have an infection at the ED were not diagnosed with an infection at discharge.

Of all 295 patients, 27 (9%) were admitted to the ICU, 62 (21%) had a positive blood culture, 16 (5%) died during admission and 48 (17%) were re-admitted within 30 days. For results of the univariate analysis considering the four outcomes, see Tables 2, 3, 4 and 5. In multivariate analysis, patients who were admitted to the ICU were more likely to have a respiration rate of >25/min than those who were not admitted. Patients with a positive blood culture had a higher heart rate and a higher percentage of segmented neutro-

Table 1 Characteristics of all 295 patients who arrived at the ED with suspicion of a severe infection. Age is given as median with interquartile range (IQR). All other numbers are percentages (%) of the total number of patients. None means that at the moment of discharge from the hospital, it was clear that the patient was not admitted with an infection, but had an alternative diagnosis

Characteristics	
N	295
Male (%)	53.9
Age*	59 (46–73)
Infection diagnoses at discharge (%):	
Respiratory tract infection	18.5
Urinary tract infection	17.1
Liver and biliary tract infection	9.2
Skin/soft tissue infection	3.7
Septicaemia	1.7
Intravenous catheter infection	2.7
Fever of unknown focus	9.8
Neutropenic fever	3.4
Bone and joint infection	0.7
Other infections	15.1
None	13.4

*Median (IQR)

phils. Patients who died during admission were more likely to be older, consciousness was described more often as confused and they had lower blood pressure at admission. Patients who were re-admitted within 30 days were more likely to be male, younger and less likely to have a positive blood culture.

Discussion

As part of a health care innovation project, we analysed easily obtainable characteristics in patients who were admitted with suspicion of a severe infection as a prognostic factor for four important outcomes and found that a respiration rate of >25/min predicts ICU admission; a faster heart rate and a higher percentage of segmented neutrophils were associated with bacteraemia; age, lower thrombocyte counts, lower consciousness and lower blood pressure with mortality; and male sex, a younger age and the absence of bacteraemia with re-admission.

Assessment of these characteristics can help physicians to improve the efficiency of treatment, with optimal monitoring of high-risk patients preventing unnecessary complications. Therefore, these variables seem practical for daily use, but of course cannot replace the clinical judgement.

Table 2 Univariate and multivariate analyses of factors predicting: ICU admission

	ICU admission	No ICU admission	P	OR (univariate)	OR (multivariate)
N	27 (9.2%)	268 (90.8%)			
Level of sickness			<0.001		
Not sick	1 (4.3%)	47 (19.3%)		1	
Moderate	9 (39.1%)	159 (65.4%)		2.66 (95% CI 0.33–21.54)	
Severe	13 (56.5%)	36 (14.8%)		16.51 (95% CI 2.07–132.06)	
Missing	4	25			
Respiration			<0.001[1]		
<25/min	8 (36.4%)	201 (87.8%)		1	
>25/min	14 (63.6%)	28 (12.2%)		12.56 (95% CI 4.84–32.63)	12.56 (95% CI 4.84–32.63)
Heart rate/min	108 (95–120)	97 (86–110)	0.043	1.019 (95% CI 1.00–1.04)	
White cells (10E9/L)	15.1 (6.7–19.7)	10.6 (6.7–14.9)	0.019		
<8.1	7 (26.9%)	89 (33.5%)		1	
8.1–14.2	4 (15.4%)	95 (35.7%)		0.55 (95% CI 0.15–1.89)	
>14.2	15 (57.7%)	82 (30.8%)		2.33 (95% CI 0.90–5.99)	
pH (blood)	7.42 (7.34–7.46)	7.46 (7.41–7.49)	0.014		
<7.35	5 (26.3%)	4 (5.3%)		1	
7.35–7.45	8 (42.1%)	32 (42.1%)		0.20 (95% CI 0.04–0.92)	
>7.45	6 (31.6%)	40 (52.6%)		0.12 (95% CI 0.25–0.58)	

Median (IQR)

All p-values with Mann-Witney *U* test

[1] Chi-square test

Table 3 Univariate and multivariate analyses of factors predicting: bacteraemia

	Positive BK (n=62)	Negative BK (n=195)	P	OR (univariate)	OR (multivariate)
Duration of symptoms	1 (1–3)	2 (1–5)	0.003	0.88 (95% CI 0.78–0.98)	
Presence of chills	32 (56.1%)	64 (37.6%)	0.014[1]	2.12 (95% CI 1.15–3.90)	
Heart rate/min	104 (94–118)	97 (87–110)	0.020	1.02 (95% CI 1.00–1.03)	1.09 (95% CI 1.02–1.17)
Fever (>38.5 C)	42 (68.9%)	94 (48.2%)	0.005[1]	2.38 (95% CI 1.29–4.37)	
White cells (10E9/L)	12.7 (7.6–18.3)	10.6 (6.7–15.2)	0.039	1.05 (95% CI 1.01–1.09)	
Segmented neutrophils %	86.4 (80.8–91.1)	80.2 (72.5–85.4)	<0.001	1.05 (95% CI 1.00–1.09)	1.03 (95% CI 1.01–1.05)
Younger WBC %	85 (75.5–90.5)	79.5 (63.3–86)	0.048	1.02 (95% CI 0.99–1.05)	
ASAT (U/L)	36.5 (22.3–72.5)	27.5 (20–49)	0.039	1.00 (95% CI 1.00–1.00)	
Alkalic phosphatase (U/L)	116 (81–218)	93 (65–152)	0.007	1.00 (95% CI 1.00–1.00)	

Median (IQR)

[1] Chi-square test

All p-values with Mann-Witney U test

Considering the first outcome, unexpected early ICU admission of an ED patient is a serious adverse event. Knowing in which patients such events will happen is necessary to find ways to prevent them. In concordance with the study of Hoogewerf et al.[7], who described that a high respiration rate of >25/min in patients with community-acquired pneumonia (CAP) was associated with early clinical failure, we also found that in our patients with all kinds of severe infections, this easily obtainable parameter was associated with ICU admission. Therefore, we recommend observation of respiration rate in all patients with severe infection at the ED. When the respiration rate is >25/min, ICU admission should be considered. In contrast to others [8], we did not find that older age was correlated with ICU admission, possibly because of the relatively small number of patients who were older than 65 years (n=110, 37%) in the present study. Other parameters, that can be used for the recognition of patients at risk are described in the systematic review of Track and Trigger systems [9], which are systems to facilitate the early identification and management of at risk or rapidly deteriorating patients. However, the conclusion of this review was that available data were insufficient to identify the best parameter.

It has been shown recently that the presence of bacteraemia with a gram-positive microorganism is associated with an increased mortality [10]. Therefore, it can be important to recognise patients who have a higher chance of a positive blood culture already during presentation in the ED. In contrast to other studies [11–14], we did not find

Table 4 Univariate and multivariate analyses of factors predicting: mortality

	Died during admission (n=16) (5.4%)	No death (n=279) (94.6%)	P	OR (univariate)	OR (multivariate)
Age	78.5 (57.8–85)	58 (46–73)	0.006	1.05 (95% CI 1.01–1.08)	1.04 (95% CI 0.99–1.00)
Thrombocytes (10E9/L)	115 (43–221)	208 (140–284)	0.044	0.99 (95% CI 0.99–1.00)	0.99 (95% CI 0.98–1.00)
Consciousness			0.005[1]		
Clear	8 (57.1%)	220 (87.6%)		1	1
Confused	5 (35.7%)	27 (10.8%)		5.09 (95% CI 1.55–16.68)	6.82 (95% CI 1.59–29.8)
Comatose	1 (7.1%)	4 (1.6%)		6.88 (95% CI 0.69–68.71)	3.28 (95% CI 0.16–65.7)
Respiration >25/min	5 (35.7%)	37 (15.6%)	0.050[1]	3.00 (95% CI 0.95–9.47)	
Systolic BP (mmHg)	117 (94–130)	128 (113–145)	0.039	0.98 (95% CI 0.95–1.00)	
Diastolic BP (mmHg)	59 (50–74)	70 (61–79)	0.008	0.95 (95% CI 0.92–0.98)	0.96 (95% CI 0.92–1.00)
ASAT (U/L)	43 (27–118)	30 (21–56)	0.032	1.00 (95% CI 1.00–1.01)	

Median (IQR)

[1] Chi-square test

All p-values with Mann-Witney U test

Table 5 Univariate and multivariate analyses of factors predicting: re-admission within 30 days

	Re-admission (n=48)	No re-admission (n=247)	P	OR (univariate)	OR (multivariate)
Male	34 (70.8%)	125 (50.6%)	0.010[1]	2.37 (95% CI 1.21–4.63)	2.43 (95% CI 1.20–4.93)
Age	56.0 (44–63)	59.0 (46–74)	0.022	0.98 (95% CI 0.96–0.997)	0.98 (95% CI 0.96–0.999)
Positive blood culture/bacteraemia	4 (10.0%) (n=40)	53 (27.3%) (n=194)	0.007[1]	0.25 (95% CI 0.09–0.73)	0.26 (95% CI 0.09–0.77)

Median (IQR)

All p-values with Mann-Witney U test

[1] Chi-square test

that the well-known risk factor, namely the presence of (the degree of) chills, was independently associated with bacteraemia, although the effect reached significance in the univariate analysis. We demonstrated that a faster heart rate and a higher percentage of segmented neutrophils were independently associated with bacteraemia. Therefore, we advise that the physician cannot only use the presence or absence of chills, but should also include the evaluation of heart rate and segmented neurophils in their estimation of the risk of a positive blood culture.

As expected, in line with others [11] we demonstrated that older age was a prognostic factor for mortality. Hypotension is a well-known measure for disease severity and mortality [1, 7, 15, 16]. We also found that patients who died had a lower blood pressure at ED admission when compared to the patients who stayed alive.

Reducing rates of readmission is an important way to improve quality of care and to reduce costs. However, in contrast to patients with heart failure [17], chronic obstructive pulmonary disease (COPD) [18] or CAP [19], little is known about factors related to rehospitalisations that occur soon after discharge in patients with all kinds of severe infections. Therefore, it is important to determine these factors. We found that even after the exclusion of the patients with neutropenic fever, nearly one fifth (19%) of our patients who were discharged was readmitted within 30 days. This proportion is high, but the same as described in a very large nationwide study among patients with all diagnoses from the USA [20]. In other studies it was shown that chronic diseases (like COPD and HIV) and inadequate patient education or discharge planning accounted for the largest group of re-admissions [19, 21]. Although the care that prevents rehospitalisation occurs largely outside hospitals, it starts in hospital. Careful attention to the clinical stability of patients with these coexisting conditions at and following hospital discharge may possibly decrease the frequency of readmissions. We found that men, younger patients and patients without a positive blood culture were more often re-admitted. It might be that health care workers consider these groups as less susceptible to serious events when considering discharge. Therefore, our results should be used to pay more attention to these patient groups. For example, it could be possible that patients with a positive blood culture are treated longer and therefore are more protected to be discharged too early.

Interestingly, recently, functional polymorphisms in genes involved in innate immunity have been described that predispose individuals to severe infections and death, and this may become part of a risk model, allowing identification of patients at risk [22]. However, these polymorphisms are not known at the moment of presentation of the patient in the ED, and therefore easily obtainable parameters will still have an added value.

The strengths of the present study are the prospective and standardized data collection, the absence of selection criteria (which is mostly done in clinical trials), since we included all patients who presented at the ED, and the determination of risk factors for four different outcomes. Unfortunately, we did not find one common predictor, indicating that the four outcomes are not strongly related. Study limitations include the relatively small number of re-admission outcomes. The lack of inclusion of very old and young patients limits the generalization of our results.

We conclude that clinical and biochemical information that is usually assessed routinely in these patients can be used to predict ICU admission, the presence of bacteraemia, mortality and readmission (within 30 days) in patients with a severe infection who present at the ED. Future research should examine whether addressing these issues improves patient care in patients with severe infections who present at the ED.

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Conflicts of interest None.

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