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Organ failure, aetiology and 7-day all-cause mortality among acute adult patients on arrival to an emergency department: a hospital-based cohort study

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Background **Organ failure is both a frequent and dangerous condition among adult patients on arrival to an emergency department (ED). The risk of an unfavourable outcome could depend on the underlying aetiology. Knowledge of the relation between aetiology and prognosis could improve the risk stratification at arrival.**

Objectives **To describe the relation between organ failure, aetiology and prognosis through 7-day all-cause mortality.**

Methods **An observational three-year cohort study at the ED at Odense University Hospital, Denmark, including all acute adult patients.**

First-measured vital signs and laboratory values were included to evaluate the presence of the following organ failures: respiratory, coagulation, hepatic, circulatory, cerebral or renal.

The primary outcome was 7-day all-cause mortality. Aetiological disease categories were based on primary discharge diagnoses. We described the association between 7-day mortality, aetiology category, site of organ failures and number of patients at risk.

Results **Of 40 423 patients with a first-time visit at the ED, 5883(14.6%) had an organ failure on arrival. The median age was 69 (IQR 54–80), and 50% were men. The most frequent aetiology was infection (1495, 25.4%). Seven-day all-cause mortality ranged between aetiologies from 0.0% (95% confidence interval [CI], 0.0–14.2) allergy) to 45.6% (95% CI, 41.3–50.0) (cardiac). Combining aetiology and site of organ failure, 7-day all-cause mortality was the highest in the cardiac category, from 14.8% (95% CI, 4.2–3.7) with hepatic failure to 79.2% (95% CI, 73.6–84.1) with cerebral failure. The combination of infection and respiratory failure characterised most patients ($n = 949$).**

Conclusion **Infection was the most prevalent aetiology, and 7-day all-cause mortality was highly associated with the site of organ failure and aetiology.** ***European Journal of Emergency Medicine*** **28: 448–455 Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc.**

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Introduction

Background

Some acute patients are in a state of organ failure on arrival to the emergency department (ED). Organ failure is a frequent and dangerous condition associated with high mortality [1]. Furthermore, organ failure is described with high mortality and morbidity outside the ED as well, and there is a clear correlation between mortality and number of organ failures [2–4]. However, only sparse evidence exists relating to the characteristics, as underlying aetiologies, of organ failure among undifferentiated acute patients at arrival to the ED [5].

The risk of an unfavourable outcome could depend on the underlying aetiology. Previous research on patients with organ failure has often focused on care, later in the clinical pathway, and often on highly selected populations [6,7]. As such, the results are less relevant to care in the early stages, for example, at arrival to the ED.

It has been described that the underlying aetiology of increased lactate or cardiac troponins is related to variation in the risk of deterioration or death, but the associations between different organ failures and aetiologies are undescribed [8–12].

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Knowledge of the relation between expected aetiology and concomitant prognosis in patients presenting at the ED with organ failure could improve the risk stratification process and awareness at an early stage, shortly after arrival to the ED. Organ failure is an acute life-threatening condition, and by early identification, followed by effective treatment, further deterioration could be avoided and prognosis improved [13,14].

Objectives

The aim of the study was to describe the relation between organ failure, aetiology and prognosis for 7-day all-cause mortality, in adult patients in an ED.

Methods

This study is reported based on the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [15].

Design and setting

This cohort has previously been described [16,17]. Briefly, this is an observational population-based study at Odense University Hospital, Denmark, on all adult acute patients presenting at the ED from 1 April 2012 to 31 March 2015.

Odense University Hospital, a 1000-bed university hospital, covers all specialties and provides hospital care to a diverse population of approximately 230 000 adults from four municipalities [18]. The trauma centre ED is the main entrance for all acute adult patients and offers 24-h emergency care. Exceptions are pre-hospital diagnosed severe cardiac disease patients, nonhigh urgency patients in ongoing nephrological or haematological treatment, in medical or radiation oncological therapy and patients in active labour.

Nonobvious acute patients are evaluated in person or through emergency calls with primary care physicians, who act as gatekeepers, before entering the ED. Acute severely ill patients arrive directly by public pre-hospital emergency transport services [19]. All patients, except patients with minor trauma (e.g. a twisted ankle), have vital signs documented upon arrival, and most have laboratory tests taken. Patients are initially evaluated by specialised nurses, and the ED uses a five-level adaptive process triage based on complaints and vital signs [20,21].

Public health-care services in Denmark are free for the entire population due to the omnipresent tax-funded welfare system, including well-established primary care, public pre-hospital emergency transport and treatment and treatment at public hospitals.

Participants

Acute adult patients' ≥18 years were retrospectively included at first visit at the ED within the study period to avoid bias from repetitive measurements. First-measured vital signs and laboratory values were included to evaluate the presence of organ failure: respiratory, coagulation, hepatic, circulatory, cerebral or renal. The recorded date of visit was defined as the index date. If the patient's residence was outside the hospital's primary catchment area, or patients were unidentified, listed with an invalid personal registration number, or known to have a hepatic, coagulation or renal organ failure within 1 year before the index date, they were excluded from the analyses. The follow-up was from index date to death, emigration or 7-days, and based on Danish population-based registers [22,23].

The target population was the acute adult Danish population, and the study population was all adult residents in four well-defined municipalities that represented the main catchment area of Odense University Hospital.

Variables

The primary outcome was 7-day all-cause mortality.

The exposure variables were organ failure based on first-documented vital signs within 6 h of arrival to the ED; systolic blood pressure, Glasgow Coma Scale score (GCS), and peripheral oxygen saturation, and first-accessible laboratory values within 24 h of arrival; creatinine, PaO_2, platelets, and bilirubin. Laboratory values within 1 year before the index date on creatinine, platelets and bilirubin were included to identify patients with known hepatic, coagulation or renal failure. Further exposure variables were aetiology-based on primary discharge diagnosis, and potential confounders for organ failure and mortality (age, sex and Charlson comorbidity index [CCI]) [24].

Data sources/measurement

Vital signs were extracted from the electronic patient records and laboratory values from the hospital laboratory. To minimise selection bias, we conducted a manual review of all electronic records without a complete set of vital values to fill in the missing data. Using the Danish personal registration number, allocated to all Danish residents since 1968, we identified all patients to combine specific patient data from the different Danish population-based registers [25]. Information from the Central Person Register was used for sex, date of birth and mortality [22]. From the Danish National Patient Registry, with data on all hospital admissions since 1995, we extracted all discharge diagnoses (primary diagnosis) based on the International Classification of Diseases 10th revision, and comorbidities (Charlson index based on the last 10 years discharge diagnoses before the index date) [23,24].

Definitions

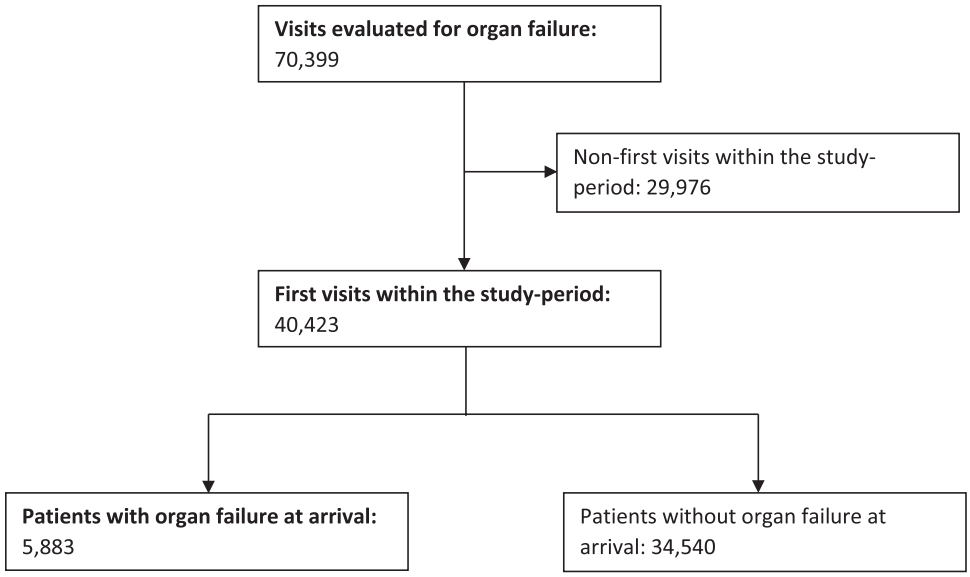
We defined organ failure as:

Respiratory failure: PaO_2<8.4 kPa or saturation<91%

Circulatory failure: systolic blood pressure <100 mm Hg

Cerebral failure: GCS <13

Fig. 1



First visits within the study period and organ failure. Parts of the flowchart were presented in previous publication on the same cohort [16].

Coagulation failure: platelet count <100 × 10^9/L and earlier platelet count >100 × 10^9/L or never previously registered.

Hepatic failure: bilirubin >33 µmol/L and earlier bilirubin <33 µmol/L or never previously registered.

Renal failure: Creatinine>171 µmol/L and earlier creatinine <171 µmol/L or never previously registered [16].

We based our organ failure definitions on the Sequential Organ Failure Assessment (SOFA)-score [26,27].

We used a slightly adjusted a priori protocol for the categorisation of primary discharge diagnoses into aetiological categories (Supplementary 1, Supplemental digital content 1, *http://links.lww.com/EJEM/A307*), based on an earlier categorisation from our group [8]. The categorisation was performed according to a clinical approach, and systemic conditions, such as infection, trauma and hypovolemia, were prioritised compared to organ-specific conditions, such as cardiac, respiratory or intestinal. Two authors independently and blindly reviewed all 2853 discharge diagnoses and merged these into 15 different aetiological groups (Supplementary 2, Supplemental digital content 1, *http://links.lww.com/EJEM/A307*). If the diagnosis did not fit into one of the 14 main categories, described in the protocol, they were placed in the 'other' category. The interobserver agreement κ-score for dividing discharge diagnoses into categories was 0.87 (CI 95, 0.86–0.89).

Statistical methods

All analyses were based on the first individual ED contact within the study period. Descriptive baseline characteristics on individual patient levels were described as numbers and percentages. Age was presented as median and interquartile ranges. CCI and age were grouped into four groups; 0, 1, 2 and >2, and 18–44, 45–64, 65–84 and >84 years of age at arrival to the ED, respectively.

Prognosis was presented as 7-day all-cause mortality stratified on aetiology categories. Proportions were presented with 95% confidence intervals (95% CI) based on binomial distribution. Cox proportional hazard regression analyses were performed on patients presenting with and without an organ failure to present hazard ratios (HR) stratified on aetiology categories, as both crude HR, and HR adjusted for sex, age and comorbidities. The reference category was the aetiology category with the lowest crude hazard.

Patients with a missing primary discharge diagnosis were placed in a 'missing' category and handled as a separate category throughout the analyses. Missing data on organ failure were treated as 'within normal range', but, as described earlier, the data were not missing at random, and there is a clear possibility of underestimating the prevalence of new organ failure at arrival, and the consequent mortality [16].

The inter-rater reliability, according to the discharge diagnoses categorisation, was presented through Cohen's kappa (κ). A κ of 0 means no agreement, other than expected by chance, and a κ of 1 means complete agreement.

To describe the prognosis through 7-day mortality, combining aetiology category, site of organ failures and number of patients, a table was constructed and shown in a bubble heat chart using Excel Version 1908 (Microsoft Excel Office 365).

Table 1 Baseline characteristics, patients with and without organ failure at arrival

		Organ failure	Without organ failure
In total	*N* (%)	5883 (100.0)	34 540 (100.0)
Age in years	Median (IQR)	69 (54–80)	55 (36–72)
Sex, *n* (%)	Women	2941 (50.0)	18 298 (53.0)
	Men	2942 (50.0)	16 242 (47.0)
Age in groups, *n* (%)	18–44	943 (16.0)	12 246 (35.5)
	45–64	1423 (24.2)	9548 (27.6)
	65–84	2557 (43.5)	9921 (28.7)
	>84	960 (16.3)	2825 (8.2)
Charlson comorbidity index, *n* (%)	0	2484 (42.2)	21 752 (63.0)
	1	1156 (19.7)	5619 (16.3)
	2	915 (15.6)	3420 (9.9)
	≥3	1328 (22.6)	3749 (10.9)
Vital signs			
Respiratory frequency	Mean±SD (*n*=missing)	19 ± 6 (585)	17 ± 4 (7133)
Systolic blood pressure	Mean±SD (*n*=missing)	128 ± 30 (253)	141 ± 23 (4118)
Heart rate	Mean±SD (*n*=missing)	91 ± 22 (277)	84 ± 18 (4091)
Glasgow Coma Scale	Median (IQR) (*n*=missing)	15 (14,15) (304)	15 (15) (5530)
Temperature	Mean±SD (*n*=missing)	36.9 ± 1.1 (1,086)	36.8 ± 0.8 (7615)
Saturation	Median (IQR) (*n*=missing)	96 (92–99) (475)	98 (97–100) (5362)
Site of organ failure, *n* (%)	Respiratory	2871 (48.8)	–
	Circulatory	1234 (21.0)	–
	Cerebral	1052 (17.9)	–
	Renal	775 (13.2)	–
	Hepatic	735 (12.5)	–
	Coagulation	309 (5.3)	–
Number of organ failures, *n* (%)	1	4,983 (84.7)	–
	2	739 (12.6)	–
	≥ 3	161 (2.7)	–

Some data presented in other publications on the same cohort [16,17].

The statistical analysis and plots described above were performed using Stata Version 16.0 (Stata Corporation LP, Texas, USA).

Ethics committee approval

According to Danish law, this observational register-based study was authorised by the Danish Health and Medicines Authority (J No 3-3013-1070/1) and the Danish Data Protection Agency (J No 2008-58-0035). No further permissions are required for register-based studies performed in Denmark.

Results

The ED had, in total, 175 278 visits that included 15 917 contacts with residency outside the catchment area and 88 962 contacts with minor injuries who were excluded from the analyses. Within the 3-year study period, 40 423 nonminor trauma patients had one or more visits. Of these, 5883 (14.6%) patients had one or more organ failures on arrival at first visit (Fig. 1). The median age was 69 years (IQR, 54–80), 50% were men, the most frequent site of organ failure was respiratory (48.8%), and 15.3% of the patients had more than one organ failure (Table 1).

Among the patients with organ failure, the most frequent aetiology was infection, 1495 (25.4%), and the least frequent was allergy, 24 (0.4%) (Table 2). Seven-day all-cause mortality ranged from allergy 0.0% (95% CI, 0.0–14.2) to cardiac 45.6% (95% CI, 41.3–50.0) (Table 2). The crude HR of death among aetiology categories compared to intoxication was haematology 1.4 (95% CI, 0.1–13.1) to cardiac 52.9 (95% CI, 16.9–165.1), and adjusted for sex, age and comorbidities, HR ranged from haematology 0.7 (95% CI, 0.1–6.9) to cardiac 28.4 (95% CI, 9.0–89.2) compared to intoxication (Table 2). Supplementary 3, Supplemental digital content 1, *http://links.lww.com/EJEM/A307* presents information on aetiology, numbers and 7-day mortality regarding patients without organ failure at arrival.

Stratifying aetiology and the site of organ failure shows that, for patients with organ failure, the 7-day all-cause mortality was highest if the aetiology was cardiac, from 14.8 to 79.2%. The highest number of patients, at risk of mortality, was those with infection. Among infected patients, the 7-day mortality varied from cerebral failure at 19% to respiratory failure at 6.2% (Table 3).

Figure 2 is a bubble heat chart that visualises the 7-day mortality for the combinations of site of organ failure and aetiology and describes the impact by numbers of patients with organ failure at risk of mortality. The combinations of cerebral failure and haematology aetiology, cerebral failure and nephrology aetiology, renal failure and cardiac aetiology, and coagulation failure and cardiac aetiology, all had high 7-day mortality but with few patients at risk.

Discussion

In this study, we described the prognosis for patients with organ failure on arrival to an ED through a combination of aetiology and site of organ failure. The prognosis was described through 7-day all-cause mortality and was highly associated with aetiology as well as the site of organ failure, but was also associated with other factors, such as age and comorbidities. Infection was the most common aetiology followed by the respiratory, cardiac, and neurologic categories, whereas allergy was almost absent as organ failure aetiology when the patient arrived at the ED. We present an overall 7-day all-cause mortality of 11.0% among patients with organ failure at arrival, but the 7-day mortality ranged between 0 and 79.2%, according to different combinations of aetiology and site of organ failure. The HR among different aetiology categories was affected by sex, age and comorbidity, but the confidence in the interpretation of impact of aetiology was low for some categories, due to the low number of patients. Furthermore, the adjusted HR could point to differences in demographics between the patients included in different aetiology categories, but this was not examined in this study.

Table 2 Patients with one or more organ failures, 7-day all-cause mortality, and hazard ratios (HR) of death stratified on aetiology category, crude and adjusted for sex, age and comorbidity

Aetiology category	Organ failure patients *n (%)*	7-day mortality		
		% (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)
Intoxication	261 (4.4)	1.2 (0.2–3.3)	1	1
Haematology	64 (1.1)	1.6 (0.04–8.4)	1.4 (0.1–13.1)	0.7 (0.1–6.9)
Endocrine	153 (2.6)	2.0 (0.4–5.6)	1.7 (0.3–8.4)	1.0 (0.2–5.0)
Hepatology	194 (3.3)	4.1 (1.8–8.0)	3.6 (1.0–13.6)	2.3 (0.6–8.6)
Intestinal	343 (5.8)	4.7 (2.7–7.5)	4.1 (1.2–14.0)	2.7 (0.8–9.4)
Infection	1,495 (25.4)	6.7 (5.5–8.1)	5.9 (1.9–18.6)	3.2 (1.0–10.2)
Nephrology	102 (1.7)	6.9 (2.8–13.6)	6.1 (1.6–23.5)	3.6 (0.9–13.8)
Malignant	161 (2.7)	9.9 (5.8–15.6)	8.8 (2.6–30.4)	4.6 (1.3–16.0)
Respiratory	637 (10.8)	10.2 (8.0–12.8)	9.1 (2.9–29.1)	5.2 (1.6–16.8)
Hypovolemic	323 (5.5)	11.5 (8.2–15.4)	10.3 (3.2–33.3)	5.3 (1.6–17.3)
Trauma	288 (4.9)	12.2 (8.6–16.5)	11.1 (3.4–36.2)	6.4 (2.0–21.0)
Neurologic	404 (6.8)	18.1 (14.4–22.2)	16.8 (5.3–53.4)	10.5 (3.3–33.4)
Cardiac	528 (9.0)	45.6 (41.3–50.0)	52.9 (16.9–165.1)	28.4 (9.0–89.2)
Allergy	24 (0.4)	0.0 (0.0–14.2)	–	–
Other	872 (14.8)	4.2 (3.0–5.8)	3.7 (1.1–12.1)	2.5 (0.8–8.2)
Missing	34 (0.4)	8.8 (1.9–23.7)	8.1 (1.6–40.0)	5.6 (1.1–27.6)

Symptoms and vital signs at arrival, followed by laboratory values, are part of the patient assessment upon arrival and are used to evaluate if the patient has one or more organ failures, and thereby to evaluate which patients to treat first in the ED. Existing descriptions of unselected patients arriving with organ failure to the ED, and their prognosis, are limited [4,28]. A better understanding of early information related to newly developed organ failure could be useful knowledge in the process of identifying severely ill patients before their condition turns critical.

For acute patients on arrival, the aetiology is not always clear, but our findings suggest that patients with organ failure should be in focus especially if the suspected underlying aetiology is cardiac, respiratory, infection or neurologic. Furthermore, the site of organ failure, in combination with the suspected aetiology category, provides prognostic information. This information is important for the health-care personnel in the ED, where crowding makes prioritising patients essential [29].

Infection is a known cause and a frequent aetiology of organ failure, and this was confirmed in our study [30]. Furthermore, hypovolemia has been described as the main pathophysiological factor of shock or circulatory failure, but we found that infection was the most predominant aetiology, and the underlying aetiology varied greatly for circulatory failure as well as for other organ failures [14].

Other studies have described varying associations between aetiology and critical outcomes. Infection is the most common aetiology when predicting ICU transfer from the ED, followed by gastrointestinal, neurological and respiratory, and organ failure represents a predictor as well [31]. In shock patients, as well as in our study, 7-day mortality is associated with aetiology, especially in the case of cardiogenic aetiology [30].

In our study, the prognostic value of organ failure is highly associated with aetiology. This association between prognosis and aetiology is also described among the single markers of disease, such as lactate level or elevated troponins [8,9,11,12]. Our data suggest that patients with organ failure due to aetiologies, such as allergy, endocrine or intoxication, for which immediate effective treatment is initiated, have more favourable prognoses than patients with organ failure due to more complex aetiologies.

According to aetiology, we present a discharge diagnosis and clinical approach-based suggestion on how to divide the aetiologies of organ failure into categories, but a clear and validated classification, as is, for example, seen in shock, with its clearly defined aetiologies or shock-classifications, are needed, especially as the aetiology could be unclear at arrival and blurred by various symptoms [32].

Strengths

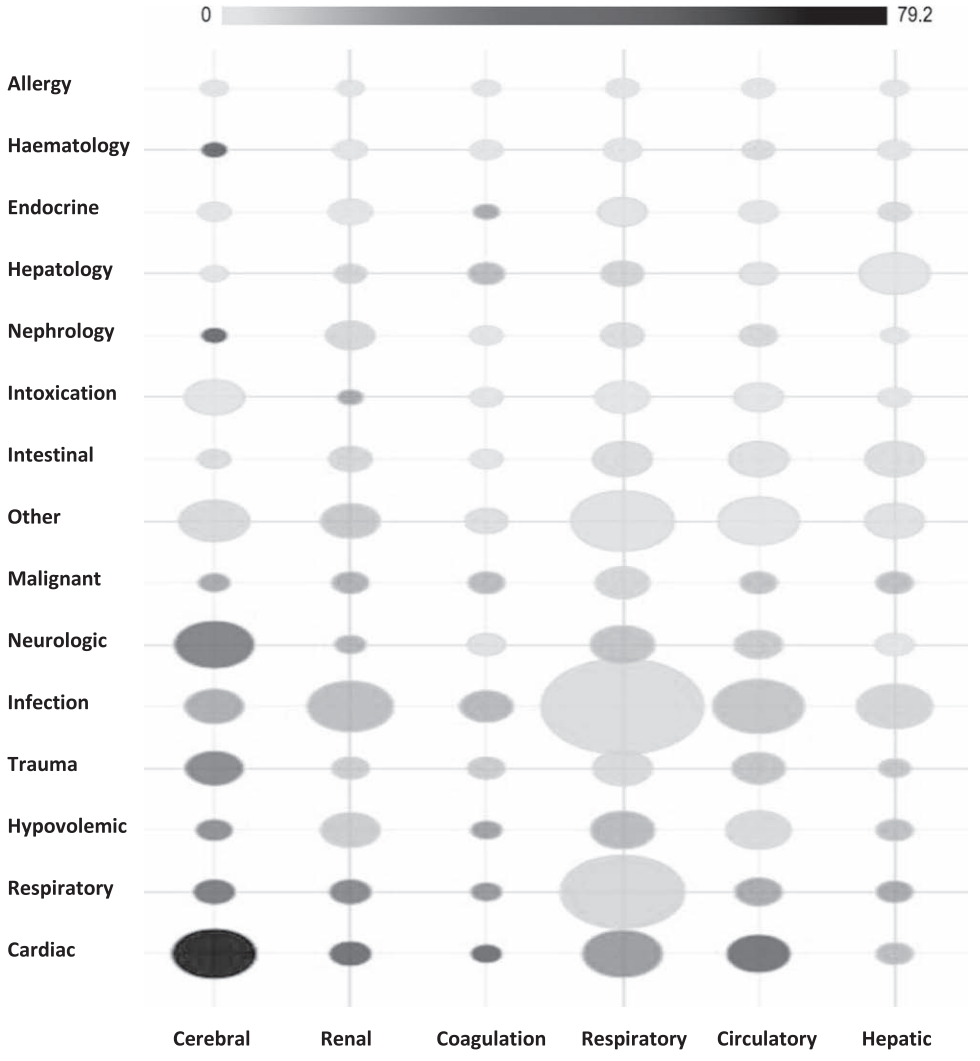
One of the strengths of this study is the high number of diverse acute patients in different clinical conditions, which closely reflects the situation in daily clinical practice when patients arrive at the ED. Because of the Danish population-based registers, it was possible to extract information regarding all patients on baseline characteristics and present 100% follow-up. Due to the retrospective nature of this study, vital signs and the need for laboratory tests were not affected by the focus on organ failure but recorded prospectively as standard. To avoid a possible overestimation of organ failure, we excluded patients with laboratory results indicating organ failure 1 year prior to the study period. In addition, to minimise the risk of bias from repeated measurements, patients were only included on the first arrival to the ED within the study period. Only a few patients (n = 34) had missing data, according to discharge diagnosis. To minimise selection bias, we did a manual review of all electronic records with missing data on systolic blood

Table 3 Site of organ failure combined with aetiology category, patients in each combination and 7-day all-cause mortality

	Cerebral	Renal	Coagulation	Respiratory	Circulatory	Hepatic
	N (%)					
Allergy	2 (0.0)	3 (0.0)	–	11 (0.0)	8 (0.0)	–
Haematology	2 (50.0)	14 (0.0)	14 (0.0)	21 (0.0)	17 (5.9)	12 (0.0)
Endocrine	17 (0.0)	35 (0.0)	5 (20.0)	68 (2.9)	31 (0.0)	16 (6.3)
Hepatology	5 (0.0)	12 (8.3)	20 (15.0)	35 (8.6)	26 (3.9)	154 (2.6)
Nephrology	4 (50.0)	55 (7.3)	7 (0.0)	34 (5.9)	27 (7.4)	5 (0.0)
Intoxication	113 (2.7)	5 (20.0)	16 (0.0)	87 (1.2)	67 (1.5)	14 (0.0)
Intestinal	17 (5.9)	38 (7.9)	11 (0.0)	100 (6.0)	106 (4.7)	107 (5.6)
Other	160 (6.9)	103 (11.7)	41 (4.9)	370 (4.3)	204 (2.9)	95 (4.2)
Malignant	10 (20.0)	28 (17.9)	20 (15.0)	76 (7.9)	31 (12.9)	29 (13.8)
Neurologic	208 (32.2)	18 (16.7)	23 (4.4)	135 (12.6)	63 (11.1)	25 (0.0)
Infection	100 (19.0)	248 (14.5)	75 (16.0)	949 (6.2)	270 (11.9)	187 (8.0)
Trauma	93 (29.0)	29 (10.3)	28 (10.7)	102 (6.9)	72 (12.5)	17 (11.8)
Hypovolemic	22 (27.3)	94 (10.6)	18 (22.2)	117 (15.4)	118 (6.8)	22 (13.6)
Respiratory	46 (34.8)	44 (29.6)	12 (25.0)	541 (7.6)	66 (19.7)	25 (20.0)
Cardiac	250 (79.2)	46 (43.5)	16 (43.8)	205 (23.9)	120 (39.2)	27 (14.8)

N = patients at risk, (%) = 7-day all-cause mortality.

Fig. 2



Bubble heat chart, combining aetiology category, site of organ failures, 7-day all-cause mortality and number of patients. Bubble size = patients at risk (0-949). Colour = 7-day all-cause mortality, from light (0%) to dark (79.2%).

pressure, GCS or saturation. Our κ-statistics agreement, on dividing discharge diagnoses into categories, at 87.4, is high and reflects reliability in categorisation. Blinding according to all patient information before categorisation was done to reduce the risk of systemic bias, and a priori definition regarding aetiology categories was performed to reduce the risk of selection bias. We also had a clearly defined catchment area with only one hospital.

Limitations

A low number of patients at risk, in some combinations of site of organ failure and aetiology category, made the interpretation of the correlation difficult and insufficient. Some aetiology categories, such as haematology, malignant, cardiac and nephrology, could be affected by the fact that most patients skip the ED and arrive directly at the specialty departments. The study was a single centre at a university teaching hospital, which limits the generalisability of the results, but we believe the results are generalisable to other acute settings that receive all patients within a clearly defined area. Moreover, different traditions and the focus on certain diseases could affect the discharge diagnoses, which could further limit the generalisability of the results. We are not certain that discharge diagnosis reflects all relevant details according to the state of the patient at arrival, but we combined the diagnoses with the site of organ failure based upon vital signs and laboratory values at arrival in order to include more information in prognosis evaluation. According to blood gasses, they were performed on initial clinical evaluation, and we have no information regarding supplemental oxygen. Furthermore, no information was available in our data on other treatment at or prior to arrival that might alter the vital signs and laboratory values. The same is true for conditions that might affect patients in the hospital as nosocomial infections.

Conclusion

Among the ED patients in our study, 5883 (14.6%) presented with one or more organ failures at first contact. Infection was the most common aetiology followed by the respiratory, cardiac, and neurologic categories, whereas allergy was almost absent. Overall, 7-day mortality among patients with organ failure was 11%. There was a wide range of 7-day all-cause mortality, with a range between 0 and 79.2%, according to different combinations of aetiology and site of organ failure. From a clinical point of view, knowledge of this wide range will support the early focus on those with the highest need.

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Conflicts of interest

There are no conflicts of interest.

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