Causes of death and determinants of outcome in critically ill patients

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Abstract: Aim: We investigated the causes of inpatient death in the intensive care unit and determined predictors of in-ICU mortality

Methods: A retrospective study was done on 891 critically ill patients were consecutive patients admitted to the Tunisian ICU.

Results: ICU mortality was 36.5% for the study population for all patients treated in the ICU during the given period. ICU mortality in patients admitted to the ICU because of septic shock was 10.7%.There is no significantly in ICU stay between survivors and nonsurvivors (p= 0.20). Seventy seven percent of non-survivors died within the first week after ICU admission. The use of Catecholamine and the need of invasive MV were the two most important risk factors for death in the ICU (p <10-3*).

Patients who were treated more than once in the ICU were significantly more likely to die than patients who required only one admission to the ICU (11.2% versus 5.2%, p=0.003).

Acute, refractory multiple organ dysfunction syndrome was the most frequent cause of death (28.5%). The two other most important risk factors for death in the ICU were presence of either central nervous system failure or cardiovascular failure.

Conclusion: To improve outcomes of critically ill patients, treatment and research should focus on effective therapy of central nervous system failure and cardiovascular failure, as well as on prevention of re-admission to the ICU.

Introduction

In recent decades, intensive care medicine has developed into a highly specialized discipline covering several fields of medicine (1). Whereas the total number of hospital beds in the United States decreased by 26.4% from 1985 to 2000, intensive care unit (ICU) beds increased by 26.2% during the same period (1), underlining the high demand for intensive care medicine. Mortality rates in the ICU strongly depend on the severity of illness and the patient population analyzed. Across different ICUs, 6.4% to 40% of critically ill patients were reported to die despite intensive care medicine (2-4). Although pathophysiological processes and new treatment approaches are extensively analyzed in laboratory and clinical research, comparably less data are available on the causes of death, short- and long-term outcomes of critically ill patients. Mostly, data on specific prognostic criteria for single diseases have been published (4). However, little is known of the exact causes of death and the impact of general risk factors that may uniformly complicate the course of critically ill patients irrespective of the underlying disease. Knowledge of such general determinants of outcome in a critically ill patient population would not only help improve prognostic evaluation of ICU patients, but also indicate what therapy and research should focus on to improve the outcomes of critically ill patients.

This prospective cohort study evaluates causes of death in a critically ill patient population in the ICU. Furthermore, independent risk factors for death during these periods are identified.

Materials and methods

This prospective cohort study was conducted in a 10-bed medical ICU in a university teaching hospital with 850 beds. The ICU is one of two adult ICU facilities in the university hospital and primarily receives patients after emergency but also treats only non-surgical patients with internal medical diseases. All patients admitted to this ICU between January 1, 2013, and December 31, 2015, were included in the study protocol.

Data collection and parameters

On admission to the ICU, pre-ICU data were documented, included the following: demographic variables (age and gender), admission diagnosis, referring unit (emergency department , recovery room, ward, or other ICU), type of disease, history of pre-existent chronic diseases (chronic obstructive pulmonary disease, coronary heart disease, myocardial infarction ,congestive heart failure, chronic arterial hypertension, chronic renal insufficiency, chronic renal insufficiency requiring hemodialysis, liver cirrhosis, diabetes mellitus, malignant tumor disease, gastroduodenal ulcer disease, cerebrovascular insufficiency, ischemic neurological deficit, other neurological pathology, psychiatric disease, immunosuppression, and obesity) . Any new complication or additional diagnosis that arose during the ICU stay was documented. Data documented at patient discharge included the Therapeutic Intervention and Simplified Acute Physiology Score (SAPS) II(5), which were both calculated from the worst physiological and laboratory parameters during the first 24 hours after ICU admission; worst PaO2/FiO2 ratio; creatinine, aspartate, alanine aminotransferase, and bilirubin serum concentrations during the ICU stay; duration of ICU stay in days; patient mortality. For all patients who died in the ICU, the cause of death was documented.

In all study patients, discharge from the ICU was initiated by senior intensivists only. In all other patients, the decision to transfer the patient to other ICUs, intermediate care units, or normal wards was made on a patient-to-patient basis according to the condition and requirements of the patient.
All patients in whom life-sustaining therapy was withdrawn received intravenous benzodiazepines and opioids, fluid therapy, as well as mechanical ventilation, if necessary.

The primary study endpoint was to define risk factors for death in the ICU.The secondary study endpoint was to evaluate the causes of death of critically ill patients in the ICU.

Statistical analysis

Descriptive statistical methods were used to analyze demographic and clinical data of the study population, as well as causes of death. Logistic regression analyses applying forward conditioning variables only were used to examine the association between study variables and ICU mortality. In each analysis, variables that were statistically significant at α = 0.05 in univariate comparisons were introduced into a multivariate model; covariates significant at <0.05 were retained in the model.

Tests for differences between study groups were performed using the unpaired Student t, χ2. A standard statistical program was used for all analyses of this study. Data are given as mean values ± standard deviation unless stated otherwise.

Results

Study population and patient characteristics during the observation period, a total of 891 critically ill patients were admitted to the ICU. Table 1, 2 and 3 give characteristics of the study population.

ICU outcome (table 3, 4 and 5)

ICU mortality was 36.5% (326/891) for the study population for all patients treated in the ICU during the given period. ICU mortality in patients admitted to the ICU because of septic shock was 10.7%.

There is no significantly in ICU stay between survivors and nonsurvivors (p= 0.20). Seventy seven percent of non-survivors died within the first week after ICU admission.

Table 4 summarizes the causes of death of critically ill patients in the ICU. Acute, refractory multiple organ dysfunction syndrome was the most frequent cause of death (28.5%).

Independent risk factors for death in the ICU are shown in **Table 6.**
The use of Catecholamine and the need of invasive MV were the two most important risk factors for death in the ICU (p <10-3*).

In table 5, Patients with catecholamine and invasive MV had a significantly higher ICU mortality rate than did patients without catecholamine and IMV (27.6% versus 76.4%, p < 0.001 and 48.3% vs 90.2%, p<0.001 respectively) or Shock (13.3 % versus 30.4%, p < 0.001) and a higher SAPS II (28.3 ± 14.2 versus 40.5 ± 19.1, p < 0.001).

Table 6 shows independent risk factors for death of critically ill patients. The most frequent risk factors of death were cardiorespiratory arrest, Nosocomial infection, Invasive MV and the use of Catecholamine

The number of ICU admissions was the most important risk factor for death. Patients who were treated more than once in the ICU were not significantly more likely than patients who required only one admission to the ICU.

Table 1. Characteristics of study patients (n =891)

Characteristic	**n** (percentage)

Male gender	521(58.5)
Age	
<40	214(24)
[40-64]	331(37)
[65-74]	89 (21.2)
[75-85]	133(14.9)
>85	24(2.7)
Pre-existent diseases	
Chronic Respiratory disease	95(29.1)
High Blood Pressure	106(32.5)
Diabetes	94(28.8)
Chronic Cardiac failure	82(25.2)
Chronic Renal failure	24(7.4)
Hepatic disease	4(1.2)
malignant tumor	44(13.5)
Immunosuppression	8(2.5)
Endocrine disease	11(3.4)
Psychiatric disease	9(2.8)
Autoimmune disease	5(1.5)
Epilepsy	30(3.4)
Neuromuscular disease	7(2.1)
Asthma	31(3.5)
Sleep apnea syndrom	35(3.9)
Thromboembolic disease	40(12.3)
Stroke	34(3.8)
Referral unit	
Emergency department	603(67.6)
Normal ward	247(27.6)
Recovery room	26(2.9)
Operation theatre	5(0.56)
Other ICU	10(1.1)
Reason for ICU admission	
Respiratory insufficiency	548(61.5)
Shock	174(19.5)
Disorder of consciousness	197(22.1)
Renal failure	21(2.4)
liver failure	2(0.2)
ICU duration of stay (days)	
[1-7]	679(76,2)
[7-14]	111(12,5)
[14-21]	49(5,5)
>21	52(5,8)

Table 2. Characteristics of study patients during intensive care unit stay (n =891)

Characteristic	**n** (percentage)[a]

SAPS II (mean±SD)	33.21±17.44 points
SOFA (mean±SD)	6.32 ±4.28 points
Organ failure	
Lung failure	220(24.7)
Cardiovascular failure	70(7.85)
Central nervous system failure	102(11.44)
Renal failure	82(9.2)
Liver failure	64(13.92)
Septic shock	47(5.27)
Acute delirium	298(33.44)
Critical illness polyneuropathy	52(5.83)
Infection	406(45.56)
Sepsis	268(30.07)
Septic shock	301(33.78)
Mechanical ventilation	
Invasive	567(63.6)
Non invasive	305(34.2)
Catecholamine	405 (45.5)
Sedation	221(24.8)
Curare	37(4.2)
Tracheotomy	48(5.4)
Renal remplacement therapy	39(4.4)
Continuous veno-venous haemofiltration Extracorporeal membrane oxygenation	3(0.3)
Plasmapheresis	5(0.6)
Antibiotic therapy	343(38.5)
Corticoides	168(18.9)
Anticoagulation	28(3.1)

a Except where other units are given. Data are given as mean values ± standard deviation except where indicated otherwise. ARDS, Acute Respiratory Distress Syndrome; SAPS, Simplified Acute Physiology Score;

Table 3. Characteristics of study patients after ICU Stay (n =891)

Characteristic	**n (percentage) a**

Normal ward	250(28.05)
Hospital discharge /Home	264(20.6)
ICU discharge unit	20(2.24)
Surgical ICU	4(0.44)
Transfer to other hospital	27(3.03)
ICU re-admission	86(9.65)
Hospital duration of stay (days)	
[1-7]	679(76,2)
[7-14]	111(12,5)
[14-21]	49(5,5)
>21	52(5,8)

a.Except where other units are given. Data are given as mean values ± standard deviation except where indicated otherwise. ICU, intensive care unit

Table 4. Causes of death of critically ill patients

Causes of death in the intensive care unit (ICU)	Percentage	*n*
Acute, refractory multiple organ dysfunction syndrome	28,5	93/326
Refractory cardiovascular failure	27,9	91/326
Central nervous system failure	20,9	68/326
Pulmonary failure	12.4	40/326
Cardiac arrest	2.1	6/326
End-stage tumour disease	2.1	6/326
Acute or chronic liver /renal failure	8	26/326

Table 5. Univariate analysis of risk factors for death of critically ill patients (n=891)

Parameters	Survivors (n=565)	died (n=326)	**p**
Age (yr) (n, %)			

<40	149	74	
40-64	182	140	
65-74	108	81	p=0.15
75-85	81	52	
>85	14	10	
Male gender (n, %)	307(34.5)	214(24)	p=0.46
Readmission (n, %)	63(11. 2)	17(5.2)	p=0.003*
Comorbidities (n, %)			
Hypertension	160(28.3)	106(32.5)	p=0.12
Diabetes	143(25.3)	94(28.8)	p=0.25
Cardiopathy	135(23.9)	82(25.2)	p=0.67
COPD	190(33.6)	79(24.2)	P=0.008*****
Chronic kidney disease	39(6.9)	24(7.4)	p=0.79
Neoplasia	25(4.4)	17(5.2)	p=0.48
Asthma	26(4.6)	5(1.5)	p=0.01*
Epilepsy	19(3.4)	7(2.1)	p=0.29
Psychiatric illness	29(5.1)	9(2.8)	p=0.69
None	91(16.1)	47(14.4)	p=0.50
Reason for ICU admission (n, %)			
Shock	75(13.3)	99(30.4)	$p<10^{-3*}$
Neurological Failure	133(23.5)	64(19.6)	p=0.17
Respiratory failure	367(65)	181(55.5)	p=0.005*
others	10(1.8)	13(3.7)	p=0.05
Diagnoses at admission (n, %)			
Decompensation of Chronic respiratory	235(41.6)	119(36,5)	p=0,13
failure	13(2.3)	7(2,1)	p=0,88
Pneumonia.	18(3.2)	1(0,3)	p=0.004
Acute asthma	2(0.4)	12(3,7)	p<10-3
ARDS	11(1.9)	3(0.9)	p=0.13
Cardiac arrest	56(10)	34(10.4)	p=0.05
Lung oedema	11(1.9)	4(1.2)	p=0.05
Cardiogenic shock	21(3.7)	20(6.1)	p=0.001
Hypovolemic shock	12(2.1)	10(3.1)	p=0.61
Septic shock	0	35(10.7)	p<10-3
Anaphylactic shock	2(0.4)	3(0.9)	p=0.28
Hemorrhagic shock	6(1.1)	3(0.9)	p=0.99
Pulmonary embolism	19(3.4)	2(0.6)	p=0.52
Seizure	20(3.4)	24(7.4)	p=0.05
Meningitis	24(4.3)	24(7.4)	p=0.79
consciousness disorder	14(2.5)	8(2.8)	p=0.83
stroke	20(3.5)	9(2.8)	p=0.13
Intoxications	42(7.4)	1(0.3)	p=0.007
Others	39(4.37)	9(1.01)	p=0.06
SAPSII(mean±SD)	28.35±14.25	40.49±19.17	p<10-3*
Invasive Mechanical ventilation	273(48.3)	294(90.2)	p<10-3*
Catecholamine	156(27.6)	249(76.4)	P<10-3*
Continue sedation	95(16.8)	126(38.7)	p<10-3
Curare	13(2.3)	24(7.4)	p<10-3
Tracheotomy	25(4.4)	23(7.1)	P=0.92
renal replacement therapy	13(2.3)	26(8)	p<10-3*
Antibiotic therapy	164(29)	179(54.9)	p<10-3*
Hospital duration of stay (days) (n, %)			
[1-7]	428(75.8)	251(77)	
[7-14]	79(14)	32(9.8)	p=0.20
>14	58(10.2)	43(13.2)	

Table 6. Independent risk factors for death of critically ill patients

Death in the ICU	Relative risk	95% CI	*p* value
ARDS	0,017*	[0,53-106,77]	0,13

Severe acute asthma	7,58	[0,00-4,53]	0,15
Immunosuppression	13	[0,93-198,44]	0,056
septic shock	2,77	[0,82-9,38]	0,10
Intoxications	0,14	[0,02-0,85]	0,03*
Catecholamine	7,87	[4,12-15,03]	<10-3*
Invasive MV	4,60	[2,20-9,60]	<10-3*
Curare	3,53	[0,77-16,03]	0,10
Cardiorespiratory arrest	38,98**	[5,76-263,84]	0,0002*
Accidental extubation	4,42	[0,99-19,76]	0,51
Nosocomial infection	19,16**	[7,11-51,58]	<10-3*
SOFA	2,12	[1,87-2,41]	<10-3*

ARDS

SOFA,Sepsis-related Organ Failure Assessment**; MV,** mechanical ventilation

Discussion

ICU mortality was 36.5% for the study population for all patients treated in the ICU during the given period. ICU mortality in patients admitted to the ICU because of septic shock was 10.7%.There is no significantly in ICU stay between survivors and nonsurvivors (p= 0.20). Seventy seven percent of non-survivors died within the first week after ICU admission. The use of Catecholamine and the need of invasive MV were the two most important risk factors for death in the ICU (p <10-3*).

The number of ICU admissions was the most important risk factor for death. Patients who were treated more than once in the ICU were significantly more likely to die than patients who required only one admission to the ICU (11.2% versus 5.2%, p=0.003).

Acute, refractory multiple organ dysfunction syndrome was the most frequent cause of death (28.5%).

The two other most important risk factors for death in the ICU were presence of either central nervous system failure or cardiovascular failure.

Impaired organ perfusion has been suggested as a contributing factor in the development of organ dysfunction(6). Recent data underline the strong prognostic impact of hypotension and cardiovascular failure in critically ill patients with sepsis (7-10). Although acute renal failure as a single-organ failure had a highly significant impact on ICU survival in several previous studies (11-15).

Exacerbation of chronic kidney disease and liver disease were the fifth most frequent causes of in-hospital death of critically ill patients. Similarly, it is conceivable that critical illness put too high a strain on chronically dysfunctional organs, which could be temporarily compensated by ICU therapy but later decompensated.

In-hospital death, malignant tumor disease was also, the most frequent causes of death of critically ill patients. This finding is in agreement with the results of an earlier study by Ridley et al.(16), who identified malignancy and respiratory failure as the two most common causes of death of survivors of critical illness.

Need for re-admission to the ICU was by far the most important risk factor for death. However, it cannot be determined from the results of this study whether increased mortality resulted from re-admission itself or was simply an epiphenomenon of the severe underlying disease. In agreement with the results of other studies, it can be hypothesized that prevention of ICU re-admission could have significantly improved outcome of these critically ill patients (16-18). Although acute renal failure played only a comparably minor role for ICU mortality as compared with central nervous system or cardiovascular failure.

When interpreting the results of this study, important limitations need to be considered. First, this cohort study was conducted as a single-centre study. Although this yielded a therapeutically homogeneous study population, it precludes wide generalization of our results to other centers because of institution-based differences in treatment, patient population, and admission policies.

Conclusion

To improve short- and long-term outcomes of critically ill patients, treatment and research should focus on effective therapy of central nervous system failure and cardiovascular failure, as well as on prevention of re-admission to the ICU.

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