Doi: 10.5152/TJAR.2019.26576

Original Article

Intensive Care

Turkish Journal of Anaesthesiology & Reanimation

Impact of Prehospital Mobile Intensive Care Unit Intervention on Mortality of Patients with Sepsis

Romain Jouffroy, Anastasia Saade, Pascal Philippe, Pierre Carli, Benoit Vivien

Department of Anaesthesia and Intensive Care Unit, SAMU, Hôpital Necker, University Paris Descartes, Paris, France

Cite this article as: Jouffroy R, Saade A, Philippe P, Carli P, Vivien B. Impact of Prehospital Mobile Intensive Care Unit Intervention on Mortality of Patients with Sepsis. Turk J Anaesthesiol Reanim 2019; 47(4): 334-41.

Abstract

Objective: The outcome of sepsis relies on the early diagnosis and implementation of appropriate treatments. For management of out-of-hospital patients with sepsis, prehospital emergency services, named Service d'Aide Médicale d'Urgence (SAMU) in France, dispatch to the scene an emergency mobile team (EMT) or a mobile intensive care unit (MICU) based on the patient's severity. Therefore, patients are admitted to the emergency department (ED) or to the intensive care unit (ICU). The impact of MICU intervention on patient's prognosis remains unclear. The aim of the present study was to describe the impact of MICU intervention on mortality on day 28 (D28) of patients with sepsis.

Methods: We performed a retrospective study on patients with sepsis managed by prehospital teams, MICU or EMT, before admission to the ED or ICU. The primary outcome was mortality on D28.

Results: The SAMU received 30,642 calls during the study period with 140 patients with suspected sepsis. The suspected origin of sepsis was mainly pulmonary for 78 (55%) patients. Thirteen (9%) patients died on D28, 12 in the ED and 1 in the ICU. Two patients were admitted to the hospital by a MICU. After adjusting for confounding factors, the relative risk of mortality on D28 for patients admitted to the hospital by a MICU was 0.40.

Conclusion: We describe an association between MICU intervention and mortality on D28. MICU intervention for out-of-hospital patients with sepsis is associated with 60% reduced mortality on D28. Larger studies are needed to confirm the impact of the intervention of MICU on mortality of patients with sepsis.

Keywords: Mobile intensive care unit, mortality, prehospital setting, sepsis

Introduction

Septic shock concerns approximately 19 million people worldwide annually (1, 2), generating 180,000 deaths in the United States (3). The in-hospital mortality rate related to septic shock still reaches 30% on day 28 (D28) (2, 4) despite continuous guidelines to improve the management of these patients within the last two decades (5). It is now clearly admitted that outcome relies on the early identification of patients with sepsis at high risk of poor outcome to initiate rapid implementation of appropriate treatments, especially haemodynamic optimisation and antibiotic administration (6-8). For out-of-hospital patients, sepsis has to be diagnosed as early as possible starting in the prehospital setting.

In France, the management of out-of-hospital emergencies is based on the emergency medical services called Service d'Aide Médicale d'Urgence (SAMU). The SAMU is reached via a national access call number, the number 15 (9). For patients requiring hospital admission, an emergency mobile team (EMT), a regular ambulance or a prehospital mobile intensive care unit (MICU) is dispatched to the scene. While an EMT always transfers patients to the emergency department (ED), patients transported by a MICU might be admitted to the ED or to the intensive care unit (ICU) according to their severity. Thus, efficient prehospital triage is crucial to enable appropriate orientation of patients. However, relevant tools to diagnose sepsis and to evaluate patients' severity are lacking in this context. In

Corresponding Author: Romain Jouffroy E-mail: romain.jouffroy@gmail.com

Received: 26.07.2018 Accepted: 18.09.2018
Available Online Date: 21.02.2019

fact, studies reported the lack of efficiency of the quick sepsis-related organ dysfunction assessment score (qSOFA) in the prehospital setting to predict ICU admission (10-14). Therefore, in this context, the evaluation of patients remains complex. Further efforts are needed to improve the early triage of patients with sepsis in this environment. Positive impact of early specialised management of patients by prehospital MICU intervention was shown for cardiac arrest and severe trauma (9). In the case of sepsis, the purpose of early management of patients by a MICU has not been evaluated yet.

The aim of the present study was to describe the impact of prehospital MICU intervention on mortality on D28 of patients with sepsis.

Methods

Population and data

Patients with suspected sepsis cared for by the SAMU of Paris (SAMU 75) between 1 April 2011 and 31 May 2011 were included in the study. Patients <18 years, pregnant women and patients with incomplete data sets were excluded from the study.

Sepsis was suspected in case of fever ≥38.0°C during 1 h or 38.3°C once or hypothermia <36°C with a medical history compatible with an infection (15, 16). The site of infection was suspected according to the patient's medical history and clinical signs.

Data including patient's demographic characteristics and clinical evaluation (systolic, diastolic and mean blood pressure (SBP, DBP and MBP), heart rate (HR), respiratory rate, temperature, Glasgow Coma Scale (GCS) and pulse oximetry) were retrieved from recorded phone calls made during prehospital care delivery and from the SAMU prehospital medical files. The primary outcome was mortality on D28 and was collected from hospital records.

To minimise the bias associated with data abstraction, data collection was performed by a single investigator using a standardised abstraction template, defined prior to data collection (17).

Immunocompromised status was retained if one or more of the following items were present in the patient's medical history: diabetes mellitus, chronic renal insufficiency, corticosteroids or another immunosuppressive treatment and infection by human immunodeficiency virus and/or viral hepatitis C.

Assessment of the prehospital qSOFA score was based on the three following clinical features: SBP ≤100 mmHg, RR ≥22 breaths min^{-1} and altered mental status determined by a GCS <15, with one point awarded for each item.

The local ethics committee of Comité de Protection des Personnes, Ile de France 2, Paris- France approved the study in accordance with the French legislation (Number: 2015-08-03-SC). Consent from patients was waived for participation in this observational study.

Study design and setting

The SAMU is composed of switchboard operators and physicians who determine, over the phone, the appropriate level of care to dispatch to the scene. The decision-making is based on the patient's medical history and symptoms as related by the patient himself, his relatives or any witness.

For life-threatening emergencies, the Service Mobile d'Urgence et de Réanimation, corresponding to a prehospital MICU, enables direct admission to the ICU or to the ED (18). The MICU is composed of a driver, a nurse and an emergency physician and is equipped with medical devices and drugs allowing the initial management of main organ deficiencies (9). In the case of sepsis, the MICU is able to initiate haemodynamic optimisation (fluid expansion and/or catecholamine infusion) and antibiotherapy. For less severe cases, an EMT (firefighters) or an ambulance, corresponding to a paramedic team, is dispatched to the scene.

After arrival to the scene of the appropriate care support, EMT or MICU, the patient's demographic characteristics and clinical evaluation (SBP, DBP and MBP; HR; rr; body temperature; GCS and pulse oximetry) are communicated to the regulation call centre to decide on the best course of action. Thereafter, patients are transferred either to the ED or to the ICU.

Statistical analysis

Univariate and multivariable analyses were conducted to evaluate the relationship between all covariates and mortality on D28.

A propensity score analysis, including age >80 years, immunocompromised status and qSOFA ≥2, was used to reduce the effect of confounders (19). Age >80 years, immunocompromised status and qSOFA ≥2 were reported to be associated with increased mortality in patients with sepsis (20-22).

The covariate balancing propensity score method was used to allow simultaneous optimisation of the prediction of the outcome and the covariate balance. As *p*-value is influenced by the sample size, standardised mean difference was used to evaluate imbalance matching using the following formulae described by Austin (23):

$$ASD = 100 * \frac{\text{x (TT)-x (CTL)}}{\sqrt{\frac{s^2(TT)+s^2(CTL)}{2}}},$$

where x corresponds to the mean or proportion for binary variables and classes of categorical variables, and s is the variance.

Cases correspond to patients admitted to the ED or to the ICU by a MICU, and controls correspond to patients admitted to the ED by an EMT. In the matched sample, baseline characteristics between cases and controls for mortality on D28 were compared using an unpaired *t*-test. All p-values were two-tailed. A p-value <0.05 was considered significant.

At least, the relative risk (RR) was used to evaluate patients' mortality on D28 transported by a MICU or an EMT.

Data are expressed as mean±standard variation for Gaussian variables, median with 1st quartile and 3rd quartile for non-normal variables or number and percentage (%).

All analyses were performed using R 3.4.2 (http://www.R-project.org; the R Foundation for Statistical Computing, Vienna, Austria).

Results

During the study period, 30,642 calls were received by the SAMU 75 call centre. Of the 30,642 calls, 140 concerned patients with suspected sepsis (Figure 1).

Of the 140 patients, 76 (54%) were male, and the median age was 72 (43–81) years (Table 1). Forty (29%) patients were >80 years. Eighty-six (61%) patients were immunocompromised. The predominant sites of infection were pulmonary for 77 (55%) patients, urinary for 20 (14%) patients and abdominal for 19 (13%) patients.

In the prehospital setting, median temperature was 38.6°C (37.9–39.0), median SBP was 110 (96–130) mmHg, and median respiratory rate was 25 (22-28) breaths min^{-1}. Forty-five (32%) patients had a qSOFA ≥2. All patients had a GCS of 15.

Among the 140 patients with suspected sepsis in the prehospital setting, 16 (11%) were transferred to the hospital by a MICU. None of them received antibiotics prior to hospital admission. Thirteen (9%) patients died on D28, 12 had been admitted to the ED, 1 to the ICU, and 2 had been transported by a MICU. Among the 2 deceased patients transported by a MICU, 1 had been admitted to the ED, and 1 to the ICU.

All deaths were related to a documented history of sepsis. A microbiological documentation was obtained in 42% of the cases and was pulmonary for 38 (65%) patients (Table 2).

In the univariate analysis, no variable was significantly associated with death on D28 (Table 3). No variables included in the propensity score significantly differed between the cases and the controls after propensity score matching (Figure 2 and Table 4).

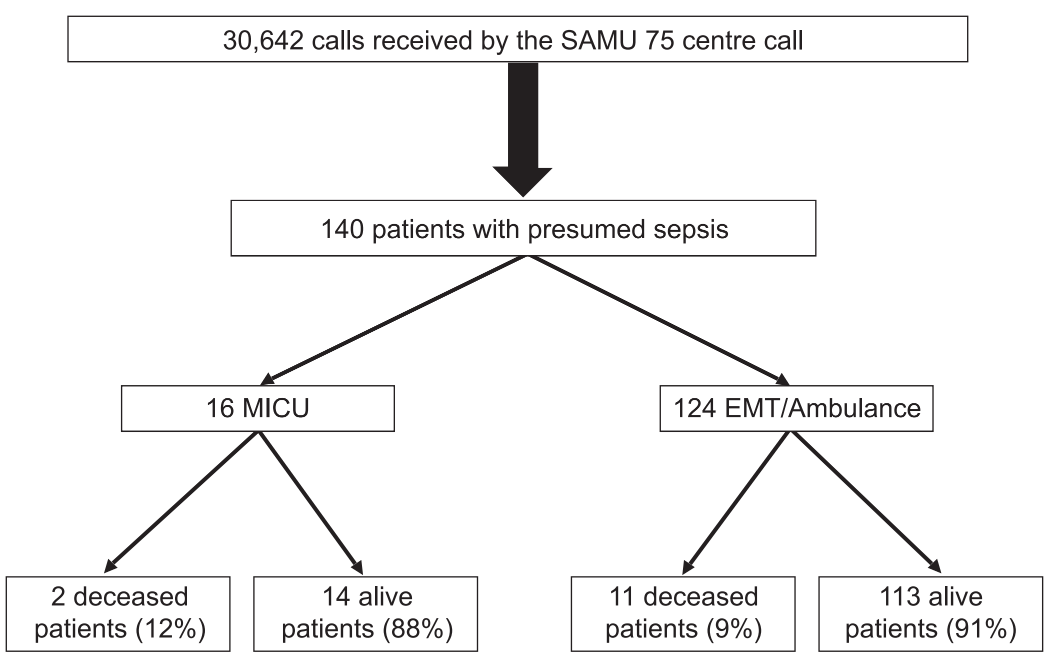

Figure 1. Flowchart
SAMU: Service d'Aide Médicale d'Urgence; MICU: mobile intensive care unit; EMT: emergency mobile team

Table 1. Demographic and clinical characteristics of patients with sepsis admitted to the hospital by a MICU or an EMT

Variables	Alive on day 28 (n=127)	Deceased on day 28 (n=13)	Overall population (n=140)
Age (years)	70 (39–81)	78 (66–87)	72 (43–81)
Age >80 years	36 (90%)	4 (10%)	40 (29%)
Male gender	67 (52%)	9 (69%)	76 (54%)
Immunosuppression	77 (61%)	9 (69%)	86 (61%)
Systolic blood pressure (mmHg)	120 (96–138)	101 (95–110)	110 (96–130)
Diastolic blood pressure (mmHg)	70 (50–80)	60 (50–70)	70 (50–80)
Mean blood pressure (mmHg)	87 (63–100)	73 (65–83)	83 (63–100)
Heart rate (beats min^{-1})	108 (97–120)	101 (81–130)	107 (96–120)
Pulse oximetry (%)	96 (90–98)	93 (90–96)	96 (90–98)
Respiratory rate (breaths min^{-1})	24 (22–28)	26 (24–30)	25 (22–28)
GCS	15 (15–15)	15 (15–15)	15 (15–15)
Body temperature (°C)	38.7 (37.9–39.0)	38.5 (37.0–39.0)	38.6 (37.9–39.0)
Prehospital management by MICU	14 (11%)	2 (15%)	16 (11%)
Patients admitted in the ED	112 (95%)	6 (5%)	118 (84%)
Patients admitted in the ICU	15 (68%)	7 (32%)	22 (16%)
qSOFA >2	39 (31%)	7 (54%)	45 (32%)

Quantitative variables are expressed as median (1st quartile–3rd quartile). Qualitative variables are expressed as absolute value and percentage (%).
GCS: Glasgow Coma Scale; qSOFA: quick sepsis-related organ dysfunction assessment score; MICU: mobile intensive care unit; EMT: emergency mobile team; ED: emergency department; ICU: intensive care unit

Table 2. Presumed site of infection in patients with sepsis admitted to the hospital by a MICU or an EMT

Site of infection	n	%
Pulmonary	77	55
Urinary	20	14
Digestive	19	13
Undefined	10	8
Meningeal	6	4
Cutaneous	4	3
Ear–nose–throat	3	2
Bone	1	1

Data are expressed as absolute value with percentage (%). MICU: mobile intensive care unit; EMT: emergency mobile team

After adjusting for confounding factors, the RR of mortality on D28 regarding patients with presumed sepsis admitted to the hospital by a MICU reached 0.40, whereas it was 2.5 for those admitted to the hospital by an EMT.

Discussion

In the present study, we report an association between mortality on D28 and intervention of a MICU for patients with sepsis cared for in the prehospital setting. The intervention of a prehospital MICU is associated with 60% reduced mortality on D28 (RR=0.4). To our knowledge, this work is the first study to investigate the role of prehospital transportation in the prognosis of patients with sepsis. Interhospital transportation of critically ill patients by a MICU was widely described showing clinical stability based on the SOFA score (24). On the contrary, prehospital transportation raises other

Table 3. Univariate analysis of factors associated with mortality on day 28 in patients with sepsis admitted to the hospital by a MICU or an EMT

	Univariate analysis	
Variables	OR (95% CI)	p
Age (years)	1.03 (0.99–1.06)	0.10
Age >80 years	1.12 (0.29–3.69)	0.85
Male gender	2.01 (0.62–7.75)	0.26
Immunosuppression	1.46 (0.45–5.63)	0.55
Systolic blood pressure (mmHg)	0.99 (0.95–1.01)	0.06
Diastolic blood pressure (mmHg)	0.98 (0.95–1.01)	0.24
Mean blood pressure (mmHg)	0.98 (0.94–1.01)	0.12
Heart rate (beats min^{-1})	1.01 (0.98–1.03)	0.59
Pulse oximetry (%)	0.99 (0.94–1.07)	0.79
Respiratory rate (breaths min^{-1})	1.06 (0.97–1.15)	0.19
GCS	1.01 (0.58–2.67)	0.98
Body temperature (°C)	0.75 (0.51–1.13)	0.14
MICU	1.47 (0.21–6.23)	0.64
qSOFA >2	1.93 (0.59–6.19)	0.26

Data are presented as p-value and OR with a 95% CI. GCS: Glasgow Coma Scale; MICU: mobile intensive care unit; EMT: emergency mobile team; qSOFA: quick sepsis-related organ dysfunction assessment score; OR: odds ratio; 95% CI: 95% confidence interval

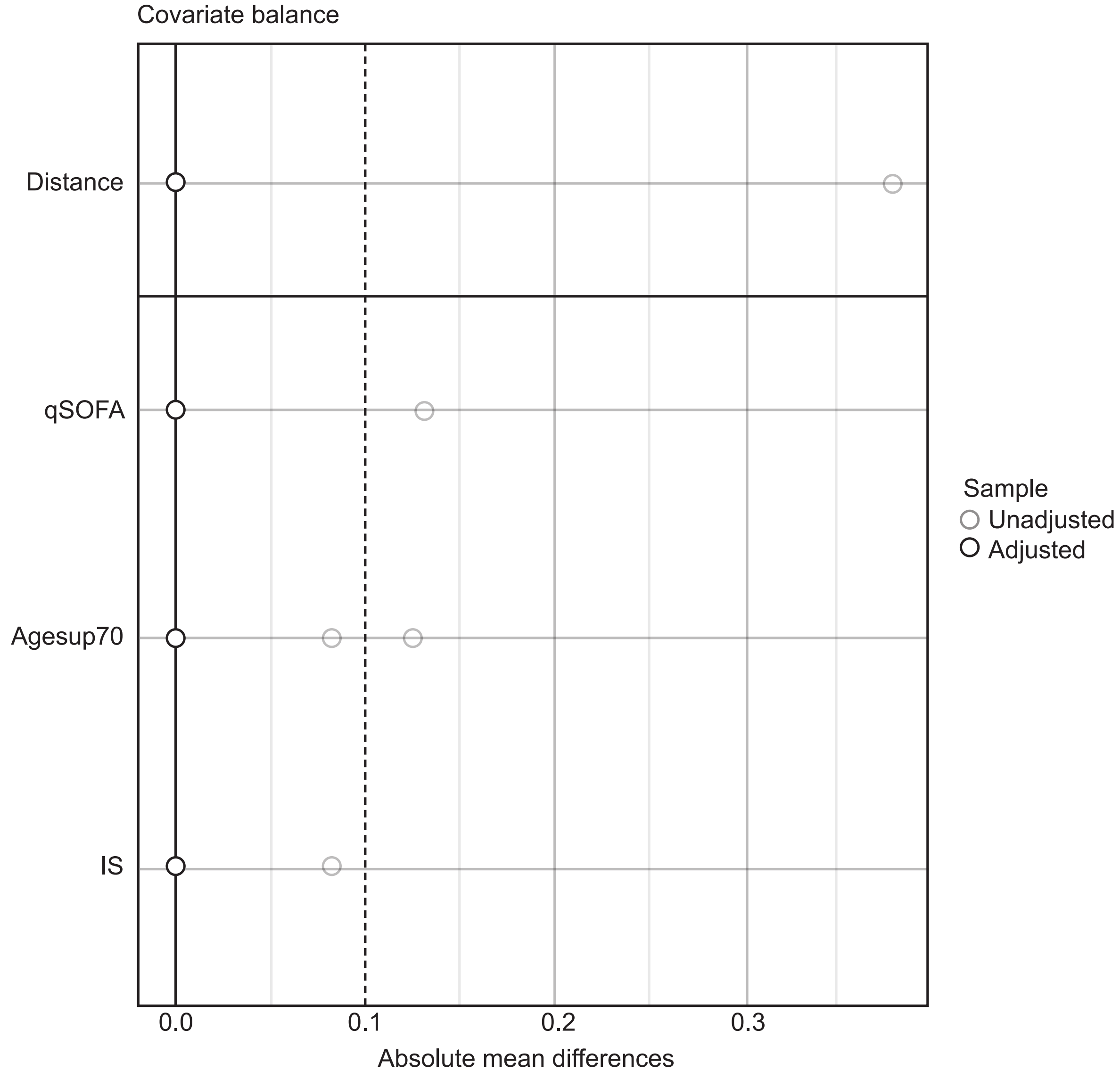

Figure 2. Standard mean deviation between cases and controls after propensity score matching. Cases correspond to patients admitted to the hospital by a MICU, and controls correspond to patients admitted by an EMT
qSOFA: quick sepsis-related organ dysfunction assessment score; MICU: mobile intensive care unit; EMT: emergency mobile team; IS: immunosuppression

Table 4. Comparison of variables predicting mortality on day 28 of patients with sepsis included in the propensity score before and after matching

	Before matching (n=140)			After matching (n=32)		
	Cases	Controls	p (d*)	Cases	Controls	p (d*)
PS covariate	n=16	n=124		n=16	n=16	
Age >80 years	6 (38%)	34 (27%)	0.21	6 (38%)	10 (63%)	<10−3
qSOFA >2	7 (44%)	38 (31%)	0.27	7 (44%)	7 (44%)	<10−3
IS	11 (69%)	75 (60%)	0.17	11 (69%)	11 (69%)	<10−3

Values are expressed as number and percentage (%). Cases correspond to patients admitted to the hospital by a MICU, and controls correspond to patients admitted by an EMT.
PS: propensity score; qSOFA: quick sepsis-related organ dysfunction assessment score; IS: immunosuppression; MICU: mobile intensive care unit; EMT: emergency mobile team

issues as the level of emergency has to be first identified by the dispatch centre. In fact, a significant proportion of patients are transported by an inappropriate mode of transport. Half of out-of-hospital patients with sepsis are transported by non-EMS (25). The relationship with mortality is controversial as some found no impact of prehospital transportation

(25), whereas others described increased mortality of patients transported by EMS (26). On the other hand, patients with sepsis transported by EMS died more often as they were more seriously ill (26) and transported with less urgent rides than needed (27). However, appropriate EMS transportation shortened the time to initiation of antibiotics and fluid expansion of approximately 30-60 min (25, 28).

The time lapse between the diagnosis of sepsis and the initiation of treatments is a well-proven prognostic factor affecting patients' outcome in sepsis (29-32). Therefore, improvement of the management of sepsis in the survival chain, in analogy to cardiac arrest management, aimed at reducing the time to treatment (30). In fact, early ICU admission significantly improved the prognosis of patients with septic shock (33). However, no defined strategy is currently used for management of prehospital patients with sepsis, contrary to the clear guidelines on acute coronary syndromes (34, 35). Should critical patients be admitted to the ICU directly or should they first transit through the ED? Should they be cared for in the prehospital setting directly by a MICU or might an EMT be sufficient? The absence of relevant tools for prehospital triage of patients with sepsis underlines the complexity of the issue. In fact, no vital sign is enough for decision-making. Additionally, biological values are time-consuming and hard to achieve in this context. These difficulties account for differences between studies on the benefit of the bundle of care strategy (29, 30, 32). Anyhow, the bundle of care concept describes key points for global management of patients with sepsis that must be performed within a time scale of 3 h to significantly decrease mortality (29).

Strengths and limitations

Some limitations restrict the interpretation of our results. First, this is a retrospective and single-centre study. Therefore, our results may not be extrapolated to other populations, medical institutions or countries. In fact, studies on prehospital transportation mode compared EMS with non-EMS without including MICUs (25, 27, 28). Moreover, the quality of care provided by EMS significantly differed between hospitals and countries. In many countries, paramedical teams have an insufficient knowledge regarding sepsis with an under evaluation of hypothermia (36) and poor recognition of sepsis (37). In parallel, in some countries, EMS teams have the ability to recognise sepsis and thus reduce the time to initiation of optimal therapies. Second, the sample size is small, decreasing the power of the study. Third, a sorting bias may exist as data were retrospectively collected from the SAMU regulation centre call recorded phone calls and ICU or ED medical reports. Finally, we could not investigate the effect of prehospital antibiotherapy as no patients received antibiotics prior to hospital admission. Similarly, we could not study haemodynamic optimisation as data lacked from the SAMU reports. Importantly, prehospital transportation in Paris is very efficient, and the time required to transfer a patient to the hospital is less likely to delay the time to treatment or interfere with mortality. Anyhow, antibiotic administration is a confounding factor and would have interfered with our results.

Despite these limitations, we observed a positive impact of the intervention of prehospital MICU on mortality of patients with sepsis on D28 initially cared for in the prehospital setting. Further larger cohorts are needed to confirm these preliminary data and to provide a causal link between mortality and prehospital MICU intervention.

Conclusion

We described an association between prehospital MICU intervention and mortality on D28 in patients with sepsis. MICU transportation of out-of-hospital patients with sepsis was associated with a RR reduction of 60% of death on D28.

These results underline the need to optimise prehospital management of patients with sepsis starting from patients' transportation to hospital admission. Larger studies are needed to confirm the impact of MICU intervention on mortality of patients with sepsis initially cared for in the prehospital setting.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Paris Ile de France 2, Paris- France approved the study in accordance with the French legislation (Number: 2015-08-03-SC).

Informed Consent: Written informed consent patients was waived for participation in this observational study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – R.J.; Design – R.J.; Supervision – R.J., B.V.; Data Collection and/or Processing – R.J.; Analysis and/or Interpretation – R.J.; Literature Search – R.J., A.S.; Writing Manuscript – R.J., A.S.; Critical Review – P.P., P.C., B.V.

Acknowledgements: Authors thank Ms Yolande Guirand, Medical Assistant (Department of Anesthesia & Intensive Care Unit, SAMU, Hôpital Necker - Enfants Malades 149 rue de Sèvres 75015 Paris, University Paris Descartes, France) for her help in gathering data from medical reports.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. Fleischmann C, Scherag A, Adhikari NK, Hartog CS, Tsaganos T, Schlattmann P, et al. Assessment of Global Incidence and Mortality

of Hospital-treated Sepsis. Current Estimates and Limitations. Am J Respir Crit Care Med 2016; 193: 259-72. **[CrossRef]**
2. Gaieski DF, Edwards JM, Kallan MJ, Carr BG. Benchmarking the incidence and mortality of severe sepsis in the United States. Crit Care Med 2013; 41: 1167-74. **[CrossRef]**
3. Epstein L, Dantes R, Magill S, Fiore A. Varying Estimates of Sepsis Mortality Using Death Certificates and Administrative Codes--United States, 1999-2014. MMWR Morb Mortal Wkly Rep 2016; 65: 342-5. **[CrossRef]**
4. Annane D, Aegerter P, Jars-Guincestre MC, Guidet B, Network CU-R. Current epidemiology of septic shock: the CUB-Rea Network. Am J Respir Crit Care Med 2003; 168: 165-72. **[CrossRef]**
5. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016; 315: 801-10. **[CrossRef]**
6. Delaney A, Peake SL, Bellomo R, Cameron P, Holdgate A, Howe B, et al. Australasian Resuscitation In Sepsis Evaluation trial statistical analysis plan. Emerg Med Australas 2013; 25: 406-15. **[CrossRef]**
7. Delaney AP, Peake SL, Bellomo R, Cameron P, Holdgate A, Howe B, et al. The Australasian Resuscitation in Sepsis Evaluation (ARISE) trial statistical analysis plan. Crit Care Resusc 2013; 15: 162-71.
8. Pro CI, Yealy DM, Kellum JA, Huang DT, Barnato AE, Weissfeld LA, et al. A randomized trial of protocol-based care for early septic shock. N Engl J Med 2014; 370: 1683-93. **[CrossRef]**
9. Adnet F, Lapostolle F. International EMS systems: France. Resuscitation 2004; 63: 7-9. **[CrossRef]**
10. Barbara P, Graziano C, Caputo W, Litvak I, Battinelli D, Hahn B. The quick sequential organ failure assessment (qSOFA) identifies septic patients in the out-of-hospital setting. Am J Emerg Med 2018; 36: 1022-6. **[CrossRef]**
11. Jouffroy R, Saade A, Carpentier A, Ellouze S, Philippe P, Idialisoa R, et al. Triage of Septic Patients Using qSOFA Criteria at the SAMU Regulation: A Retrospective Analysis. Prehosp Emerg Care 2018; 22: 84-90. **[CrossRef]**
12. Jouffroy R, Saade A, Ellouze S, Carpentier A, Michaloux M, Carli P, et al. Prehospital triage of septic patients at the SAMU regulation: Comparison of qSOFA, MRST, MEWS and PRESEP scores. Am J Emerg Med 2018; 36: 820-4. **[CrossRef]**
13. Tusgul S, Carron PN, Yersin B, Calandra T, Dami F. Low sensitivity of qSOFA, SIRS criteria and sepsis definition to identify infected patients at risk of complication in the prehospital setting and at the emergency department triage. Scand J Trauma Resusc Emerg Med 2017; 25: 108. **[CrossRef]**
14. Seymour CW, Liu VX, Iwashyna TJ, Brunkhorst FM, Rea TD, Scherag A, et al. Assessment of Clinical Criteria for Sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016; 315: 762-74. **[CrossRef]**
15. Bone RC, Sibbald WJ, Sprung CL. The ACCP-SCCM consensus conference on sepsis and organ failure. Chest 1992; 101: 1481-3. **[CrossRef]**
16. Pottecher T, Calvat S, Dupont H, Durand-Gasselin J, Gerbeaux P, workgroup SS. Haemodynamic management of severe sepsis: recommendations of the French Intensive Care Societies (SFAR/SRLF) Consensus Conference, 13 October 2005, Paris, France. Crit Care 2006; 10: 311. **[CrossRef]**
17. Gearing RE, Mian IA, Barber J, Ickowicz A. A methodology for conducting retrospective chart review research in child and adolescent psychiatry. J Can Acad Child Adolesc Psychiatry 2006; 15: 126-34.
18. Telion C, Greffet A, Rozenberg A, Lejay M, Janniere D, Carli P. Is the direct admission to the recovery service or to the intensive care unit of patients cared for by the Smur system justified?. Ann Fr Anesth Reanim 2000; 19: 654-61.
19. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. Multivariate Behav Res 2011; 46: 399-424. **[CrossRef]**
20. Martin GS, Mannino DM, Moss M. The effect of age on the development and outcome of adult sepsis. Crit Care Med 2006; 34: 15-21. **[CrossRef]**
21. Rowe T, Araujo KL, Van Ness PH, Pisani MA, Juthani-Mehta M. Outcomes of Older Adults With Sepsis at Admission to an Intensive Care Unit. Open Forum Infect Dis 2016; 3: ofw010.
22. Tolsma V, Schwebel C, Azoulay E, Darmon M, Souweine B, Vesin A, et al. Sepsis severe or septic shock: outcome according to immune status and immunodeficiency profile. Chest 2014; 146: 1205-13. **[CrossRef]**
23. Austin PC. Goodness-of-fit diagnostics for the propensity score model when estimating treatment effects using covariate adjustment with the propensity score. Pharmacoepidemiol Drug Saf 2008; 17: 1202-17. **[CrossRef]**
24. Strauch U, Bergmans DC, Winkens B, Roekaerts PM. Short-term outcomes and mortality after interhospital intensive care transportation: an observational prospective cohort study of 368 consecutive transports with a mobile intensive care unit. BMJ Open 2015; 5: e006801.
25. Band RA, Gaieski DF, Hylton JH, Shofer FS, Goyal M, Meisel ZF. Arriving by emergency medical services improves time to treatment endpoints for patients with severe sepsis or septic shock. Acad Emerg Med 2011; 18: 934-40. **[CrossRef]**
26. Pedersen PB, Henriksen DP, Mikkelsen S, Lassen AT. Dispatch and prehospital transport for acute septic patients: an observational study. Scand J Trauma Resusc Emerg Med 2017; 25: 51. **[CrossRef]**
27. Groenewoudt M, Roest AA, Leijten FM, Stassen PM. Septic patients arriving with emergency medical services: a seriously ill population. Eur J Emerg Med 2014; 21: 330-5. **[CrossRef]**
28. Studnek JR, Artho MR, Garner CL, Jr., Jones AE. The impact of emergency medical services on the ED care of severe sepsis. Am J Emerg Med 2012; 30: 51-6. **[CrossRef]**
29. Leisman DE, Doerfler ME, Ward MF, Masick KD, Wie BJ, Gribben JL, et al. Survival Benefit and Cost Savings From Compliance With a Simplified 3-Hour Sepsis Bundle in a Series of Prospective, Multisite, Observational Cohorts. Crit Care Med 2017; 45: 395-406. **[CrossRef]**
30. Peltan ID, Mitchell KH, Rudd KE, Mann BA, Carlbom DJ, Hough CL, et al. Physician Variation in Time to Antimicrobial Treatment for Septic Patients Presenting to the Emergency Department. Crit Care Med 2017; 45: 1011-8. **[CrossRef]**
31. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001; 345: 1368-77. **[CrossRef]**
32. Seymour CW, Gesten F, Prescott HC, Friedrich ME, Iwashyna TJ, Phillips GS, et al. Time to Treatment and Mortality during Mandated Emergency Care for Sepsis. N Engl J Med 2017; 376: 2235-44. **[CrossRef]**

33. Surat T, Viarasilpa T, Permpikul C. The impact of intensive care unit admissions following early resuscitation on the outcome of patients with severe sepsis and septic shock. J Med Assoc Thai 2014; 97(Suppl 1): S69-76.
34. Steg PG, Cambou JP, Goldstein P, Durand E, Sauval P, Kadri Z, et al. Bypassing the emergency room reduces delays and mortality in ST elevation myocardial infarction: the USIC 2000 registry. Heart 2006; 92: 1378-83. **[CrossRef]**
35. Task Force on Myocardial Revascularization of the European Society of C, the European Association for Cardio-Thoracic S, European Association for Percutaneous Cardiovascular I, Wijns W, Kolh P, Danchin N, et al. Guidelines on myocardial revascularization. Eur Heart J 2010; 31: 2501-55.
36. Shime N. A Survey of the Competency of Ambulance Service Personnel in the Diagnosis and Management of Sepsis. J Emerg Med 2015; 49: 147-51. **[CrossRef]**
37. Smyth MA, Brace-McDonnell SJ, Perkins GD. Identification of adults with sepsis in the prehospital environment: a systematic review. BMJ Open 2016; 6: e011218.