Changes in the incidence and outcome of multiple organ failure in emergency non-cardiac surgical admissions: a 10-year retrospective observational study

Short title: incidence and outcome of multiple organ failure

Miia M Jansson *

Postdoctoral researcher

Research Group of Medical Imaging, Physics and Technology, University of Oulu, Oulu, Finland.

Oulu University Hospital, Oulu, Finland

miia.jansson@oulu.fi

Postal address: Faculty of Medicine, P.O. Box 5000, FI-90014 University of Oulu, Finland

ORCID: 0000-0001-5815-0325

Pasi P Ohtonen

pasi.ohtonen@oulu.fi

Division of Operative care, Oulu University Hospital, Oulu, Finland

Medical Research Center Oulu, University of Oulu, Oulu, Finland

Hannu P Syrjälä

hannu.syrjala@ppshp.fi

Department of Infection Control, Oulu University Hospital, Oulu, Finland

Tero I Ala-Kokko

tero.ala-kokko@ppshp.fi

Division of Intensive Care, Department of Anesthesiology, Oulu University Hospital, Oulu, Finland.

Research Group of Surgery, Anesthesiology and Intensive Care, Medical Research Center Oulu, Oulu, Finland

Word count: 3513

Abstract

Background: During the past decades, epidemiologic data of independent predictors of multiple organ failure (MOF), incidence, and mortality have changed. The aim of the study was to assess the potential changes in the incidence and outcomes of MOF during one decade (2008–2017) . In addition, resource utilization was taken into account.

Methods: Patients were eligible for inclusion if they were adults, admitted to the ICU between January 1, 2008 and December 31, 2017, and had complete data sets regarding MOF. MOF was defined as organ failure separately with and without central nervous system (CNS) failure. The onset of MOF was defined as being early (≤ 48 h of ICU admission) and late (> 48 h after ICU admission).

Results: Of a total of 13,270 patients enclosed in this study, 44.6% of the patients developed MOF with and 31.4% without CNS failure. MOF-related mortality decreased in patients with (adjusted IRR 0.972 [95% CI 0.948 to 0.996], $p = 0.022$) and without (adjusted IRR 0.957 [95% CI 0.931 to 0.983], $p = 0.0013$) CNS failure. In addition, the incidence (adjusted IRR 0.970 [95% CI 0.950 to 0.991], $p = 0.006$) and mortality (adjusted IRR 0.968 [95% CI 0.940 to 0.996], $p = 0.025$) of early-onset MOF decreased, while the incidence and mortality of late-onset MOF remained constant. The length of ICU ($p = 0.024$) and hospital ($p = 0.032$) stays decreased while the length of mechanical ventilation remained constant ($p = 0.41$).

Conclusion: Despite all improvements in intensive care during the last decades, the incidence of late-onset MOF remains a resource-intensive, morbid, and lethal condition. More research on etiologies, signs of organ failure, and where and when to start treatment is needed to improve the prognosis of late-onset MOF.

Keywords: epidemiology, mortality, multiple organ failure

INTRODUCTION

Multiple-organ failure (MOF) is the main cause of morbidity, mortality, and intensive care unit (ICU) resource utilization among patients with sepsis, surgery, multiple trauma, and severe burns¹⁻¹³ requiring prolonged mechanical ventilation and length of ICU and hospital stays.⁸⁻¹⁰ In the literature, MOF has been characterized by the presence of 2–4 organ failures on average.³⁻⁴ The most commonly affected system has been the respiratory system.^{2, 5-8}

During the past decades, epidemiologic data of independent predictors of MOF have changed. At admission, the independent predictors of MOF have been age (>65 years), gender (male), number of comorbidities, alterations in serum biomarkers, injury severity, coagulopathy, reduced consciousness, low systolic blood pressure, and the amount of packed red blood cells and fresh frozen plasma.^{2, 8-10, 14} In addition, the admission type and centralization of trauma care have been associated with multiple-organ dysfunction and its unfavorable prognosis.^{7, 11, 15}

MOF affects not only in-hospital prognosis but also long-term morbidity and mortality.¹²⁻¹⁴ The 5-year mortality has been around 60% and around 80% in patients with severe organ failure.⁵ In addition, the mortality has varied by the severity and the number of organ failures.^{6-7, 12, 14, 16} Age, elevated serum lactate concentrations, pH, and the Sequential Organ Failure Assessment (SOFA) score on the day of admission have been independent predictors of MOF-related mortality^{3, 13, 17}, whereas unplanned ICU admission and unplanned surgery have increased the risk of death by 4-fold.^{3, 18}

Previous reports of temporal trends in the incidence and prognosis of MOF have been conducted on selected patient groups in emergency departments (ED) and trauma centers^{2, 9-10}, which complicates the comparability regarding risk factors, treatment recommendations, and patients' outcome. In addition, the current body of literature varies decisively between timing, scoring, and cut-off points defining MOF; the most decisive variation has been related to central nervous system (CNS) failure, which is not

included in the Denver score^{2, 7-8, 10} or the modified SOFA scores,^{5, 11} even though neurologic dysfunction has been associated with short- and long-term mortality.^{6, 13-14}

Even though the early detection and treatment are believed to improve the prognosis, the timing of MOF and its relation to the outcomes is rarely described,⁷ particularly upfront ICU presentation. In the literature, the total maximum SOFA score within 48 h of ED admission has correlated with hospital mortality,¹³ while the time to present the greatest number of organ failures has been less than 24 h.¹²

Despite its importance, the onset of MOF with and without CNS failure among non-selected ICU patients is unknown. Comprehensive assessment of evolving epidemiology is needed to improve prevention, early detection, quality of treatment, resource allocation, and most importantly to improve patient prognosis.

Objectives

Our objectives was to assess potential changes in the incidence and outcomes of MOF during one decade (2008–2017) using two different definitions together with two different onsets of failures. In addition, resource utilization was taken into account.

MATERIALS AND METHODS

This retrospective cohort study was conducted in a 900-bed tertiary-level teaching hospital in Finland. At the beginning of 2019, the hospital's special area of responsibility covers 68 municipalities—accounting for more than half of Finland's geographical area and home to 741,000 people. The hospital has the capacity to handle the most demanding emergencies in the whole of Northern Finland, which is geographically large and sparsely populated. The hospital has an adult, closed, mixed medical-surgical ICU with 22 beds and admits approximately 2,000 patients per year, for a mean stay of three days. The study was reviewed and approved by the relevant academic center (Declaration of Helsinki 2013). According to Finnish legislation (Medical Research Act 488/1999), neither approval from the ethics committee nor informed consent from the study populations is required for registry linkage studies.

Study population

All admissions were identified from the hospital institutional database. Patients with emergency admission were eligible for inclusion if they were adults (≥ 18 years) and admitted to the ICU between 1st of January 2008 and 31st of December 2017. Elective admissions with and without cardiac surgery were excluded to reduce case-mix heterogeneity. Therefore, a total of 13,270 patients were included for further analysis (Figure 1).

Definitions

Organ failure was defined by the SOFA score, which is commonly used in ICU settings.¹⁷ The SOFA score consists of scores from six organ systems (respiratory, cardiovascular, renal, liver, coagulation, and CNS). Each organ system was graded using a five-step scale (0–4 points) to evaluate the severity of

organ dysfunction or failure. A score of 3 or 4 per one of the six organ systems were given separately as a failure of this organ:

- respiratory failure: $\text{PaO}_2/\text{FiO}_2 < 200$ mmHg with respiratory support,
- cardiovascular failure: Dopamine > 5.0 (mcg/kg/min), Epinephrine ≤ 0.1 or > 0.1 or (mcg/kg/min) or norepinephrine ≤ 0.1 or 0.1 (mcg/kg/min),
- renal failure: creatinine ≥ 3.5 mg/dL or ≥ 300 $\mu\text{mol/L}$ (or urine output < 500 mL/day),
- liver failure: bilirubin ≥ 6.0 mg/dL or ≥ 102 $\mu\text{mol/L}$,
- coagulation failure: platelets < 50 ($\times 10^3/\mu\text{L}$), and
- CNS failure: Glasgow Coma Scale ≤ 9 (if on sedatives, assumed GCS estimated off sedatives).

MOF was defined as organ failure for at least two of the listed organs or systems separately with and without CNS failure. According to previous literature,^{6, 13} the onset of MOF was defined as being early (within 48h of ICU admission) and late (> 48 h after ICU admission). However, only the first episode of MOF was considered.

The occurrence of MOF was assessed and recorded prospectively on a daily basis starting from the day of admission at 11–12 pm until ICU discharge or death for all included patients. Auto-filled fields were checked daily by the nurse and IT support.

Data collection and outcomes

The primary outcome was the incidence of MOF, and secondary outcomes were MOF-related mortality (death from any cause in MOF patients) and resource utilization (e.g., ICU and hospital lengths of stay, ventilator days). For comparing different cohorts, the following data were obtained from the clinical medical records: Simplified Acute Physiology Score (SAPS II), Acute Physiology and Chronic Health Evaluation (APACHE II) score, age, gender, specialty, and admission types (surgical/non-surgical,

emergency/elective).¹⁹⁻²⁰ SAPS II and APACHE II scores were recorded prospectively on a daily basis. Ventilator days were calculated by counting the cumulative duration of invasive pressure or volume controlled ventilation.

Data analysis

Demographic and clinical data are presented using frequencies with percentages and means with standard deviations (SDs).²¹ Between-group comparisons for continuous variables were performed by the Student's t-test and categorical variables were compared with Pearson's χ^2 -test. Poisson regression was used to calculate the change in incidence rate (per 1,000 ICU days) in MOF and in patients over 65 years of age over the study period. The change in MOF was also adjusted with the change in the rate of patients over 65 years of age. The results of Poisson regression are shown as the incidence rate ratio (IRR) with a 95% confidence interval (95% CI). IRR <1.0 indicates a decreasing incidence rate, and IRR >1.0 indicates an increasing incidence rate. Two-tailed *P*-values are presented. Statistical analyses were performed using IBM SPSS for Windows (IBM Corp. Released 2018, Version 25.0. Armonk, NY: IBM Corp.). This article followed the STROBE reporting standard for cohort studies (see Supplementary File 1).²²

RESULTS

Demographics

We screened 21,625 patients in total, of which 13,270 patients were included in the final analysis (Figure 1). The patients were predominately male patients (62.5%) with a mean age of 58.8 (SD 17.5) years. The mean APACHE II score was 17.4 (SD 7.6), while the SAPS II score was 39.8 (SD 16.6) at admission. The mean ICU and hospital length of stays were 3.7 (SD 5.3) days and 14.6 (SD 18.1) days, respectively. The overall ICU and hospital mortalities were 7.2% and 12.4%, respectively. Detailed characteristics for patients with and without MOF are summarized in Table I.

Incidence from 2008 to 2017

During a study period of 10 years, 44.6% (121 per 1,000 ICU days) of the patients developed MOF with CNS failure and 31.4% (85 per 1,000 ICU days) of the patients developed MOF without it. Ninety percent of MOF cases occurred within 48 h of ICU admission (Table II), with the highest rate (38.1%) seen in patients admitted to the ICU from ED.

The adjusted IRR for the whole study period showed a decreasing trend in the incidence of MOF with (144 [48.9%] in 2008 vs. 121 [43.4%] in 2017, IRR 0.970 [95% CI 0.950 to 0.990], $p = 0.003$) and without CNS failure (107 [36.4%] in 2008 vs. 86 [30.9%] in 2017, IRR 0.967 [95% CI 0.944 to 0.991], $p = 0.0072$), particularly in the respiratory ($p < 0.0001$) and renal ($p < 0.0001$) failures (Table III). However, the year 2008 seemed to be a single peak year (Figure 2), and the adjusted IRR for years 2009–2017 was 0.980 (95% CI 0.959 to 1.001, $p = 0.056$).

In the subgroup analysis, the incidence of early-onset MOF with CNS failure (132 [44.6%] in 2008 vs. 108 [38.7%] in 2017, adjusted IRR 0.970 [95% CI 0.950 to 0.991], $p = 0.006$) decreased (Figure 3),

while the incidence of late-onset MOF remained stable (13 [4.3%] in 2008 and 13 [4.6%] 2017, adjusted IRR 0.966 [95% CI 0.907 to 1.030], $p=0.29$).

Mortality from 2008 to 2017

The highest mortality rates were observed in patients with early-onset MOF (Table II), with the highest occurrence (40.1%) seen in patients admitted to the ICU from ED. Twenty-three percent of the MOF-related deaths occurred within two days of the MOF diagnosis and 36.5% within a week of MOF onset.

During one decade (Figure 2), the incidence of mortality of all patients decreased (40 [13.7%] in 2008 vs. 30 [10.9%] in 2017, adjusted IRR=0.961 [95% CI 0.925 to 1.000], $p=0.047$). In addition, the incidence of MOF-related mortality decreased in patients with (34 [23.5%] in 2008 vs. 22 [18.3%] in 2017, adjusted IRR 0.972 [95% CI 0.948 to 0.996], $p=0.022$) and without (27 [24.9%] in 2008 vs. 18 [21.5%] in 2017, IRR 0.957 [95% CI 0.931 to 0.983], $p=0.0013$) CNS failure even though the patients with MOF were approximately 3 years older (age 60.2 [SD 15.2] in 2008 vs. 63.3 [SD 14.8] in 2017, difference -3.1 [95% CI -4.7 to -1.4], $p<0.001$).

In the subgroup analysis, the a incidence of mortality in patients with early-onset MOF decreased (52 [25.0%] in 2008 vs. 35 [19.2%] in 2017, adjusted IRR 0.968 [95% CI 0.940 to 0.996], $p=0.025$), while the incidence of mortality in patients with late-onset MOF remained constant (9 [7.5%] in 2008 vs. 13 [11.1%] in 2017, adjusted IRR 0.971 [95% CI .896 to 1.053], $p=0.48$) (Figure 3).

Resource utilization

The highest resource utilization was observed in patients with MOF (Table I), with the highest rates seen in patients with late-onset MOF (Table II). During the study period, MOF-related resource utilization regarding the length of ICU (5.1 days [SD 4.7] in 2008 vs. 5.9 days [SD 6.5], difference -0.7 [95% CI -1.4 to 0.1], $p=0.024$) and hospital (19.9 [SD 26.7] in 2008 vs. 16.9 [SD 22.1], difference 3.0 [95% CI

0.3 to 5.7], $p = 0.032$) stays decreased without any changes in the duration of mechanical ventilation (3.0 [SD 3.4] days in 2008 vs. 3.2 [SD 4.7] days, difference -0.2 [95% CI -0.7 to 0.3], $p = 0.41$).

DISCUSSION

The presented retrospective analysis displays the incidence of MOF and MOF-related mortality and resource utilization in 13,270 mixed medical-surgical patients over one decade. According to our best knowledge, this is the first and longest study assessing the potential changes in the incidence and outcomes of MOF using two different definitions together with two different onsets of failures.

The occurrence of MOF with CNS failure was slightly higher than previously reported rates (5.2%–32.7%) among patients with surgery, multiple trauma, and severe burns^{1-3, 5, 7-10} and adult ED patients,¹⁴ but lower than previously reported rates in patients with sepsis (61%–80%).^{13, 16} In this population, however, patients were relatively older than those reported in other studies^{1, 5, 8-10}, which can partially explain the difference between the studies. On the one hand, differences in inclusion criteria, patient's treatment, trauma systems, as well as scores and cut-off points defining MOF may explain some of these differences. For instance, Pedersen et al.¹⁴ used a modified definition based on the SOFA and quick-SOFA scores covering a population-based incidence and ED-based prevalence of MOF, whereas Bennis et al.⁷ used the Denver postinjury MOF score and focused solely on a national trauma population.

In this study, the majority of MOF cases (89.8%) occurred within 48 hours of ICU admission, which is higher than previously reported rates (51.4%–65.0%) among mixed medical-surgical ICU patients.^{6, 11-12} The majority of patients with early-onset MOF were admitted to ICU from ED and general wards, with the highest mortality rates (40.1%) seen in patients admitted to the ICU from ED. In the literature, ICU admission that has been delayed more than one hour has been a strong determinant of mortality,²³⁻²⁴ and it has been associated with a longer ICU stay and a need for longer mechanical ventilation.²⁵

To date, however, the majority of MOF studies have been performed in ICU^{3, 5-6, 11-12}, burn^{1, 4} and trauma centers^{2, 7-9} as well as EDs¹³⁻¹⁴, whereas a general non-ICU¹⁵⁻¹⁶ is rarely included, although the

patients admitted to ICU from the general wards have had a higher mortality rates than those admitted from EDs.²³⁻²⁴ This highlights the need for awareness regarding organ failure as soon as possible after admission, or even earlier in the pre-hospital setting to improve treatment and thus, prognosis.¹⁴

During one decade, an equal but non-significant change was seen in the incidences of MOF with and without CNS failure (Figure 2). The incidence and mortality of early-onset MOF, however, decreased, which might be due to the standardized critical care patient pathway, improved prehospital trauma triage, and implementation of Medical Emergency Team services. The incidence and mortality of late-onset MOF, however, remained constant and needs to be explored further in the future. In the previous literature^{1-2, 10}, the incidence of MOF has declined steadily, likely owing to new therapeutic approaches, resuscitation, and other improvements in the treatment of critically ill patients.^{8, 10} On the other hand, the incidence of MOF has increased in severely injured patients.⁹

In concordance with the previous literature, the most commonly affected systems were cardiovascular and respiratory systems.^{1, 5-6, 14} During the study period, however, the incidence of respiratory and renal failures decreased. In the study by Sauaia et al.¹⁰ respiratory and cardiovascular dysfunction became less frequent, while renal and liver failure rates did not change during the study period. On the other hand, a slight increase in failure of the respiratory and cardiovascular dysfunction and coagulation system was observed in the Benms et al.⁷ and Fröhlich et al.⁹ studies, respectively.

According to Evans et al.,²⁶ MOF causes up to 30% of possibly preventable deaths. In this study, MOF-related hospital mortality was less than published previously, depending on the period evaluated.^{1-4, 7, 14, 27} In the study by Pedersen et al.,¹⁴ for instance, the one-year all-cause mortality in patients with MOF was 29.8%. In addition, mortality rates associated with organ dysfunction were the highest in patients older than 65 years.⁷

In the literature, reports of temporal trends in MOF-related mortality are discordant.^{2, 9-10} For instance, in the study by Sauaia et al.¹⁰, the MOF-related death rate increased from 33% during 2003–

2004 to 36% during 2009–2010, while in the study by Fröhlich et al.⁹, the MOF-related death rate decreased from 42.6% in 2002 to 33.3% in 2011. Twenty-three percent of the MOF-related deaths occurred within two days of the MOF diagnosis and 36.5% within a week of MOF onset, while in the literature, 58% of the MOF-related deaths occurred within two days of the MOF diagnosis and 80% within a week of MOF onset.¹⁰ In the study by Pedersen et al.,¹⁴ the 7-day mortality was 11.0%.

Among specific organ systems, cardiovascular failure has proved to be the deadliest with a 41.5% mortality rate.⁷ According to autopsy reports, however, the most frequently encountered organ failure in MOF deaths has been renal failure. In addition, sepsis has always been affiliated with MOF as a cause of death in patients with severe burns.⁹ However, the primary cause of death was not established in this study due to the unavailability of autopsy data.

During the study period, MOF-related resource utilization regarding the length of stays decreased. Patients with MOF stayed approximately four days longer in ICU than patients without MOF, requiring five times more ventilator days. However, MOF-related resource utilization was significantly lower than previously reported rates in trauma patients.⁸⁻¹⁰

Our study is not without limitations. This study was conducted in a large Finnish university hospital over a 10-year study period. However, there are several limitations to our study. First of all, this is a single-center, retrospective observational study, which limits the generalizability of the obtained results. The number of males was somewhat smaller than previously published; however, the proportion was in harmony with the previous literature.⁸⁻⁹ In addition, the study population was relatively older than those reported in other studies.⁸⁻⁹ These demographic findings are not surprising, because the Finnish population is ageing, especially in Northern Finland. However, the results may not be transferable to dissimilar populations. Secondly, the validity of documentation is not controlled by external monitoring, as is possible in prospective trials. Contrary to previous studies⁷, however, we were able to define the day of onset. Unfortunately, clear definition of the onset of MOF, however, is absent in literature. Thirdly,

in line with Pedersen et al.,¹⁴ only the first episode of MOF was considered, which may underestimate its occurrence. Fourthly, the applied conventional statistical analyses are problematic in large populations, where clinically non-relevant results may reach statistical significance. Therefore, interpretation has to consider the clinical importance of the observed differences. Finally, both the clinical treatment of patients and research are conducted by the same clinicians. The data, however, was analyzed by a blinded researcher and biostatistician in order to reduce the risk of potential bias.

MOF is a time-dependent organ dysfunction that requires rapid and earlier diagnosis and prompt treatment to improve prognosis. In the future, prediction models should be developed to help critical care clinicians identify patients at risk of MOF and MOF-related death. In addition, prediction of MOF is important for planning intensive care resource allocation and identifying patients for potential interventional studies.¹ The signs of organ failure should be recognized far before they become obvious; the presence of clinically recognizable signs of organ failure have resulted in increased compliance to guidelines and thus, better treatment.²⁸ In addition, patients who are developing MOF (except for DNI and DNR) should be transferred to ICU when possible; according to Kakebeeke et al.,²⁸ the time to antibiotics has been shorter in patients admitted to ICU compared to patients admitted to a general ward. In addition, delayed ICU admission has been a strong determinant of mortality,²³⁻²⁴ and it has been associated with a longer ICU stay and a need for longer mechanical ventilation.²⁵ More research on etiologies, signs of organ failure, and where and when to start treatment is needed to improve the prognosis of late-onset MOF.

CONCLUSION

In conclusion, despite all improvements in intensive care during the last decades, the incidence of MOF remains a resource-intensive, morbid, and lethal condition. More research on etiologies, signs of organ failure, and where and when to start treatment is needed to improve the prognosis of late-onset MOF.

WHAT IS KNOWN

- Epidemiologic data of independent predictors of MOF, incidence, and mortality have changed.

WHAT IS NEW

- An equal but non-significant change was seen in the incidence of MOF with and without CNS failure.
- The incidence of MOF-related mortality decreased in patients with and without CNS failure.
- The incidence of late-onset MOF remains a resource-intensive, morbid, and lethal condition.

Authorship

M.J., H.S., and T.A.-K. contributed to the study design. The study nurse contributed to the data collection. M.J. and P.O. performed the data analysis. M.J., P.O., H.S., and T.A.-K. contributed to data interpretation and manuscript preparation. All authors have read and approved the final version of this manuscript.

Disclosure

The authors declare no funding or conflicts of interest.

Acknowledgements

The authors thank study nurse S.S. for providing valuable help during the data collection.

Figure captions:

- Figure 1: Flow chart of included patients.
- Figure 2: The incidences of multiple-organ failure (MOF) with and without central nervous system (CNS) failure.
- Figure 3: The incidences of multiple-organ failure (MOF) and mortality in patients with early- and late-onset MOF with central nervous system failure.

REFERENCES

1. Cumming J, Purdue GF, Hunt JL, O'Keefe GE. Objective estimates of the incidence and consequences of multiple organ dysfunction and sepsis after burn trauma. *J Trauma* 2001;50:510–5.
2. Ciesla DJ, Moore EE, Johnson JL, Burch JM, Cothren CC, Sauaia A. A 12-year prospective study of postinjury multiple organ failure: has anything changed? *Arch Surg* 2005;140:432–40.
3. Lobo SM, Rezende E, Knibel MF, Silva NB, Paramo JA, Nacul FE, et al. Early determinants of death due to multiple organ failure after noncardiac surgery in high-risk patients. *Anesth Analg* 2011;112:877–83.
4. Kallinen O, Maisniemi K, Böhling T, Tukiainen E, Koljonen V. Multiple organ failure as a cause of death in patients with severe burns. *J Burn Care Res* 2012;33:206–11.
5. Lone NI, Walsh TS. Impact of intensive care unit organ failures on mortality during the five years after a critical illness. *Am J Respir Crit Care Med* 2012;186:640–7.
6. Sakr Y, Lobo SM, Moreno RP, Gerlach H, Ranieri VM, Michalopoulos A, et al. Patterns and early evolution of organ failure in the intensive care unit and their relation to outcome. *Crit Care* 2012;16: R222.
7. Bennis M, Carr B, Kallan MJ, Sims CA. Benchmarking the incidence of organ failure after injury at trauma centers and nontrauma centers in the United States. *J Trauma Acute Care Surg* 2013; 75: 426–31.
8. Dewar DC, Tarrant SM, King KL, Balogh ZJ. Changes in the epidemiology and prediction of multiple-organ failure after injury. *J Trauma Acute Care Surg* 2013;74:774–9.
9. Fröhlich M, Lefering R, Probst C, Paffrath T, Schneider MM, Maegele M, et al; Committee on Emergency Medicine, Intensive Care and Trauma Management of the German Trauma Society

- Sektion NIS. Epidemiology and risk factors of multiple-organ failure after multiple trauma: An analysis of 31,154 patients from the TraumaRegister DGU. *J Trauma Acute Care Surg* 2014;76:921–8.
10. Sauaia A, Moore EE; Johnson JL, Chin TL, Banerjee A, Sperry JL, et al. Temporal trends of postinjury multiple-organ failure: still resource intensive, morbid, and lethal. *J Trauma Acute Care Surg* 2014;76:582-593.
 11. Bingold TM, Lefering R, Zacharowski K, Meybohm P, Weydhas C, Rosenberg P, et al. Individual Organ Failure and Concomitant Risk of Mortality Differs According to the Type of Admission to ICU - A Retrospective Study of SOFA Score of 23,795 Patients. *PLoS One* 2015;10:e0134329.
 12. Ranzani OT, Zampieri FG, Besen BAMP, Azevedo LCP, Park M. One-Year survival and resource use after critical illness: impact of organ failure and residual organ dysfunction in a cohort study in Brazil. *Crit Care* 2015;19: 269.
 13. Schuler A, Wulf DA, Lu Y, Iwashyna TJ, Escobar GJ, Shah NH, Liu VX. The Impact of Acute Organ Dysfunction on Long-Term Survival in Sepsis. *Crit Care Med*. 2018;46:843–9.
 14. Pedersen PB, Henriksen DP, Brabrand M, Lassen AT. 2019. Prevalence of organ failure and mortality among patients in the emergency department: a population-based cohort study. *BMJ Open* 2019; 9: e032692.
 15. Churpek MM, Zdravetz FJ, Winslow C, Howell MD, Edelson DP. Incidence and Prognostic Value of the Systemic Inflammatory Response Syndrome and Organ Dysfunctions in Ward Patients. *Am J Respir Crit Care Med* 2015; 192: 958–64.
 16. Dat VQ, Long NT, Hieu VN, Phuc NDH, Van Kinh N, Trung NV, et al. Clinical characteristics, organ failure, inflammatory markers and prediction of mortality in patients with community acquired bloodstream infection. *BMC Infect Dis* 2018;18:535.

17. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonca A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. *Int Care Med* 1996;22:707–10.
18. Bellomo R, Goldsmith D, Russell S, Uchino S. Postoperative serious adverse events in a teaching hospital: a prospective study. *Med J Aust* 2002;176:216–8.
19. Le Gall JR, Lemeshow S, Saulnier F. A new simplified acute physiology score (SAPS II) based on a European/North American multicenter study. *J Am Med Assoc* 1993; 270:2957–63.
20. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med* 1985;13:818–29.
21. Cesana BM, Cavaliere F. Basics to perform and present statistical analyses in scientific bionon-surgical reports Part 1. *Minerva Anestesiol* 2016; 82: 822–6.
22. Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, STROBE Initiative. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007;370:1435–7.
23. Cardoso LT, Grion CM, Matsuo T, Anami EH, Kauss IA, Seko L, et al. Impact of delayed admission to intensive care units on mortality of critically ill patients: a cohort study. *Crit Care* 2011;15:R28.
24. Harris S, Singer M, Rowan K, Sanderson C. Delay to admission to critical care and mortality among deteriorating ward patients in UK hospitals: a multicenter, prospective, observational cohort study. *Lancet* 2015;26:S40.
25. Hsieh CC, Lee CC, Hsu HC, et al. Impact of delayed admission to intensive care units on patients with acute respiratory failure. *Am J Emerg Med* 2017; 35: 39–44.
26. Evans JA, van Wessem KJ, McDougall D, Lee KA, Lyons T, Balogh ZJ. Epidemiology of traumatic deaths: comprehensive population-based assessment. *World J Surg.* 2010;34:158–63.

27. Ranzani OT, Shankar-Hari M, Harrison DA, Rabello LS, Salluh JIF, Rowan KM, Soares M. A comparison of mortality from sepsis in Brazil and England: the impact of heterogeneity in general and Sepsis-Specific patient characteristics. *Crit Care Med* 2018; 47: 76–84.
28. Kakebeeke D, Vis A, Deckere ER, et al. Lack of clinically evident signs of organ failure affects ED treatment of patients with severe sepsis. *Int J Emerg Med* 2013; 6:4.

Table I. Clinical characteristics at admission and outcome of patients with and without MOF (2008–2017).

	Patients without MOF (<i>n</i> = 7,352)	Patients with MOF ^a (<i>n</i> = 5,918)	<i>P</i> -value ^b
Age (years), mean (SD)	57.0 (18.6)	61.1 (15.7)	<0.001
Gender (male), No. (%)	4,377 (59.5)	3,922 (66.3)	<0.001
Specialty			<0.001
Surgery, No. (%)	3,240 (44.1)	1,756 (29.7)	
Neurosurgery, No. (%)	1,188 (16.2)	1,462 (24.7)	
Internal Medicine, No. (%)	1,870 (25.4)	2,087 (35.3)	
Gynecology/Obstetrics, No. (%)	253 (3.4)	21 (0.4)	
Infectious Diseases, No. (%)	13 (0.2)	14 (0.2)	
Otorhinolaryngology, No. (%)	267 (3.6)	80 (1.4)	
Neurology, No. (%)	459 (6.2)	460 (7.8)	
Other, No. (%)	62 (0.8)	38 (0.6)	
Admission source, No. (%)			<0.001
ED	3,148 (42.8)	2,230 (37.7)	
Ward	1,712 (23.3)	1,355 (22.9)	
Other	2,492 (33.9)	2,333 (39.4)	
Surgical (yes), No. (%)	1,818 (24.7)	1,326 (27.4)	<0.001
APACHE II score, mean (SD)	13.8 (5.9)	21.8 (7.0)	<0.001
SAPS II score, mean (SD)	31.4 (12.5)	50.1 (15.2)	<0.001
Ventilator days, mean (SD)	0.6 (1.2)	3.3 (4.5)	<0.001
Length of ICU stay (days), mean (SD)	1.8 (1.8)	6.1 (7.0)	<0.001
Length of hospital stay (days), mean (SD)	12.4 (16.5)	17.3 (19.7)	<0.001
ICU mortality, No. (%)	82 (1.1)	879 (14.9)	<0.001
Surgical, No. (%)	13 (0.2)	175 (3.0)	<0.001
Non-surgical, No. (%)	69 (0.9)	704 (11.9)	<0.001
Hospital mortality, No. (%)	298 (4.1)	1,347 (22.8)	<0.001
Surgical, No. (%)	52 (0.7)	275 (4.7)	<0.001
Non-surgical, No. (%)	246 (3.4)	1,072 (18.1)	<0.001

^a MOF with central nervous system failure.

^b The significance level is 0.05.

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation Score; ED, Emergency Department; ICU, Intensive Care Unit; N/A, Not Available; NIV, Noninvasive ventilation; MOF, Multiple organ failure; SAPS II, Severity of the patient illness score.

Table II. Clinical characteristics at admission and outcome of patients with early- and late-onset

	Patients with early-onset MOF (<i>n</i> = 5,313)	Patients with late-onset MOF ^a (<i>n</i> = 605)	<i>P</i> -value ^b
Age (years), mean (SD)	61.2 (15.6)	59.7 (16.3)	0.028
Gender (male), No. (%)	3,519 (66.2)	403 (66.6)	0.89
Specialty			<0.001
Surgery, No. (%)	1,504 (28.3)	252 (41.7)	
Neurosurgery, No. (%)	1,307 (24.6)	155 (25.6)	
Internal Medicine, No. (%)	1,959 (36.9)	128 (21.2)	
Gynecology/Obstetrics, No. (%)	16 (0.3)	5 (0.8)	
Infectious Diseases, No. (%)	14 (0.3)	0 (0.0)	
Otorhinolaryngology, No. (%)	64 (1.2)	16 (2.6)	
Neurology, No. (%)	415 (7.8)	45 (7.4)	
Other, No. (%)	34 (0.6)	4 (0.7)	
Admission from, No. (%)			0.037
ED	2,023 (38.1)	207 (34.2)	
Ward	1,193 (22.5)	162 (26.8)	
Other	2,097 (39.5)	236 (39.0)	
Surgical (yes), No. (%)	1,470 (27.7)	153 (25.3)	0.23
APACHE II score, mean (SD)	22.4 (6.9)	16.5 (5.7)	<0.001
SAPS II score, mean (SD)	51.5 (14.9)	37.1 (11.4)	<0.001
Ventilator days, mean (SD)	3.1 (4.4)	4.5 (5.0)	<0.001
Length of ICU stay (days), mean (SD)	5.6 (6.7)	9.9 (8.3)	<0.001
Length of hospital stay (days), mean (SD)	16.5 (19.3)	23.9 (21.6)	<0.001
ICU mortality, No. (%)	822 (15.5)	57 (9.4)	<0.001
Hospital mortality, No. (%)	1,244 (23.4)	103 (17.0)	<0.001

^a MOF with central nervous system failure.

^b The significance level is 0.05.

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation Score; ED, Emergency Department; ICU, Intensive Care Unit; N/A, Not Available; NIV, Noninvasive ventilation; MOF, Multiple organ failure; SAPS II, Severity of the patient illness score.

Table III. Organ system failure in patients with MOF (incidence per 1,000 ICU day). ^a

Organ failure	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	IRR (95% CI) ^b	<i>P</i> -value ^c
Respiratory, yes (%)	83 (28.1)	69 (25.7)	66 (25.3)	66 (24.9)	64 (23.3)	63 (22.9)	58 (23.0)	59 (21.1)	57 (22.1)	65 (22.1)	0.975 (0.963 to 0.986)	<0.0001
Cardiovascular, yes (%)	127 (43.0)	107 (39.8)	104 (39.7)	103 (38.9)	108 (39.7)	111 (40.3)	101 (39.6)	106 (37.7)	102 (39.1)	113 (40.7)	0.993 (0.984 to 1.003)	0.148
Renal, yes (%)	29 (9.9)	22 (8.1)	23 (9.0)	24 (9.0)	23 (8.5)	27 (9.9)	19 (7.6)	19 (6.9)	16 (6.0)	18 (6.4)	0.953 (0.933 to 0.973)	<0.0001
Liver, yes (%)	3 (0.9)	3 (1.0)	4 (1.5)	4 (1.4)	3 (1.0)	3 (1.0)	5 (2.0)	4 (1.3)	4 (1.5)	3 (1.0)	1.023 (0.97 to 1.079)	0.399
Coagulation, yes (%)	10 (3.5)	7 (2.7)	10 (4.0)	5 (2.0)	8 (3.0)	8 (3.1)	8 (3.3)	9 (3.1)	7 (2.5)	7 (2.4)	0.972 (0.939 to 1.007)	0.113
CNS, yes (%)	73 (24.7)	67 (25.1)	61 (23.2)	65 (24.4)	72 (26.3)	72 (25.9)	60 (23.8)	68 (24.3)	58 (22.3)	64 (23.0)	0.989 (0.978 to 1.001)	0.08

^a MOF with CNS failure.

^b IRR < 1.0 indicates a decreasing incidence rate and IRR > 1.0 indicates an increasing incidence rate.

^c Two-tailed *P*-value < 0.05 was considered as statistically significant.

Abbreviations: CI, Confidence Interval; IRR, incidence rate ratio; CNS, central nervous system; MOF, Multiple organ failure.

Supplementary File 1

STROBE Statement—Checklist of items that should be included in reports of cohort studies.

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract
	2	(b) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	3	Explain the scientific background and rationale for the investigation being reported
Objectives	4-5	State specific objectives, including any prespecified hypotheses
Methods		
Study design	6	Present key elements of study design early in the paper
Setting	6	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(b) For matched studies, give matching criteria and number of exposed and unexposed
Variables	6-7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/measurement	6-7	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	6	Describe any efforts to address potential sources of bias
Study size	6	Explain how the study size was arrived at
Quantitative variables	6-7	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why

Statistical methods	8	<p>(a) Describe all statistical methods, including those used to control for confounding</p> <p>(b) Describe any methods used to examine subgroups and interactions</p> <p>(c) Explain how missing data were addressed</p> <p>(d) If applicable, explain how loss to follow-up was addressed</p> <p>(e) Describe any sensitivity analyses</p>
Results		
Participants	9	<p>(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed</p> <p>(b) Give reasons for non-participation at each stage</p> <p>(c) Consider use of a flow diagram</p>
Descriptive data	9	<p>(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders</p> <p>(b) Indicate number of participants with missing data for each variable of interest</p> <p>(c) Summarise follow-up time (eg, average and total amount)</p>
Outcome data	9-11	Report numbers of outcome events or summary measures over time
Main results	9-11	<p>(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included</p> <p>(b) Report category boundaries when continuous variables were categorized</p> <p>(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period</p>
Other analyses	Na	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses

Discussion		
Key results	12	Summarise key results with reference to study objectives
Limitations	13-14	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	13-14	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalizability	13-14	Discuss the generalizability (external validity) of the study results
Other information		
Funding	15	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based