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Post-ICU mortality in critically ill infected patients: an international study

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Abstract *Objective:* To determine the incidence and risk factors for post-ICU mortality in patients with infection. *Design and setting:* International observational cohort study including 28 ICUs in eight countries. *Patients:* All 1,872 patients discharged alive from the ICU over a 1-year period were screened for infection at ICU admission and daily throughout the ICU stay. Outcomes at ICU and hospital discharge were recorded. *Measurements and results:* Post-ICU death occurred in 195 (10.4%) patients and was associated in the multivariable analysis with age, chronic respiratory failure, immunosuppression, cirrhosis, Simplified Acute Physiology Score II on the first day with infection, and LOD score at ICU discharge. Post-ICU death was more common among medical patients and patients with hospital-acquired infection or microbiologically documented infection and was less common in patients with pneumonia. *Conclusions:* Post-ICU death in patients with infection was within previously reported ranges in overall ICU populations. The main risk factors were patient and infection characteristics, severity at ICU admission, and persistent organ dysfunction at ICU discharge. Further interventions such as further ICU management, discharge to a step-down unit, or follow-up by intensivists on the ward should be evaluated in patients with a high risk of post-ICU mortality

Keywords Sepsis · Infection · Post-ICU mortality · Intensive care · Outcome · Multicenter

Introduction

Sepsis is a major challenge. Hospital mortality in patients with sepsis has ranged from 25% to 80% over the past few decades [1]. Although there is considerable heterogeneity in the epidemiology of sepsis [2], previous studies suggest that both the incidence of and mortality from sepsis may be diminishing [3]. However, severe sepsis remains a common reason for intensive care unit (ICU) admission with a high mortality rate and high management costs [4, 5]. Considerable effort has been expended to elucidate the pathophysiology of the systemic inflammation and multiorgan failure characteristic of severe sepsis [6]. Risk factors for death include severe physiological derangement, organ dysfunction, underlying illness, site of infection, and causative organism [2, 7]. Although massive resources have been invested in developing and evaluating potential treatments and strategies, there have been few successes [8, 9, 10] and many failures [11, 12].

After hospital discharge ICU patients have a fivefold higher risk of death than the general population [13]. Recent guidelines stress the importance of capturing long-

term survival and quality-adjusted survival [14]. However, the hospital stay following discharge from the ICU also contributes to mortality, with wide variations across studies, from 6.1% to 27% [15, 16, 17]. Post-ICU in-hospital mortality (PIIHM) can be related to factors occurring before [18], during [17], or after [19, 20] the ICU stay. Goldfrad and Rowan [21] recently found that in-hospital mortality was higher among patients discharged from the ICU at night. Moreover, Daly et al. [22] suggested that keeping at-risk patients in the ICU for another 48 h might reduce PIIHM after ICU discharge by 39%. No studies specifically designed to investigate the characteristics of PIIHM in critically ill patients with infection have been published.

Infected patients are at higher risk of ICU mortality than ICU patients overall [4, 5]. Whether there is a similar difference regarding mortality on the ward after ICU discharge is unknown. We investigated risk factors for PIIMH in patients with infection from a large prospective cohort of unselected consecutive adults admitted to ICUs in Europe, Canada, and Israel between May 1997 and May 1998.

Patients and methods

Eligibility criteria

This prospective cohort study was conducted over a 1-year period in 28 ICUs in six European countries, Canada, and Israel (see Electronic Supplementary Material). Of these ICUs 25 (89%) were in teaching hospitals. The median number of beds was 632 per hospital (5th–95th percentiles, 450–1660) and 14 per ICU (6–28). There were 2 (7.1%) surgical units, 8 (28.6%) medical units, and 18 (64.3%) mixed units. Five units incompletely recorded hospital vital status and were excluded from the present analysis (one in Canada, two in Italy, one in Portugal, one in Spain). All 14,364 adults (age $\geq$18 years) consecutively admitted to the participating ICUs between 1 May 1997 and 30 April 1998 were entered into a database. Tables 1, 2, 3 report characteristics of the patients, ICU admissions, and infections; overall, there were 1,171 men (63%), median age was 60 years (range 43–71), and median Simplified Acute Physiology Score (SAPS) II on the first day of infection was 35 (range 26–44). Among these patients there were 2,984 with either clinically diagnosed or microbiologically documented infection. These were included in the study regardless of the severity of their infection [4] provided they had a ICU follow-up of 28 days or less after the onset of infection and were discharged alive from the ICU and followed until their discharge from the hospital. The final series for the present analysis thus included 1,872 patients. Among these, 195 (10.4%) died on the ward. To test the hypothesis that residual organ dysfunction at ICU discharge negatively influences hospital survival, organ dysfunctions were recorded daily in the ICU. If a patient was admitted more than once, only the data from the first admission were analyzed.

Data collection and definitions

In each participating ICU a single trained data collector recorded the data using standardized forms and dedicated database software derived from FoxPro (Microsoft Visual FoxPro 5.0, 1995). The data collector was a physician in 22 ICUs and a research nurse in 6 ICUs. For each patient the data collectors obtained and recorded data prospectively both by interviewing the physician in charge of the patient and by reviewing the medical charts. For all the study variables detailed definitions were provided in an operating manual.

The study variables are reported in Tables 1, 2, and 3. Comorbidities were recorded using the definitions included in the SAPS II [23] and the Acute Physiology and Chronic Health Evaluation II (APACHE II) [24]. Immunocompromised status included AIDS, cancer, bone marrow transplantation, and hematological malignancy. For computing SAPS II and LOD scores unavailable clinical and laboratory data were assigned zero values [23, 25]. Use at any time during the ICU stay of isotropic or vasopressor agents, ventilatory assistance, and renal replacement therapy were recorded.

Infection was defined as a suggestive clinical history, clinical symptoms, physical findings, and laboratory findings (a known or strongly suspected source of infection with positive cultures for a pathogen or gross pus in a closed space) that led to anti-infective treatment (excluding prophylaxis). Infections were categorized as clinically diagnosed or microbiologically documented and as community, hospital, or ICU acquired; they were also characterized according to the anatomical site or sites involved and to the causative micro-organism(s) [4]. Definitions of infection were those from the Centers for Disease Control [26].

Microbiologically documented infection was defined as infection confirmed by positive cultures of blood or samples from a site of suspected infection. Clinical infection was presence of gross pus or abscess formation (anatomical and/or by imagery and/or by histology) with negative microbiological studies. Community-acquired infection was defined as infection present at or within 48 h after hospital admission and hospital-acquired infection as infection developing 48 h or more after admission or in relation to a medical or surgical procedure. ICU-acquired infection was infection developing 48 h or more after ICU admission or related to a medical or surgical procedure performed during the ICU stay. When a patient experienced more than one episode of ICU-acquired infection, only the first episode was used in the analysis.

Follow-up and outcome variable of interest

Outcomes at hospital discharge were recorded. PIIHM was defined as mortality on the ward after ICU discharge. Median hospital length of stay calculated from ICU discharge to hospital discharge was 13 days [interquartile range 6–23, range 1–220]. Some patients remained in hospital for a long period or time (>3 months).

Quality of the data

Reliability checks, data audit, a hotline for queries and management of problems, and resolution of missing data and inconsistencies were performed as previously reported [4].

Statistical analysis

Categorical data are expressed as numbers and percentages and continuous data as medians and 25th–75th percentiles. Logistic regression was used to examine for independent predictors of PIIHM. First, univariate logistic regression was performed. Then variables for the multivariable logistic regression model were selected using bootstrapping, which involved analyzing a large number (500 independent replicates) of subsamples with replacement from the full sample followed by application of a stepwise logistic model to each sample with a backward-forward selection

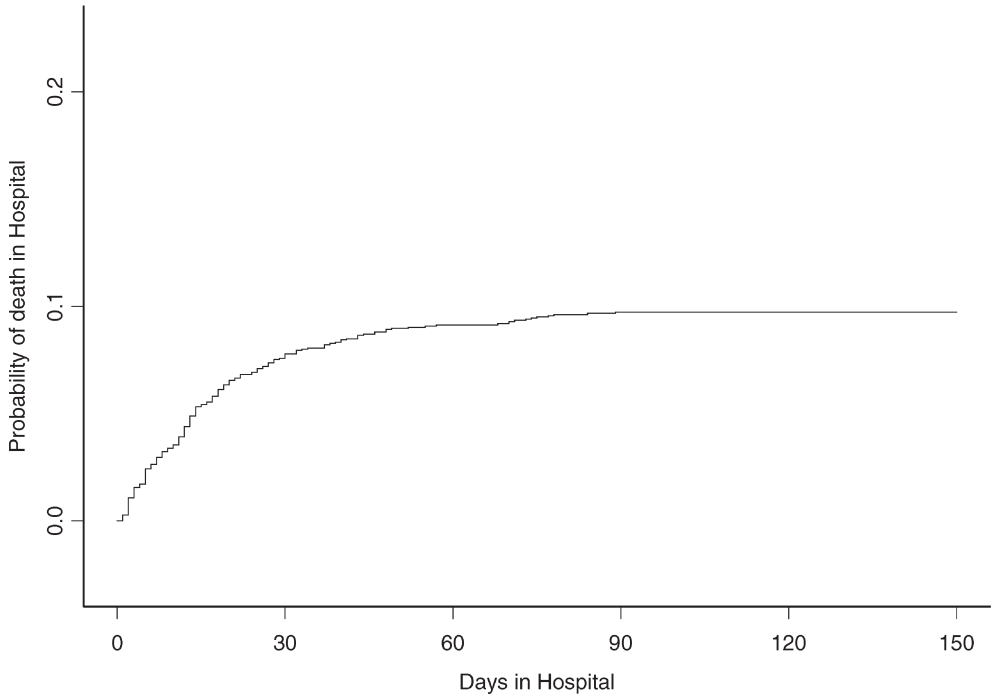

Fig. 1 Cumulative incidence of death after ICU discharge

procedure at the 0.05 level. Covariates that were selected in more than 60% of the 500 samples were included in the final set of covariates and were fitted together [27]. We considered p values less than 0.05 statistically significant. The absence of a significant increase in the likelihood value upon omission of each of the remaining variables was checked. The results are expressed as the odds ratios with their 95% confidence intervals.

To determine homogeneous subgroups of PIIHM risk (i.e., low-risk <5% or high-risk >30%), we performed classification and regression tree (CART) analysis with variables identified as prognostic factors at the last step of the logistic regression analysis [28]. The first step consists in creating a model (building the tree) that includes all the variables (full model). In the second step the tree is pruned to a simpler tree that fits the information. The main advantage of CART is that no assumptions are made regarding the underlying distribution of values of the predictor variables. All statistical tests were two-tailed. CIs are presented with a 5% risk of type I error. Statistical analysis was performed using SAS 8.02 (SAS, Cary, N.C., USA) and S-plus 2000 (MathSoft, Seattle, Wash., USA) software packages for PCs.

Results

Figure 1 presents data on the cumulative incidence of death. Most deaths occurred during the first month after ICU discharge; some patients remained in hospital for a long period or time (>3 months). As shown in Tables 1, 2, and 3, several variables differed significantly between the patients who died after ICU discharge on the ward and those who were discharged alive from the hospital. Using bootstrap selection of these variables, we first introduced in the model those variables significantly associated with PIIHM in at least 60% of the selected samples. This identified ten variables independently associated with PIIHM by multivariable analysis (Table 4). Nine variables were associated with higher PIIHM: older age, immunocompromised status, cirrhosis, chronic respiratory failure, nonsurgical status, more severe disease (SAPS II) on the day of infection onset, more severe organ dysfunction (LOD score) on the day of ICU discharge, hospital-acquired infection, and microbiologically documented infection. The only protective variable was pulmonary infection compared to infection at other sites. Duration of mechanical ventilation, renal replacement therapy, and use of inotropic agents/vasopressors were not independently associated with PIIHM.

The final CART analysis (Fig. 2) used five of the ten predictors (LOD at ICU discharge, age, SAPS II at infection onset, origin of infection and immunosuppression). It successfully classified 91% of the patients. For each branch the mortality rate and the number of patients (in parentheses) are reported. The tree selected LOD at ICU discharge as the first variable, and the best split was a value of 4 which identified the patients with the highest PIIHM (threefold the overall value) as those who were also older than 50 years of age, had a SAPS II at onset of infection equal to or than 69 and a hospital-acquired infection. Hospital mortality of 56% was observed in the oldest and the most severely ill patients at onset of infection in ICU. The branch for LOD$\leq$4 indicated the patients with the lowest PIIHM (tenfold less than overall) as those who either had an SAPS II at infection onset no greater than 27 or a SAPS II at infection onset greater

Table 1 Patient characteristics, associated Post-ICU in-hospital mortality frequencies and risk factors of PIIHM (bivariate logistic regression): qualitative variables. Odds ratio computed by bivariate logistic regression; 95% confidence interval calculated by bivariate logistic regression

	All patients (*n*=1,872)		Survivors on the ward (*n*=1,677, 89.6%)		Odds ratio	95% confidence interval	*p*
	n	%	*n*	%			
Sex							
Male	1,171	62.6	1,047	10.6	1	–	
Female	701	37.4	630	10.1	0.95	0.70–1.30	0.75
Admission categories							
Scheduled surgery	219	11.7	201	8.2	1	–	–
Medical	1,180	63.0	1,047	11.3	1.42	0.85–2.37	0.18
Emergent surgery	333	17.8	294	11.7	1.48	0.82–2.66	0.19
Trauma	140	7.5	135	3.6	0.41	0.15–1.14	0.09
Comorbidities							
Chronic respiratory failure	98	5.2	81	17.4	1.88	1.09–3.25	0.02
Chronic heart failure	168	9.0	137	18.5	2.12	1.39–3.24	0.0005
Chronic renal failure	167	8.9	130	22.2	2.79	1.87–4.16	<0.0001
Cirrhosis	96	5.1	77	19.8	2.24	1.33–3.80	0.003
Immunosuppression	471	25.2	396	15.9	2.02	1.48–2.76	<0.0001
Chronic obstructive pulmonary disease	334	17.8	291	12.9	1.35	0.94–1.93	0.11
McCabe score							
1	1,267	67.7	1,165	8.1	1	–	–
2	496	26.5	427	13.9	1.85	1.33–2.55	0.0002
3	109	5.8	85	22.0	3.23	1.96–5.30	<0.0001
Reason for ICU admission							
Coma	184	9.8	166	9.7	0.93	0.56–1.54	0.77
Respiratory failure	804	42.9	720	10.5	1.01	0.75–1.36	0.97
Renal failure	133	7.1	109	18.0	2.02	1.26–3.23	0.003
Shock	378	20.2	327	13.5	1.46	1.04–2.06	0.03
Transfer from another hospital	329	17.6	302	8.2	0.73	0.48–1.12	0.15
ICU discharge on the weekend	471	25.2	430	8.7	0.77	0.54–1.11	0.16
Inotropic or vasopressor treatment	710	37.9	610	14.1	1.84	1.37–2.48	<0.0001
Ventilatory assistance (invasive or noninvasive)	1,366	73.0	1,213	11.2	1.39	0.97–1.99	0.07
Renal replacement therapy	206	11.0	177	14.1	1.48	0.97–2.26	0.07

Table 2 Patient characteristics, associated Post-ICU in-hospital mortality frequencies and risk factors of PIIHM (bivariate logistic regression): quantitative variables (*IQR* interquartile range)

	Survived (*n*=1,677)		Died on the ward (*n*=195)		*p*
	Median	IQR	Median	IQR	
Age	60	43–71	67	56–75	<0.0001
SAPS II on the first day of infection	35	26–44	42	35–53	<0.0001
Length of ICU stay (days) from first day of infection	8	4–14	9	5–16	0.05
LOD at ICU discharge	2	1–4	4	2–6	<0.0001

than 27 but without immunodepression and with an age of 50 years or younger.

Discussion

This is the first international study focusing specifically on in-hospital death after ICU discharge of patients with infection. There are two major findings. First, PIIHM in patients treated for infection while in the ICU was within the ranges of PIIHM reported in overall ICU populations [15, 17, 29, 30, 31], but persistent organ dysfunction at ICU discharge was closely associated with PIIHM. Second, risk factors for PIIHM were similar to those reported previously for long-term mortality. The data from this study should help intensivists identify patients with infection who are at highest risk for PIIHM, and who consequently may be more likely to benefit from preventive strategies such as further ICU treatment, discharge to a step-down unit, or follow-up on the ward by the ICU team.

ICU mortality is higher in patients with infection than in other patients [4, 5, 32]. Our data suggest that this difference does not extend to the stay on the ward after

Table 3 Characteristics of infections, associated post-ICU in-hospital mortality (*PIIHM*) frequencies and risk factors of PIIHM (univariate logistic regression). Primary bacteremia include catheter-related infections and endocarditis; other sites include neurological, ears, nose, and throat (sinusitis, epiglottitis, otitis, tracheitis), thoracic, genital tract, skin and soft tissue, and bone and joint. Odds ratio computed by univariate logistic regression; 95% confidence interval calculated by bivariate logistic regression. Some patients had infection at more than one site, and at more than one organism

	All patients (*n*=1,872)		Survivors on the ward (*n*=1,677)		Dead on the ward (*n*=195)		Odds ratio	95% confidence interval	*P*
	n	%	*n*	%	*n*	%			
Origin of infection									
Community-acquired	946	50.5	875	92.5	71	7.5	1	–	–
Hospital-acquired	593	31.7	502	84.7	91	15.6	2.23	1.61–3.11	<0.0001
ICU-acquired	333	17.8	298	89.5	35	9.8	1.36	0.88–2.09	0.17
Documentation of infection									
Microbiologically documented	1,184	63.3	1,038	87.7	146	12.3	1.83	1.31–2.57	0.0004
Clinical	688	36.8	639	92.9	49	7.1	1	–	–
Site of infection									
Pulmonary	1,133	60.5	1,031	91.0	102	9.0	0.69	0.51–0.93	0.01
Gastrointestinal	236	12.6	206	87.3	30	12.7	1.30	0.86–1.97	0.22
Urinary tract	196	10.5	172	87.8	24	12.2	1.23	0.77–1.94	0.38
Primary bacteremia	198	10.6	167	84.3	31	15.7	1.71	1.13–2.59	0.01
Unknown	40	2.1	37	92.5	3	7.5	0.69	0.21–2.27	0.54
Other	306	16.4	275	89.9	31	10.1	0.96	0.64–1.44	0.86
Micro-organisms									
Staphylococcus aureus	229	12.2	198	86.5	31	13.5	1.41	0.94–2.13	0.10
Gram-positive cocci other	392	20.9	347	88.5	45	11.5	1.15	0.81–1.64	0.44
Aerobic Gram-negative bacilli	208	11.1	180	86.5	28	13.5	1.39	0.91–2.14	0.12
Candida and fungi	108	5.7	91	84.3	17	15.7	1.66	0.97–2.86	0.06
Enterobacteriaceae	515	27.5	456	88.5	59	11.5	1.16	0.84–1.61	0.36

Table 4 Results of the multivariable analysis (selection of variables by bootstrapping)

	Adjusted odds ratio	95% confidence interval	*p*
Age (per year)	1.02	1.01–1.03	0.0007
Immunosuppression	1.82	1.28–2.58	0.0008
Cirrhosis	1.75	1.00–3.11	0.05
Chronic respiratory failure	2.18	1.20–3.93	0.01
Admission categories			
Scheduled surgery	1	–	
Medical	1.81	1.03–3.19	0.04
Emergent surgery	1.56	0.83–2.94	0.17
Trauma	0.85	0.29–2.48	0.77
SAPS II on the first day of infection (per additional 10 points)	1.16	1.02–1.31	0.02
LOD at ICU discharge (per point)	1.26	1.18–1.34	<0.0001
Origin of infection			
Community-acquired	1		
Hospital-acquired	1.65	1.14–2.37	0.007
ICU-acquired	1.51	0.92–2.47	0.10
Respiratory infection	0.72	0.52–1.00	0.05
Microbiologically documented infection	1.70	1.17–2.47	0.006

ICU discharge. PIIHM was 10.4% in our study of patients with infection while in the ICU, which is within the PIIHM values in studies of overall ICU populations [15, 17, 29, 30, 31].

Mechanical ventilation, renal replacement therapy, and use of inotropic agents/vasopressors were not independently associated with PIIHM. Nevertheless, the LOD score at ICU discharge independently predicted PIIHM. A LOD score greater than 4, although implying a wide difference from a clinical point of view, discriminated between patients with and without PIIHM. However, the range of LOD scores at ICU discharge indicated that some patients were still critically ill and may have been discharged as an end-of-life decision [17, 33]. For instance, a switch to less aggressive treatment and ICU discharge may have been decided because acute organ dysfunctions had become chronic, indicating failure of ICU management or terminal disease [2]. In keeping with this possibility, PIIHM was higher in older patients and in those with severe comorbidities or with a poor chronic health

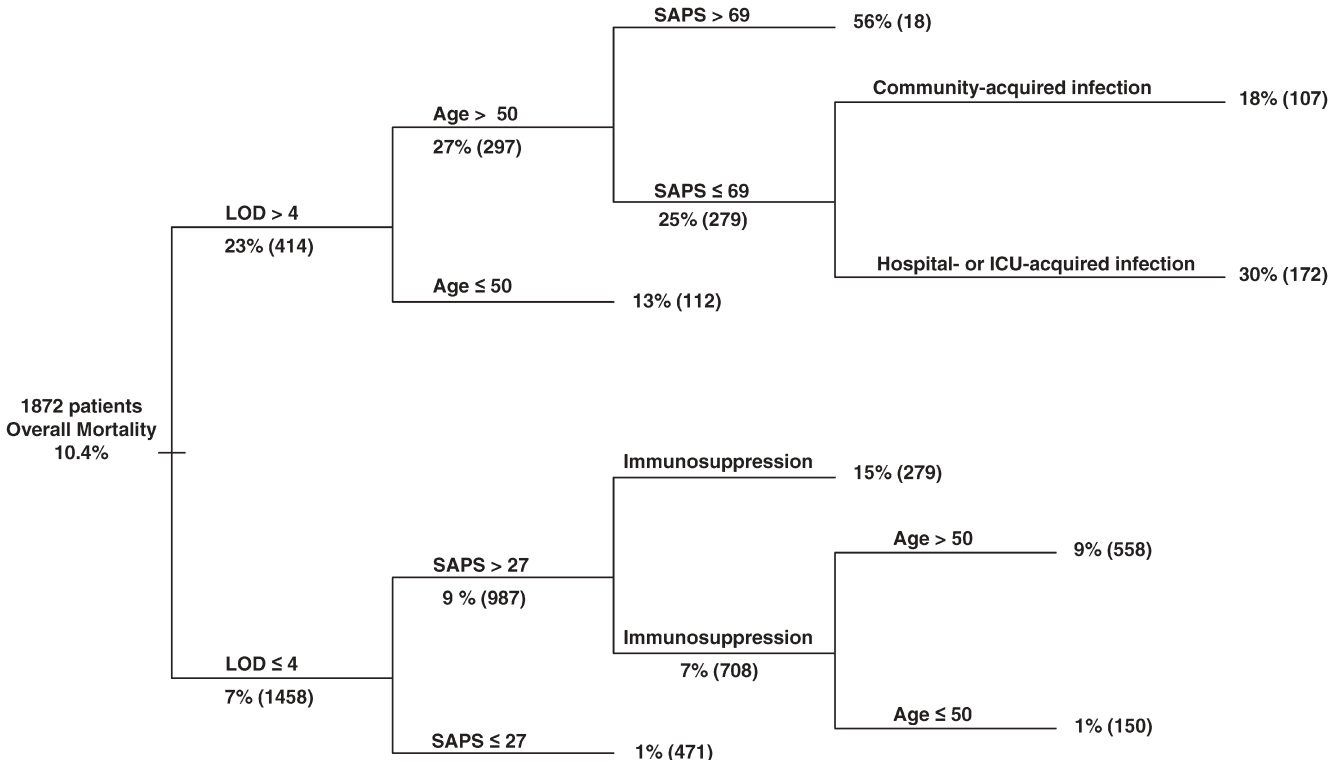

Fig. 2 Classification and regression tree analysis of PIIHM prognostic factors

status, as indicated by the McCabe scale. We have no evidence that any of the participating ICUs discharged patients prematurely to make room for other patients or discharged their patients from the ICU inappropriately, i.e., too early, at night, or on the weekend. However, the variable "discharged on the week-end" was not identified as a risk factor for PIIHM.

Risk factors for PIIHM in our study were similar to those previously reported to affect long-term mortality after ICU discharge, i.e., age, severe comorbidities (immunodepression, cirrhosis, and chronic respiratory failure), SAPS II on the day of infection, and LOD score on the day of ICU discharge. Previous research showed that severe underlying disease and preexisting organ dysfunction were associated with 28-day PIIHM in 1,052 patients meeting criteria for severe sepsis [34]. Similarly, Perl et al. [35] found that 6-month mortality was influenced by the severity of underlying illness and number of active comorbidities. In another study acute physiological derangement remained strongly associated with mortality up to 1 month after hospital discharge but was not predictive of 3-month mortality, in contrast to severe comorbidities [36]. Infection-related variables associated with PIIHM in our study, namely microbiological documentation and acquisition in the hospital, are related to disease severity and extent of organ dysfunction [4]. The absence of ICU-acquired infection among risk factors for PIIHM may be due to limited of statistical power or to death of a large majority of these patients in the ICU. Because the value of the sepsis classification has been challenged [4], we focused on infection itself. Our finding that older patients (surprisingly, starting at only 50 years of age) and those with comorbidities had higher PIIHM rates suggests that PIIHM may increase in the near future as ICUs increasingly provide care to the oldest and sickest members of the community [37].

None of the risk factors for PIIHM identified in this study are amenable to modification, with the possible exception of acute organ dysfunction severity at ICU discharge, for which further ICU management might improve the post-ICU outcome. Daly et al. [22] suggested that PIIHM in high-risk patients could be reduced by 39% by prolonging the ICU stay by 48 h. However, we do not know the proportion of patients who were discharged from the ICU as an end-of-life decision, i.e., who were expected to die on the ward. Without this information we cannot conclude from our data that further ICU management to improve organ dysfunction before ICU discharge would decrease PIIHM [17]. Thus our data are useful mainly for identifying patients at higher risk of death after ICU discharge.

A limitation of the study is the exclusion of patients who stayed in the ICU more than 28 days after onset of their infection. However, these patients had more severe

disease at infection onset, suggesting that their longer ICU stay reflected a need for longer treatment to improve their organ dysfunctions. Their PIIHM rate was 15%, slightly higher than in the study patients, so that inclusion of these patients would probably have provided further support for the prognostic value of LOD at ICU discharge. The CART analysis has also some limitations. It requires the absence of correlation among independent variables and the multiplicative or additive role of the variables on the response variable. However, the variables selected by the CART analysis are these independently associated with PIIHM in multivariable logistic regression. Moreover, we did not use Bonferroni's reduction for multiple testing.

In conclusion, our study provides useful data for identifying patients at high risk for PIIHM. These patients may be particularly likely to benefit from careful timing of ICU discharge, discharge to step-down units, follow-up by the ICU team on the ward, and efforts to improve communication with the team on the ward. Studies are needed to determine whether these strategies reduce PIIHM in patients with infection.

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