# Incidence and prognosis of early hepatic dysfunction in critically ill patients—A prospective multicenter study

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***Objective:*** **In critically ill patients, hepatic dysfunction is regarded as a late organ failure associated with poor prognosis. We investigated the incidence and prognostic implications of early hepatic dysfunction (serum bilirubin >2 mg/dL within 48 hrs of admission).**

***Design:*** **Prospective, multicenter cohort study.**

***Setting:*** **Thirty-two medical, surgical, and mixed intensive care units.**

***Patients:*** **A total of 38,036 adult patients admitted consecutively over a period of 4 yrs.**

***Interventions:*** **None.**

***Measurements and Main Results:*** **Excluding patients with preexisting cirrhosis (n = 691; 1.8%) and acute or acute-on-chronic hepatic failure (n = 108, 0.3%), we identified 4,146 patients (10.9%) with early hepatic dysfunction. These patients had different baseline characteristics, longer median intensive care unit stays (5 vs. 3 days; $p < .001$) and increased hospital mortality (30.4% vs. 16.4%; $p < .001$). Hepatic dysfunction was also associated with higher observed-to-expected mortality ratios (1.02 vs. 0.91; $p < .001$). Multiple logistic regression analysis showed an independent mortality risk of hepatic dysfunction (odds ratio, 1.86; 95% confidence interval, 1.71–2.03; $p < .001$), which exceeded the impact of all other organ dysfunctions. A case-control study further confirmed these results: Patients with early hepatic dysfunction exhibited significantly increased raw and risk-adjusted mortality compared with control subjects.**

***Conclusions:*** **Our results provide strong evidence that early hepatic dysfunction, occurring in 11% of critically ill patients, presents a specific and independent risk factor for poor prognosis. (Crit Care Med 2007; 35:1099–1104)**

**Key Words: hepatic failure; liver; outcome; bilirubin; epidemiology**

Hepatic dysfunction is traditionally considered to indicate poor outcome in critically ill patients, but no large systematic investigation into its exact incidence and prognostic relevance has been performed (1). Since no physiologic variable allows for early detection of hepatic dysfunction, current diagnostic criteria are based on laboratory tests, mostly serum bilirubin levels (for review, see Ref. 2). Although some authors have used more specific definitions, such as hepatic encephalopathy, ascites (3), or elevated serum activity of aspartate aminotransferase or alkaline phosphatase (4, 5), such variability in definitions has precluded an accurate overall assessment of hepatic dysfunction in critically ill patients.

Unlike ascites, transaminases, or alkaline phosphatase activity, serum bilirubin is a stable and powerful marker of hepatic dysfunction, with elevated levels reflecting impairment in the energy-consuming processes of heme metabolism, conjugation, and bile secretion (6). Serum bilirubin is a key component of prognostic scores for patients with chronic liver disease (7) and cirrhosis (8) (including the Child-Pugh classification and the Model for End-Stage Liver Disease score) and also of prognostic models in patients with acute liver failure (9). Bilirubin levels are also used in scoring algorithms for assessing prognosis in critically ill patients (for review, see Ref. 10). Since clinical jaundice tends to develop only several days after hepatic injury ensues, hepatic dysfunction is traditionally considered a late event in sepsis and multiorgan failure (11). Only comparatively small studies have specifically investigated hepatic dysfunction (12).

Considering the pivotal and possibly underappreciated role of the liver in the pathogenesis of systemic inflammatory response syndrome, sepsis, and multiorgan failure (13), we hypothesized that early hepatic dysfunction, in the absence of preexisting liver disease, independently increases mortality in critically ill patients. To test this hypothesis, we analyzed a large prospective database of patients admitted to Austrian multidisciplinary intensive care units (ICUs) between 1999 and 2003. The study protocol was approved by institutional review. Since no additional interventions were performed and no individualized data were analyzed, the need for individual informed consent was waived.

## MATERIALS AND METHODS

*Database.* Data were collected by the Austrian Center for Documentation and Quality Assurance in Intensive Care Medicine (ASDI), a nonprofit organization that has established an intensive care database and benchmarking project (14, 15). The prospectively collected data included sociodemographic data, such as age,

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Supported, in part, by a grant for statistical analysis from the Fund of the Austrian National Bank, project 10995 ONB.

The authors have not disclosed any potential conflicts of interest.



**DOI: 10.1097/01.CCM.0000259462.97164.A0**

gender, and comorbid conditions; causes of ICU admission according to a predefined list of medical and surgical diagnoses (16); severity of illness, as measured by the Simplified Acute Physiology Score (SAPS) II (17); numbers and severity of organ dysfunction, as measured by the Logistic Organ Dysfunction system (LOD) (18); level of provided care, as measured by the Simplified Therapeutic Intervention Scoring System-28 (19); length of ICU and hospital stay; and outcome data, including survival status at ICU and hospital discharge.

A total of 42,394 patients were admitted to the 32 ICUs during the study period. For patients who were admitted more than once (n = 1,923), only the first admission was evaluated. Patients who were <18 yrs of age (n = 774), those with records that lacked an entry in the field "hospital outcome" (n = 460), and those without a valid SAPS II score (n = 1,201) were excluded, leaving 38,036 patients for analysis (Fig. 1).

*Data Quality.* To assess the reliability of data collection, we sent an independent observer to each unit to obtain SAPS II data from the clinical charts of a random sample of patients. Variance-component analyses with the random factors "units," "patients within units," and "observers within units" were performed (SAS, procedure varcomp) as previously described (14). To assess completeness of documentation, we also calculated the number of missing variables for the SAPS II score. Additional details have been reported elsewhere (14).

*Statistical Analysis.* Statistical analysis was performed using SAS software, version 9.1 (SAS Institute, Cary, NC). Unless otherwise specified, descriptive results are expressed as median and first and third quartiles. Student's *t*-test or Wilcoxon's rank-sum test if appropriate was used to compare quantitative variables between groups. The chi-square test was used for categorical variables. A $p$ value of <.05 (two-sided) was considered significant. Observed-to-expected mortality ratios were calculated by dividing the number of observed deaths per group by the number of SAPS II-predicted deaths per group. Ninety-five percent confidence intervals were calculated according to Hosmer and Lemeshow (20).

Two logistic regression models were constructed to explore the influence of several static and dynamic variables on vital status at hospital discharge (hospital mortality) as the dependent variable. Univariate analysis was performed using Student's *t*-tests for continuous variables and chi-square for categorical variables to assess those related to mortality. A set of predefined variables affecting ICU mortality were entered into the logistic regression models. Moreover, ICU was added as a dummy variable to adjust for the effect of different treatment centers. From univariate analysis, age, gender, diagnosis, organ failure scores, and bilirubin values >2 mg/dL within 48 hrs of admission (indicating early hepatic dysfunction) were entered as dummy variables. A second model was constructed in a similar way, but instead of the dummy variable, abnormal serum bilirubin values were entered as 6 different strata (mg/dL): 0–1 (reference level), >1–2, >2–3, >3–6, >6–10, and >10.

To test the validity of the findings from the logistic regression analysis, we further investigated independent associations between early hepatic failure and mortality using a case-control design. After patients with preexisting cirrhosis or acute hepatic failure—which are known to have increased mortality—had been excluded from the population of patients with bilirubin >2 mg/dL, patients with early hepatic dysfunction were identified (n = 4,146). For each of these patients, a control patient was chosen, using gender, age (±5 yrs), and bilirubin-corrected SAPS II scores (calculated as original SAPS II score minus the allocated bilirubin points) as matching criteria. Matching controls were found for all but eight patients. ICU was used as an additional matching criterion to minimize the influence of ICU-specific factors on prognosis. Matching controls from the same ICU were found for 3,942 patients. Conditional logistic regression was then performed to show the influence of early hepatic dysfunction on mortality.

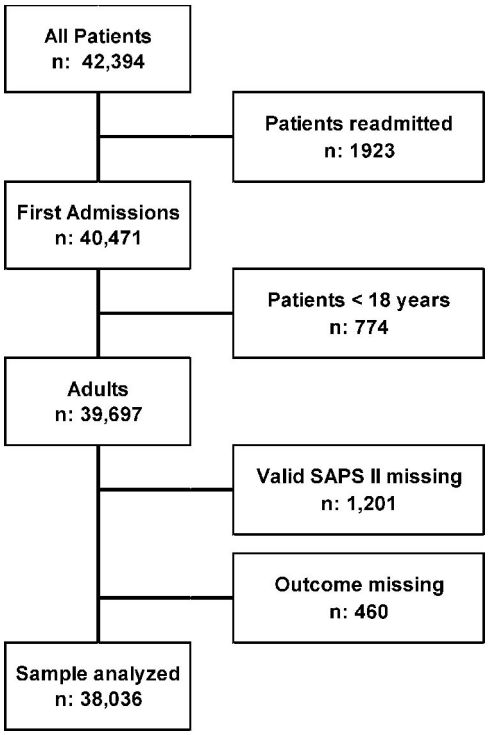


**Figure 1.** Study flowchart. *SAPS,* Simplified Acute Physiology Score.

## RESULTS

A total of 38,036 consecutive ICU admissions were included in the cohort (Table 1). Data quality was satisfactory with respect to both completeness of records and interrater variability. The median number of missing variables necessary for the calculation of the SAPS II was 0 (interquartile range, 0–2). Interrater quality control indicated an excellent grade of agreement: For all tested variables, practically no deviations between the observers were detected, the contribution to the variability being <1%.

Types of ICU admission were medical and neurologic disorders in 16,879 patients, elective surgery procedures in 12,498, and emergency surgery in 8,559. One hundred patients (0.3%) were not classified for admission type. Preexisting cirrhosis was present in 691 patients (1.8%), and 108 patients (0.3%) were admitted with either acute (n = 40) or acute-on-chronic hepatic failure (n = 68). After both groups were excluded, 4,146 patients (10.9%) with early hepatic dysfunction (serum bilirubin >2 mg/dL within 48 hrs of admission) were identified. Patients with early hepatic dysfunction differed from other patients in most baseline characteristics and were more likely to be admitted after surgery, in particular emergency surgery. They showed an increased severity of illness, a higher level of treatment, and an increased length of stay in the ICU (Table 1). Both raw and risk-adjusted hospital mortality rates were significantly higher in patients with early hepatic dysfunction compared with patients without early hepatic dysfunction.

**Table 1.** Characteristics of patients with and without early hepatic dysfunction

| Group | Early Hepatic Dysfunction | No Early Hepatic Dysfunction | *p* Value |
|---|---|---|---|
| Patients analyzed | 4,146 | 33,890 | |
| Age, yrs, mean ± SD | 62.9 ± 16.5 | 62.4 ± 17.1 | .08 |
| Types of ICU admission, % | | | <.001 |
| Medical | 30.2 | 46.1 | |
| Surgery—elective | 35.7 | 32.5 | |
| Surgery—emergency | 33.8 | 21.1 | |
| Length of ICU stay, days, median (quartiles) | 5 (3–12) | 3 (2–6) | <.001 |
| Number of organ failures, median (quartiles) | 3 (3–4) | 2 (1–3) | <.001 |
| TISS-28 score per patient per day, median (quartiles) | 34.5 (29–40) | 27.5 (20–34) | <.001 |
| SAPS II score, median (quartiles) | 36 (26–50) | 26 (18–38) | <.001 |
| SAPS II predicted mortality, % | 29.8 | 17.9 | <.001 |
| Observed ICU mortality, % | 23.4 | 11.4 | <.001 |
| Observed hospital mortality, % | 30.4 | 16.4 | <.001 |

ICU, intensive care unit; TISS, Therapeutic Intervention Scoring System; SAPS, Simplified Acute Physiology Score.

**Table 2.** Logistic regression model A: Impact of early hepatic dysfunction on mortality[a]

| Effect | Estimate | Odds Ratio | 95% Confidence Interval | *p* Value |
|---|---|---|---|---|
| Age | 0.036 | 1.036 | 1.034–1.039 | <.0001 |
| Male gender | 0.085 | 1.089 | 1.018–1.165 | .0131 |
| ICU code | | | | <.0001 |
| Diagnosis | | | | <.001 |
| Organ dysfunction | | | | |
| Hematologic | 0.182 | 1.199 | 1.097–1.311 | <.0001 |
| Renal | 0.341 | 1.406 | 1.372–1.441 | <.0001 |
| Neurologic | 0.386 | 1.470 | 1.441–1.500 | <.0001 |
| Respiratory | 0.393 | 1.481 | 1.434–1.530 | <.0001 |
| Cardiovascular | 0.465 | 1.591 | 1.533–1.653 | <.0001 |
| Hepatic | 0.622 | 1.863 | 1.707–2.034 | <.0001 |

ICU, intensive care unit.

[a]Area under the receiver operating characteristic curve, 0.865; $R^2$, .2473; maximum rescaled $R^2$, .4057.

**Table 3.** Logistic regression model B: Impact of early hepatic dysfunction within the strata of serum bilirubin levels on mortality[a]

| Effect | Estimate | Odds Ratio | 95% Confidence Interval | *p* Value |
|---|---|---|---|---|
| Age | 0.036 | 1.037 | 1.034–1.039 | <.0001 |
| Male gender | 0.078 | 1.081 | 1.010–1.157 | .0237 |
| ICU code | | | | <.0001 |
| Diagnosis | | | | <.0001 |
| Organ dysfunction | | | | |
| Renal | 0.336 | 1.400 | 1.366–1.435 | <.0001 |
| Neurologic | 0.385 | 1.469 | 1.440–1.499 | <.0001 |
| Cardiovascular | 0.467 | 1.595 | 1.536–1.657 | <.0001 |
| Respiratory | 0.390 | 1.477 | 1.429–1.526 | <.0001 |
| Hematologic | 0.168 | 1.183 | 1.082–1.293 | .0002 |
| Bilirubin groups | | | | |
| >1–2 | 0.215 | 1.240 | 1.143–1.345 | <.0001 |
| >2–3 | 0.401 | 1.494 | 1.314–1.699 | <.0001 |
| >3–6 | 0.801 | 2.228 | 1.945–2.553 | <.0001 |
| >6–10 | 0.957 | 2.604 | 2.097–3.234 | <.0001 |
| >10 | 1.384 | 3.991 | 3.105–5.130 | <.0001 |

ICU, intensive care unit.

[a]Area under the receiver operating characteristic curve, 0.865; $R^2$, .2473; maximum rescaled $R^2$, .4057.

Model A of the logistic regression demonstrated that effects of early hepatic dysfunction independently increased mortality (odds ratio, 1.863; 95% confidence interval, 1.707–2.034, $p < .001$) and exceeded the mortality effects of all single extrahepatic organ dysfunctions (Table 2). As demonstrated in the logistic regression model B, risk-adjusted mortality rates increased ($p < .001$) with increasing levels of serum bilirubin, even after adjustment for the severity of illness and different ICUs (Table 3, Fig. 2). The size of the different bilirubin strata and their relationship to crude hospital mortality are shown in Table 4, demonstrating that even a slight increase in bilirubin was associated with a marked reduction of survival. Inclusion of admission type did not improve the overall fit of the model (data not shown).

To further test the validity of our findings and explore the influence of early hepatic dysfunction on hospital mortality, we performed a case-control study using a matching algorithm as detailed previously. Patients developing early hepatic dysfunction were more severely ill (Table E1, electronic data supplement) and differed with respect to the reasons for admission (Table E2, electronic data supplement) and comorbid conditions (Table E3, electronic data supplement). Confirming results from the cohort study, conditional logistic regression analysis in the case-control study matched for age, gender, treatment center effects, and severity of illness showed a relative mortality risk of 1.65 (95% confidence interval, 1.46–1.86) in patients with early hepatic dysfunction.

## DISCUSSION

In this large cohort study, early hepatic dysfunction occurred in 11% of critically ill patients and was a strong predictor of in-hospital death. Both logistic regression and conditional logistic regression using a case-control design demonstrated independent and substantial effects of early hepatic dysfunction on mortality that exceeded those of traditional predictors of death, including circulatory, renal, and central nervous system dysfunction. Consequently, early hepatic dysfunction should be recognized as a major independent prognostic factor in critically ill patients.

Our results confirm those of smaller studies reporting worse survival for several groups of critically ill patients with impaired hepatic function. A recent study

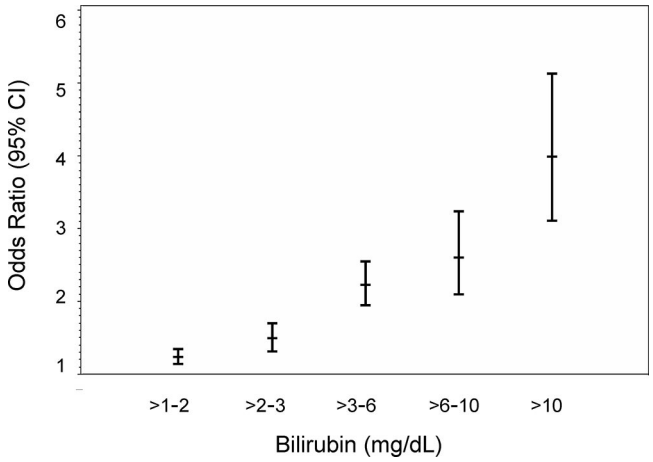


**Figure 2.** Logistic regression model B: adjusted risk of hospital mortality (odds ratio and 95% Wald confidence limits) stratified by maximum bilirubin levels within 48 hrs of admission. *CI*, confidence interval.

**Table 4.** Distribution of patients and hospital mortality within strata of serum bilirubin levels used in the logistic regression model B

| Group | Bilirubin, mg/dL | No. of Patients | % | Hospital Mortality Rate, % |
|---|---|---|---|---|
| Controls | 0–1 | 26,074 | 68.55 | 14.44 |
| Group 1 | >1–2 | 7,345 | 19.31 | 21.25 |
| Group 2 | >2–3 | 2,049 | 5.39 | 26.65 |
| Group 3 | >3–6 | 1,621 | 4.26 | 33.31 |
| Group 4 | >6–0 | 562 | 1.48 | 38.49 |
| Group 5 | >10 | 385 | 1.01 | 46.75 |

using the same definition as we did (serum bilirubin >2 mg/dL) reported hepatic dysfunction to occur in 31% of ICU patients and showed the independent roles of severe shock, sepsis, positive end-expiratory pressure ventilation, and major surgery as promoting factors (12). Similar to our results, the risk of death in acute critically ill patients was more closely related to liver dysfunction than to the acute physiology component of the Acute Physiology and Chronic Health Evaluation II score. In trauma patients, hepatic dysfunction was an independent predictor of increased ICU length of stay and mortality, irrespective of the presence or absence of additional renal dysfunction (21). Hepatic derangement, including high peak alanine aminotransferase levels, was also identified as an independent predictor of severe illness and worse clinical outcome in patients with severe acute respiratory syndrome (22).

Confirming our findings, the Marshall multiple organ dysfunction score (23) and further scores from the surgical literature (24) recognized hepatic dysfunction as an important factor of mortality in surgical patients. Abdominal surgery, with its implications for intestinal motility and perfusion, could also contribute to postoperative hepatic dysfunction (12, 25, 26). Although surgical patients represented the largest proportion of our patients with early hepatic dysfunction, logistic regression analysis revealed no direct effect of surgery on the development of early hepatic dysfunction and an even reduced risk with elective surgery. Rather than resulting from the surgical trauma itself, liver dysfunction could be due to development of postoperative systemic inflammatory response syndrome, whose severity at day 2 after operation correlates with organ dysfunction, length of stay, and mortality (27).

The results of our study, which specifically addressed the clinical and prognostic implications of early hepatic dysfunction in a large multidisciplinary cohort, prove that hepatic dysfunction is not necessarily a late organ dysfunction (18) but has a high incidence early in the course of critical illness. Such early development of hepatic dysfunction is supported by pathophysiologic data: Canalicular bile secretion is reduced within minutes of experimental endotoxemia (28), and impaired biliary secretion may be considered the main component of early hepatic dysfunction in sepsis and the systemic inflammatory response syndrome (6). There is increasing evidence that the liver plays a major role in modulating the systemic inflammatory response to sepsis, as hepatocytes and hepatic macrophages synthesize and release acute-phase proteins and cytokines (13). The liver contains most of the macrophages of the body, clearing endotoxin and bacteria from the splanchnic area. Bacterial translocation in liver dysfunction is associated with spillover of endotoxin and bacteria and thus exerts a substantial impact on systemic inflammation (29).

Both clinical and experimental data suggest that hepatic ischemia and hepatotoxic actions of inflammatory mediators such as cytokines or nitric oxide (30) are major etiological factors for the development of early and late hepatic dysfunction. Jaundice in critically ill patients is traditionally associated with infectious complications, occurring in as many as 63% of patients with septic shock (31). Serial bilirubin determinations have been used as a prognostic marker in persisting infection (32), and jaundice was associated with bacterial infection in patients after cardiac surgery (33). Bilirubin itself could be causally related to sepsis development: Because of its antioxidative properties, bilirubin impairs the bactericidal activity of neutrophils and reduces bacterial killing rates in a dose-dependent manner *in vitro* (34). In critically ill patients, side effects of parenteral nutrition, steatosis, drug toxicity, ischemic cholangiopathy, or secondary sclerosing cholangitis may additionally contribute to development of hyperbilirubinemia and hepatic dysfunction.

Our results are at odds with those of a previous study in critically ill patients: Le Gall and coworkers (18) suggested that hepatic failure, scoring a maximum of 1 LOD point, was not associated with mortality by itself, but only in association with the dysfunction of the other organ systems. A possible reason for this discrepancy could be that the LOD study collected data at admission, whereas our database included pathologic variables for up to 48 hrs, allowing us to detect early hepatic dysfunction more accurately. Moreover, advances in the treatment of extrahepatic organ failures between completion of the LOD trial and this study (35, 36) may have increased the relative contribution to mortality of hepatic fail-

ure, where no comparable therapeutic advances have been made (37). Also, a subanalysis of the Sequential Organ Failure Assessment score study found no independent effect of hepatic dysfunction on mortality, whereas circulatory function had the most significant effect (11). It is conceivable that circulatory failure is more directly related to mortality in patients developing multiorgan failure after 48 hrs; this could have obscured the effects of early hepatic dysfunction. Moreover, differences in design (the Sequential Organ Failure Assessment study assessed morbidity in a multinational setting) (38) and statistical power (in that study, only 272 patients developed hepatic failure) might have contributed to the different conclusions in the two studies.

There are several limitations to the current study: First, we were unable to retrieve bilirubin levels later than 48 hrs of admission and therefore cannot calculate the incidence of late hepatic failure. As hyperbilirubinemia may occur as late as 2–3 days after hepatic injury, future studies including patients with prolonged ICU stays will make it possible to assess serial changes in serum bilirubin and to analyze their impact on prognosis (39). Second, we were unable to identify the exact causes of death in patients with hepatic failure. Given the vast implications of hepatic failure on immunologic, renal, and circulatory dysfunction, it can be assumed that the majority of deaths occurred from septic shock with multiorgan failure, the current leading cause of mortality in ICUs. The low incidence of shock at admission (Table 2) could be due to our policy to record only the most specific admission diagnosis. Third, increased heme turnover due to transfusions might have contributed to a spuriously high incidence of early hepatic dysfunction in surgical patients. As demonstrated, prognostic effects of early hepatic dysfunction were equally pronounced in patients with nonsurgical conditions and were detected over the whole range of disease severity, making a major role of transfusion unlikely. A direct role of hemolysis is also refuted by late development of hyperbilirubinemia in trauma patients despite transfusion requirements early after trauma (21). Finally, we cannot exclude the possibility of occult cirrhosis in a proportion of patients developing early hepatic dysfunction as a contributing factor to increased risk of sepsis, respiratory failure, and mortality.

## CONCLUSIONS

Early hepatic dysfunction occurred in 11% of critically ill patients and predicted an excess risk of death, even after adjustment for illness severity. Given the vast number of metabolic, regulatory, and immunologic functions performed by the liver, early hepatic dysfunction has widespread pathophysiologic implications and should be recognized as a major independent risk factor in critically ill patients. The strong prognostic role of early hepatic dysfunction should foster research into liver-protecting strategies, as these could have a significant effect on mortality.

## ACKNOWLEDGMENTS

We thank Lorenz Dolanski and Johanna Einfalt, Core Unit for Medical Statistics and Informatics, Section of Medical Statistics, Medical University of Vienna, Vienna, Austria, for their help in statistical analysis.

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## APPENDIX

We thank the members of the ASDI study group and the respective study coordinators in each intensive care unit: H. Artmann, KH Schwarzach, Salzburg; A. Braunegg, UKH Klagenfurt, Carinthia; K. Dörre, KH Waidhofen a.d. Thaya, Lower Austria; G. Edelmann, KA Rudolfstiftung, Vienna; I. Eder, UKH Linz, Upper Austria; F. Ernst, KH Mistelbach, Lower Austria; S. Fitzal, Wilhelminenspital, Vienna; N. Gaberszig, KH Wiener Neustadt, Lower Austria; G. Haberhofer, UKH Kalwang, Styria; S. Klaunzer, UKH Salzburg, Salzburg; D. Krucher, KH St. Pölten, Lower Austria; F. Marian, KH Mistelbach, Lower Austria; W. Mauritz, UKH Lorenz Böhler, Vienna; A. Meguscher, KH Lainz, Vienna; G. Naderer, LKH Hollabrunn, Lower Austria; B. Plainer, KH Mödling, Lower Austria; G. Racz, LKH Oberwart, Burgenland; W. Regal, Kaiser-Franz-Josef-Spital, Vienna; G. Sagmüller, UKH Meidling, Vienna; I. Schindler, KH Floridsdorf, Vienna; F. Schwameis, Waldviertelklinikum Horn, Lower Austria; W. Steflitsch, Pulmologisches Zentrum, Vienna; K. Steinbach, Wilhelminenspital, Vienna; H. Steltzer, University Hospital, Vienna; I. Sudar, LKH Oberwart, Burgenland; A. Valentin, KA Rudolfstiftung, Vienna; H. Vesely, Hanuschkrankenhaus, Vienna; F. Wimmer, KH Schwarzach, Salzburg; E. Zadrobilek, Kaiserin-Elisabeth-Spital, Vienna; and A. Zeilinger, KH Floridsdorf, Vienna.

**Table E1.** Case-control study: Comparison of clinical characteristics, interventions, and outcomes in patients with early hepatic dysfunction and control subjects

| | Early Hepatic Dysfunction (n = 4,146) | Controls (n = 4,146) | *p* Value |
|---|---|---|---|
| Age, yrs, mean ± SD | 62.9 ± 16.5 | 62.9 ± 16.4 | NS |
| Bilirubin-corrected SAPS II scores, median (quartiles) | 34 (24–48) | 33 (24–48) | .69 |
| ICU length of stay, days, median (quartiles) | 5 (3–12) | 4 (2–9) | .003 |
| LOD 1, median (quartiles) | 5 (3–7) | 3 (2–6) | <.001 |
| Organs failing, median (quartiles) | 3 (3–4) | 2 (1–3) | <.001 |
| TISS-28 score per patient, median (quartiles) | 174 (84–428) | 124 (64–321) | <.001 |
| TISS-28 score per patient per day, median (quartiles) | 34.5 (29–40) | 32.5 (27.0–37.8) | <.001 |
| SAPS II-predicted mortality, n (%) | 1,237 (29.8) | 1,097 (26.4) | <.001 |
| ICU mortality, n (%) | 969 (23.4) | 715 (17.2) | <.001 |
| Hospital mortality, n (%) | 1,261 (30.4) | 985 (23.8) | <.001 |
| O/E ratio (95% CI) | 1.02 (0.98–1.06) | 0.90 (0.86–0.94) | <.001 |

NS, not significant; SAPS, Simplified Acute Physiology Score; LOD, Logistic Organ Dysfunction score; TISS, Therapeutic Intervention Scoring System; ICU, intensive care unit; O/E, observed-to-expected mortality; CI, confidence interval.

**Table E2.** Case-control study: Comparison of admission characteristics between patients with early hepatic dysfunction and control subjects

| | Early Hepatic Dysfunction (n = 4,146) No. (%) | Controls (n = 4,146) No. (%) | *p* Value |
|---|---|---|---|
| Type of ICU admission | | | |
| Medical | 1,254 (30.2) | 1,501 (36.2) | |
| Scheduled surgery | 1,482 (35.7) | 1,385 (33.4) | |
| Unscheduled surgery | 1,402 (33.8) | 1,255 (30.3) | |
| Missing | 8 (0.2) | 5 (0.1) | <.001 |
| Main diagnosis | | | |
| Metabolic disease | 30 (0.7) | 52 (1.3) | .007 |
| Respiratory disease | 217 (5.2) | 287 (6.9) | .001 |
| Cardiovascular disease | 308 (7.4) | 452 (10.9) | <.001 |
| Shock | 95 (2.3) | 74 (1.8) | .05 |
| Renal disease | 64 (1.5) | 48 (1.2) | .06 |
| Neurologic disorders | 59 (1.4) | 150 (3.6) | <.001 |
| Sepsis | 98 (2.4) | 47 (1.1) | <.001 |
| Trauma (not operated) | 60 (1.4) | 75 (1.8) | .10 |
| Gastrointestinal disease | 140 (3.4) | 65 (1.6) | <.001 |
| Hematologic disease | 15 (0.4) | 7 (0.2) | .04 |
| Medical disease, other | 15 (0.4) | 15 (0.4) | .50 |
| Pregnancy | 6 (0.1) | 3 (0.1) | .16 |
| Thoracic surgery | 49 (1.2) | 65 (1.6) | .06 |
| Cardiovascular surgery | 530 (12.8) | 619 (14.9) | .002 |
| Neurosurgery | 57 (1.4) | 163 (3.9) | <.001 |
| Transplant surgery | 197 (4.8) | 100 (2.4) | <.001 |
| Trauma surgery | 466 (11.2) | 496 (12.0) | .15 |
| Abdominal surgery | 891 (21.5) | 664 (16.0) | <.001 |
| Surgery, other | 456 (11.0) | 450 (10.9) | .42 |
| Missing | 393 (9.5) | 314 (7.6) | .001 |
| Total | 4,146 (100.0) | 4,146 (100.0) | |

ICU, intensive care unit.

**Table E3.** Case-control study: Comparison of comorbidities in patients with early hepatic dysfunction and control subjects

| | Early Hepatic Dysfunction No. (%) | Controls No. (%) | *p* Value |
|---|---|---|---|
| Hematologic disease | 109 (2.6) | 54 (1.3) | <.001 |
| AIDS | 3 (0.1) | 1 (0.0) | .16 |
| Metastatic malignant tumor | 340 (8.2) | 280 (6.8) | .01 |
| Immunosuppression | 94 (2.3) | 66 (1.6) | .01 |
| Chronic renal failure | 256 (6.2) | 248 (6.0) | .36 |
| Chronic respiratory failure | 315 (7.6) | 358 (8.6) | .04 |
| Congestive heart failure | 437 (10.5) | 451 (10.9) | .31 |
| Chronic alcoholism | 170 (4.1) | 132 (3.2) | .01 |
| Insulin-dependent diabetes | 63 (1.5) | 59 (1.4) | .36 |
| Acute renal failure | 61 (1.5) | 35 (0.8) | .01 |
| Nonmetastatic malignant tumor | 219 (5.3) | 183 (4.4) | .03 |
| Intravenous drug abuse | 8 (0.2) | 10 (0.2) | .32 |
| No comorbidities | 2,071 (50.0) | 2,269 (54.7) | <.01 |