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Factors associated with outcome of liver surgery and hepatocellular carcinoma

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CHAPTER 9

SYSTEMATIC COMPARISON OF ROUTINE LABORATORY VALUES WITH OUTCOMES IDENTIFIES PARADOXICAL RELATION OF GAMMA-GLUTAMYL TRANSPEPTIDASE WITH MORTALITY: ICU-LABOME, A LARGE COHORT STUDY OF CRITICALLY ILL PATIENTS

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ABSTRACT

PURPOSE: In ICU patients the relation of a laboratory measurement with outcome may not primarily depend on its deviation from the standard reference interval (RI). The ICU-Labome study systematically evaluated the univariate association of routine laboratory measurements with outcome.

METHODS: We studied the 35 most frequent blood-based measurements in adults admitted ≥ 6 h to the ICU of our university hospital in 1992-2013. Measurements were obtained from the first 14 ICU-days and directly before ICU-admission. Various metrics (including variability) of the laboratory measurements were related with hospital survival. ICU-based ranges were derived from laboratory measurements obtained just before ICU-discharge in patients with a good long-term outcome, defined as no ICU-readmission and 1-year survival.

RESULTS: In 49,464 patients we assessed $>20 \cdot 10^6$ measurements. ICU-readmissions, in-hospital, and 1-year mortality were 13%, 14%, and 19%. On ICU-admission, lactate had the strongest relation with hospital mortality. Variability was independently related with hospital mortality in 30 of the 35 parameters and 13 of the 35 parameters displayed a U-shaped outcome-relation. The medians of 14 of 35 ICU-based ranges that we derived were outside the standard RI. Remarkably, gamma-glutamyl transpeptidase (GGT) had a paradoxical relation with hospital mortality in the second ICU week since more abnormal GGT-levels were observed in hospital survivors.

CONCLUSIONS: ICU-based ranges for blood-based measurements may be more useful than standard RIs in identifying ICU patients at risk. The association of variability with outcome for many laboratory tests, calls the importance of this metric into question. Late elevation of GGT may confer protection to ICU-patients.

INTRODUCTION

In critically ill patients laboratory measurements are frequently abnormal when compared with standard reference intervals (RI, also denoted by reference range or reference values). The use of standard RIs derived from healthy persons to assess the severity of disease or to identify complications may sometimes be inappropriate in ICU patients. In order to identify specific pathophysiological mechanisms or to develop multivariate predictive models for critically ill patients, many ICU studies have evaluated the relation between selected measurements and outcome.¹⁻⁵ Depending on which measurements are selected or which clinical phase is considered of interest, measurements from patients who have a good outcome may be outside the standard RI. It has been proposed to define RIs for specific patient groups such as hospitalized patients.⁶ Moreover the implicit assumption that a more deranged measurement will be associated with a worse clinical situation may not always be correct.

The goal of the ICU-Labome study was to comprehensively evaluate the univariate relation of regular laboratory measurements with outcome in ICU patients, and identify 'ICU-based' reference ranges, derived from ICU patients with a good outcome. Parameter-specific a priori assumptions or multivariate models such as APACHE-IV or SAPS-3^{2,3} were not the scope of this study. This study also assessed a potential U-shaped relation with outcome and whether, in addition to the measurement itself, measurement variability was also associated with outcome, as was previously observed for glucose and potassium.⁷⁻⁹

PATIENTS AND METHODS

[A] PATIENTS

The observation period spanned 22 years, from January the 1st 1992 through December the 31st 2013 during which all laboratory values from all patients admitted to our regional tertiary 44-bed ICU were evaluated (Fig. 1). Patients aged 15 years or older were included and data were directly anonymized before further analysis. We recorded the type of ICU admission, and only one ICU admission per patient was evaluated. When patients were admitted multiple times to the ICU the first ICU admission during the last hospital admission was used as the reference ICU-admission. Patients who stayed shorter than 6 hours at the ICU were excluded.

This study was approved by our Medical Ethical Committee (METC 2014.264). Because only anonymized data that had been obtained during routine care were analysed and no additional sampling or interventions were performed for this retrospective study, the institutional review board considered patients' informed consent not necessary.

[B] OUTCOME

In-hospital mortality was used as main outcome measure. ICU mortality, ICU readmission, ICU length of stay, hospital length of stay and 1 year survival were also recorded. Good outcome was defined as no ICU-readmission and 1-year survival.

[C] SELECTION, CORRECTION AND PRIMARY REDUCTION OF VALUES

We selected the 35 most frequently assessed laboratory measurements in the blood during the first 14 days of ICU stay admission, or directly preceding ICU-admission. This number was arbitrarily chosen to include the vast majority of measurements. Derived values such as base excess were excluded. The standard RIs that we used were provided by our central laboratory in December 2013 (Table 1). Impossible values were searched for and deleted. Since the standard RI or some measurement techniques were repeatedly modified over the 22 year study period, for each of the 35 laboratory parameters we verified whether abrupt time-dependent long-term changes had occurred. For all laboratory measurements, we determined for each calendar day (day 1=01-01-1992, day 8036=31-12-2013) its overall median value. Then, a 100-day running mean was plotted and when evident structural changes were visually noted, we performed a linear correction to adjust the mean and median value over this period to the mean and median of the most recent period.

ICU-days (1 through 14) were determined in 24 hour blocks counting from the date and time of actual ICU-admission. When patients had multiple measurements of the same parameter within the same ICU-day, the mean of these values was calculated before further analysis, with the exception of the analysis of variability. When patients also had laboratory measurements directly preceding ICU-admission, the mean of all available values in the 5 days (120 hours) before ICU-admission was considered the baseline value.

[D] BIVARIATE CORRELATIONS.

We performed bivariate analysis for the $35 \times (35-1)/2$ parameter pairs to identify strongly overlapping or obviously redundant parameters, with a very high correlation (R) indicating that the same underlying signal is measured. All patients/ICU-days were pooled for this analysis.

[E] AREA UNDER THE RECEIVING OPERATING CHARACTERISTICS CURVE (AUROC)

To assess the univariate monotonic association between the studied parameters on ICU day 1 with in-hospital mortality, we performed a AUROC. Likewise AUROCs were calculated for all parameters at baseline, ICU-day 2, and for the 12h window before ICU-discharge.

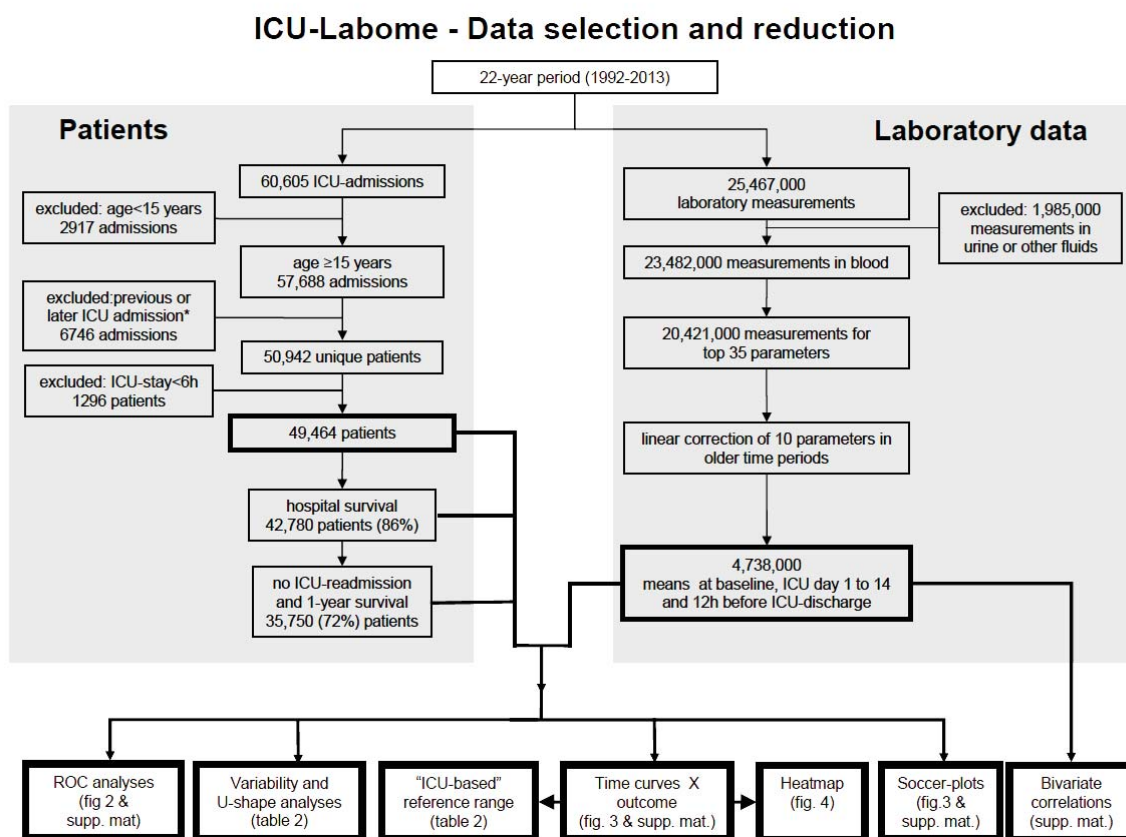


Figure 1. Flowchart depicting selection of patients, selection of the top 35 laboratory parameters and subsequent data reduction and analysis. *In case of multiple ICU-stays only the first ICU stay of the last hospital admission was used.

[F] VARIABILITY (SD) AND OUTCOME

We also assessed the variability for all 35 parameters over the whole ICU stay (with a maximum of 14 days) in relation with in-hospital mortality. Similar to how variability has been determined for glucose⁸ or potassium⁹, variability for each parameter for each patient was simply defined as the standard deviation (SD) of all individual measurements, including multiple measurements on the same day, obtained during the ICU-admission. Whether the SD was relevantly associated with outcome was assessed by performing logistic regression analysis with in-hospital mortality as dependent and the parameter's mean and SD as independent factors. The association of SD with outcome was then classified as:

- ' - ' SD was not associated with outcome.
- ' + ' Both SD and mean were related with outcome, but mean had a stronger relation.
- ' ++ ' Both SD and mean were related with outcome, but SD had a stronger relation,
- ' +++ ' Only SD was related with outcome.

[G] U-SHAPED RELATION WITH OUTCOME

For some tests, both abnormally low and abnormally high levels may be associated with poor outcome, e.g. glucose. To assess the presence of such a U-shaped relation with outcome, logistic regression analysis was performed with the individual mean measurement value and squared mean measurement value on ICU-day 1 as independent parameters and in-hospital mortality as dependent parameter. A relevant U-shaped relation was considered present when both coefficients of the quadratic function were significant and the minimum of the parabola (i.e. lowest point of the U-curve) was situated within the 10%-90% range of all individual means.

[H] TIME-COURSE OF MEDIANS IN SURVIVORS AND NON-SURVIVORS AND SOCCER PLOTS.

Over 14 ICU-days, we compared the time course of the medians (with IQR) of the 35 laboratory parameters between the patients who did or did not survive hospital admission. Likewise, baseline medians were compared. So-called soccer plots¹⁰ were constructed to provide additional graphical information on the frequency distribution of values in relation with the standard RI, over the ICU-stay for in-hospital survivors and non-survivors. Values within the standard RI are green, whereas yellow, orange and red reflect values both below and above the standard RI, according to criteria detailed in supplementary material. The observed distribution of laboratory measurements may have structurally changed over the years either because changes in the ICU-treatment (e.g. glucose control) or because of changes in the laboratory (e.g. a new assay). For visual recognition and identification of these mechanisms, soccer plots were also made for the 1992-2002 and 2003-2013 periods.

[I] 'ICU-BASED'- INTERQUARTILE RANGES

The use of patient groups themselves to extract reference values has been described before.⁶ We defined ICU-patients who subsequently demonstrated an uncomplicated course (i.e. no ICU-readmission and survival > 1 year) as the reference population with a good outcome to generate these 'ICU-based' reference ranges. The clinical period that was used to extract these laboratory values from, was the last 12h of the ICU-admission before ICU-discharge. In order to obtain conservative estimates of ICU-based ranges, the P25% and P75% (i.e. IQR) were determined, and not the P2.5% and P97.5% as is usually done for standard RI derived from normal individuals.

[J] HEAT MAP TO SUMMARIZE RELATION OF DERANGEMENTS WITH OUTCOME

One would expect that when laboratory measurements are deranged, i.e. below or above the standard reference range, that in the sickest patients such measurements would be furthest from the reference range. To verify if this was indeed the case, we plotted at which time the median levels were more deranged in patients who did not survive the in-hospital admission

compared to those who did survive. A heat-map was constructed to summarize into a single figure for all the 35 parameters at all time points whether they were more deranged (orange or red), similarly deranged (grey) or less deranged (green or dark green) in non-survivors than survivors on ICU day 1 through 14, at baseline and in the 12h window before ICU-discharge (fig. 4).

GENERAL STATISTICS AND SOFTWARE USED

Frequencies between groups were compared using the chi-square test. Medians (interquartile range; IQR) were compared with the Mann-Whitney U-test. Analyses were performed with SPSS 22 (IBM SPSS, Chicago, IL) and graphical representations were generated with Excel (Microsoft, Redmond, WA)

RESULTS

DATA FLOW AND SUPPLEMENTARY MATERIAL

Fig.1 depicts the study design and the major data reduction and data synthesis stages with the accompanying number of patients/laboratory measurements at the various stages. Given the scope of this study, the vast majority of the (intermediate) results of various analysis that were performed are reported in a large supplementary material file (supp. mat. 169 pages), to allow consistent reporting of the analyses for all the 35 parameters.

[A] PATIENTS

Over the study-period there were 60,605 ICU admissions (Fig. 1). Excluded were 18% admissions since 5% were <15 years, 11% had multiple ICU admissions, and 2% had an ICU-stay <6h. The mean \pm SD age of the selected population was 60 \pm 16 years, 37% were females and 18% were admitted from the emergency department. The largest admission category was cardiothoracic surgery (Table 2).

[B] OUTCOME

Mean ICU and hospital length of stay were 4.3 \pm 9.6 and 18 \pm 21 days and the frequency distribution of the ICU lengths of stay did not markedly change from 1992-2002 to 2003-'13 (supp. mat. p 6). 13% of the patients were readmitted to the ICU during the same hospital stay. ICU, in-hospital and one-year mortality were 11%, 14% and 19% respectively. A good outcome, as defined as no ICU-readmission and one-year survival, was reached by 72%.

[C] SELECTION, CORRECTION AND PRIMARY REDUCTION OF MEASUREMENTS

Of all 23 million blood measurements recorded, 20 million (87%) were included (Fig. 1). Creatinine, glucose, hemoglobin and potassium were the four most frequently performed measurements and APTT, PT and troponin the least performed (supp. mat. P 4). For 10

Table 1. Key characteristics and results of 35 laboratory parameters evaluated

Abbr.	Parameter	Unit	Standard IR	Univariate relation with in-hospital survival ¹	SD related with in-hospital mortality ²	'ICU-based' IQR ³	Median D=discharge value in patients with good outcome relative to SIR ⁴
ALAT	alanine aminotransferase	U/L	<45	monotonic	+++	30 (20 - 48)	in SIR
Alb	Albumin	g/L	35-50	U-shaped	+	28 (24 - 32)	< SIR
Amy	Amylase	U/L	<107	monotonic	+	67 (38 - 115)	in SIR
AP	alkaline phosphatase	U/L	<115	monotonic	+	55 (43 - 75)	in SIR
aPCO ₂	arterial pCO ₂	kPa	4.6-6.0	U-shaped	++	5.0 (4.7 - 5.5)	in SIR
apH	arterial ph		7.35-7.45	U-shaped	++	7.40 (7.37 - 7.43)	in SIR
aPO ₂	arterial PO ₂	kPa	9.5-13.5	U-shaped	++	12.4 (10.6 - 15.0)	in SIR
APTT	activated partial prothrombin time	Sec	23-33	monotonic	+	27 (25 - 31)	in SIR
ASAT	Aspartate aminotransferase	U/L	<35	monotonic	+	40 (28 - 62)	> SIR
aSatO ₂	arterial oxygen saturation		0.96-0.99	monotonic	+	0.98 (0.96 - 0.99)	in SIR
Bic	Bicarbonate	mmol/L	21-25	monotonic	+	23 (21 - 25)	in SIR
Ca	calcium (total)	mmol/L	2.20-2.60	U-shaped	++	1.96 (1.84 - 2.08)	< SIR
CK-MB	creatinine MB kinase	U/L	<5	monotonic	+	14 (8 - 24)	> SIR
CKT	total creatine kinase	U/L	<170	monotonic	-	215 (121 - 415)	> SIR
Cl	Chloride	mmol/L	97-107	U-shaped	+++	107 (104 - 110)	> SIR
creat	Creatinine	umol/L	50-110	monotonic	++	68 (57 - 83)	in SIR
CRP	C-reactive protein	Mg/L	<5	monotonic	-	57 (23 - 107)	> SIR
DBI	direct bilirubin	umol/L	<5	monotonic	+	4 (2 - 7)	in SIR
GGT	gamma-glutamyl transpeptidase	U/L	<55	monotonic	-	36 (18 - 86)	in SIR
Glu	Glucose	mmol/L	4.0-5.5	U-shaped	++	7.4 (6.3 - 8.9)	> SIR
Hb	hemoglobin	mmol/L	7.7 - 10.6	U-shaped	+++	6.4 (5.8 - 7.2)	< SIR
Ht	Hematocrit	mmol/L	0.37-0.52	U-shaped	++	0.30 (0.28 - 0.3)	< SIR
K	Potassium	mmol/L	3.5 - 5.0	U-shaped	++	4.3 (4.0 - 4.6)	in SIR
Lac	Lactate	mmol/L	0.5 - 2.2	monotonic	-	1.0 (0.8 - 1.4)	in SIR
LDH	lactate dehydrogenase	U/L	< 248	monotonic	++	297 (213 - 408)	> SIR
Leukos	leukocyte count	10 ⁹ /L	4 - 10	monotonic	++	12.2 (9.7 - 15.3)	> SIR
Mg	Magnesium	mmol/L	0.70 - 1.00	monotonic	-	0.95 (0.82 - 1.11)	in SIR
Na	Sodium	mmol/L	135 - 145	U-shaped	++	137 (135 - 139)	in SIR
P	Phosphate	mmol/L	0.70-1.50	monotonic	++	1.02 (0.85 - 1.20)	in SIR
PLC	platelet count	10 ⁹ /L	150-350	U-shaped	++	180 (138 - 239)	in SIR
PT	prothrombin time	Sec	9.0 - 12.0	monotonic	+	11.6 (10.8 - 12.7)	in SIR
TBI	total bilirubin	umol/L	< 17	monotonic	+	10 (7 - 16)	in SIR
TP	total protein	g/L	60-80	U-shaped	+	53 (47 - 59)	< SIR
Trop	Troponin	ng/L	<14	monotonic	+	51 (15 - 124)	> SIR
Urea	Urea	mmol/L	2.2-7.5	monotonic	+	6.4 (4.9 - 8.7)	in SIR

¹All parameters obtained showed a univariate relation with hospital mortality, and for 13 parameters relation was U-shaped. ²The relation of standard deviation (SD) as a measure of variability with in-hospital mortality was classified as detailed in the methods section: '-' : no relation of SD with mortality to '+++' SD related with outcome, but mean is not. Thus an independent association of variability with outcome was present for the majority of parameters and that in 16 of the 35 parameters SD has stronger relation with outcome than the mean (i.e. '++' and '+++'). ³the median (iqr) values obtained at discharge in patients with good outcome were be used as 'icu-based' interquartile ranges. A good outcome was defined as no readmission to the icu and long term survival (≥ 1 year). SIR: standard reference range, 'in sir', "< sir" and "> sir" respectively denote that median value provided in the previous column is within, below or above the standard reference range. For 14 of the 35 parameters, the median of the "icu-reference range" was found to be outside the standard reference range.

parameters linear adjustments were made (supp. mat. 130) due to evident structural changes in reported laboratory values over time. The 35 day-to-day running means of the median laboratory values after these corrections still indicated more several more gradual changes as well as changes in spread of the medians (supp. mat. p 132 – 166).

[D] BIVARIATE CORRELATIONS

Many parameter pairs showed a positive R (supp. mat. p 8-10) and two pairs displayed an $R > 0.90$. R was 0.96 for (hemoglobin, hematocrit) and 0.96 for (direct bilirubin, total bilirubin). Negative correlations were less often than positive correlation and were not as marked as positive correlations. The most negative R was -0.50 as observed for (arterial pH, lactate) pair.

[E] AUROC ANALYSIS

In 32 out of 35 laboratory measurements we found an AUROC > 0.50 . Lactate showed the strongest predictive power for in-hospital mortality on ICU-day 1 with an AUROC of 0.731 (95% CI: 0.722 to 0.740; Fig 2) as well as on ICU-day 2. Complete AUROC data values at baseline, ICU-day 1 and 2, the change from ICU-day 1 to 2, and at < 12 h before ICU-discharge were determined (supp. mat.11-14).

[F] RELATION OF PARAMETER VARIABILITY (SD) WITH OUTCOME

For 30 of 35 parameters, SD had an independent relation with in-hospital mortality. Moreover in 16 of these parameters the SD had a *stronger* relation with outcome than the mean (ALAT, aPCO₂, apH, aPO₂, Ca, Cl, creat, glu, Hb, Ht, K, LDH, leukos, Na, P and PLC; Table 1).

[G] U-SHAPED RELATION WITH OUTCOME

At ICU-day 1, all 35 parameters evaluated showed a univariate relation with in-hospital mortality and 13 of them (Table 1) this relation was U-shaped.

Table 2. Patient characteristics

Nr of patients	49,464
Age (SD)	60 (16)
Sex, male	63%
Admission from emergency department	18%
Type of admission	
Cardiothoracic surgery	42.5%
Abdominal, vascular and miscellaneous surgery	14.5 %
Neurosurgery	11.2%
Medical	5.8%
Trauma	3.8%
Transplantation	1.8%
Miscellaneous	20.4%
Mean (SD) ICU stay* (days)	4.3 (9.6)
Median (IQR) ICU stay* (days)	1.0 (0.8 - 3.1)
Mean (SD) hospital stay (days)	18 (21)
Median (IQR) hospital stay (days)	12 (7- 21)
ICU readmissions	12.8%
ICU mortality	11.0%
In-hospital mortality	13.5%
1 year mortality	19.1%

ICU: intensive care unit, IQR: interquartile range, SD: standard deviation. *ICU stay includes ICU-stay for readmissions.

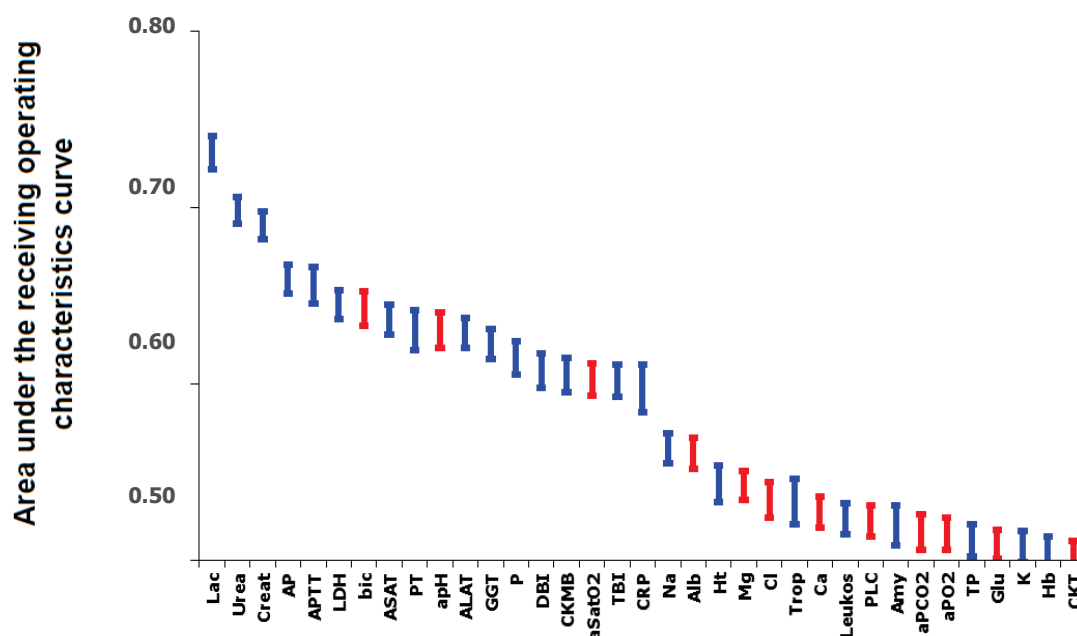
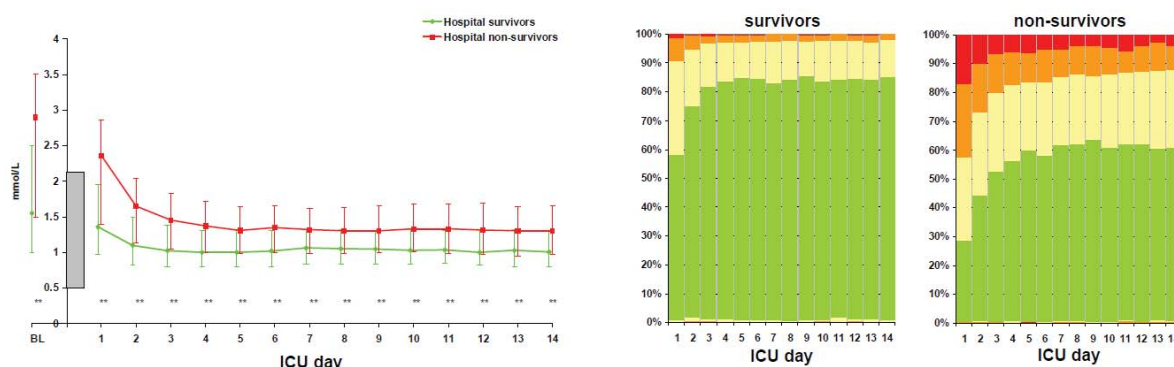


Figure 2: AUROC displayed with 95% confidence intervals. Univariate relation of laboratory parameters on ICU day 1 with in-hospital mortality as assessed by area under the receiver operating curve (AUROC). We assessed univariately the prognostic relevance of 35 studied laboratory variables on ICU day 1. All parameters had an AUC higher than 0.5, except for the total creatine kinase (CKT), hemoglobin (Hb), and potassium (K). Lactate (Lac), urea, and creatinine were the strongest predictors of in-hospital mortality at ICU day 1. Blue color reflects positive relation with mortality; red color reflects inverse relation with mortality. Note that the AUROC will do poorly for variables with a U-shaped outcome relation.

[H] TIME-COURSE OF MEDIANS IN SURVIVORS AND NON-SURVIVORS AND SOCCER PLOTS

Time courses of the medians of all 35 measurements for hospital survivors and non-survivors are provided in the supplementary material (supp. mat p 15-50) including the significances of differences. Two of the most remarkable time courses, lactate and gamma-glutamyl transpeptidase (GGT), are shown in Fig. 4. Lactate was markedly higher at all time-points in non-survivors ($P < 10^{-21}$ to $P < 10^{-300}$) and GGT was initially significantly higher ($P < 3 \times 10^{-156}$) and then significantly lower in non-survivors ($P < 5 \times 10^{-7}$). The soccer plots (supp. mat. 58-128) indicate that for some parameters virtually all measurements were outside the standard RI (e.g. albumin), whereas for other parameters (e.g. potassium) virtually all measurements were inside the standard RI but extreme values predominantly occurred in non-survivors. Comparison of soccer plots between 1992-2002 and 2003-2013 show that many temporal trends during ICU-trends appear unchanged, but that some (i.e. Alb, $a\text{PCO}_2$, Cl, Hb, Ht, Na) become more deranged during ICU-stay in the 2003-2013 period whereas glucose becomes less deranged. All these effects might be accounted for by well-known changes in therapeutic strategies or changes in attitude regarding which laboratory deviations are deemed acceptable.¹⁰

Lac (lactate)



GGT (gamma-glutamyl-transpeptidase)

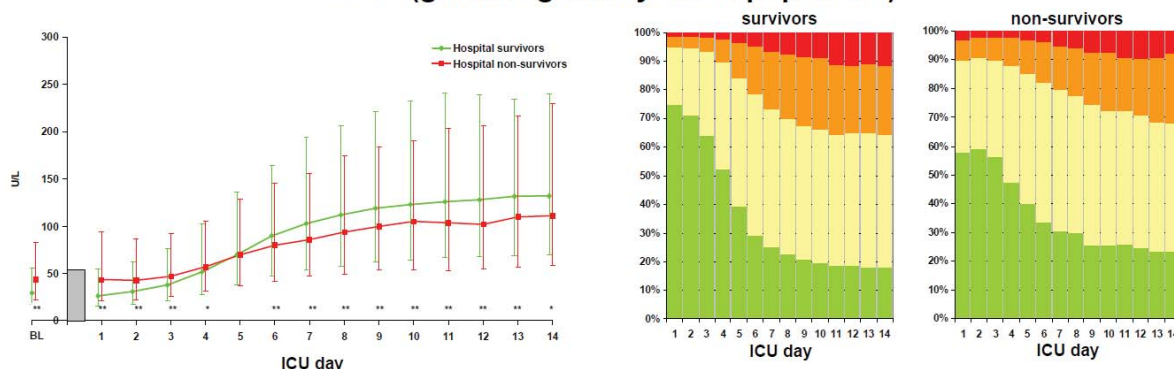


Figure 3. Time courses of lactate and gamma-glutamyl transpeptidase and outcome. Changes in lactate and GGT during the first 14 ICU-days graphically represented in two different manners. Lactate showed the strongest discrimination between survivors and non-survivors compared to all other 34 parameters that were evaluated. At all time-points non-survivors had higher lactate levels. GGT was initially significantly lower for in-hospital survivors but it increased to levels that are higher than and more out of range than those of non-survivors from ICU day 6 onwards. Gray bars denote standard reference ranges; BL denotes the baseline values; * P<0.05; ** P<0.001.

A clear feature of some parameters was their sharp changes over time. Most extreme was the behavior of the leukocyte count with four phases during the 14 ICU-days, both in survivors and non-survivors (supp. mat. p 41,83,119). Although at each ICU-day the leukocyte count was significantly higher in non-survivors, it can be appreciated that the repeated fluctuations over time impede the association of leukocytosis with prognosis.¹¹

[I] 'ICU-BASED' RANGES

The median (IQR) laboratory values observed within 12h of ICU discharge in patients with a good outcome were considered as ICU-based IQRs. We found that the median value of ICU based IQRs for 14 parameters (Alb, ASAT, Ca, CK-MB, CKT, Cl, CRP, Glu, Hb, Ht, LDH, leukos,

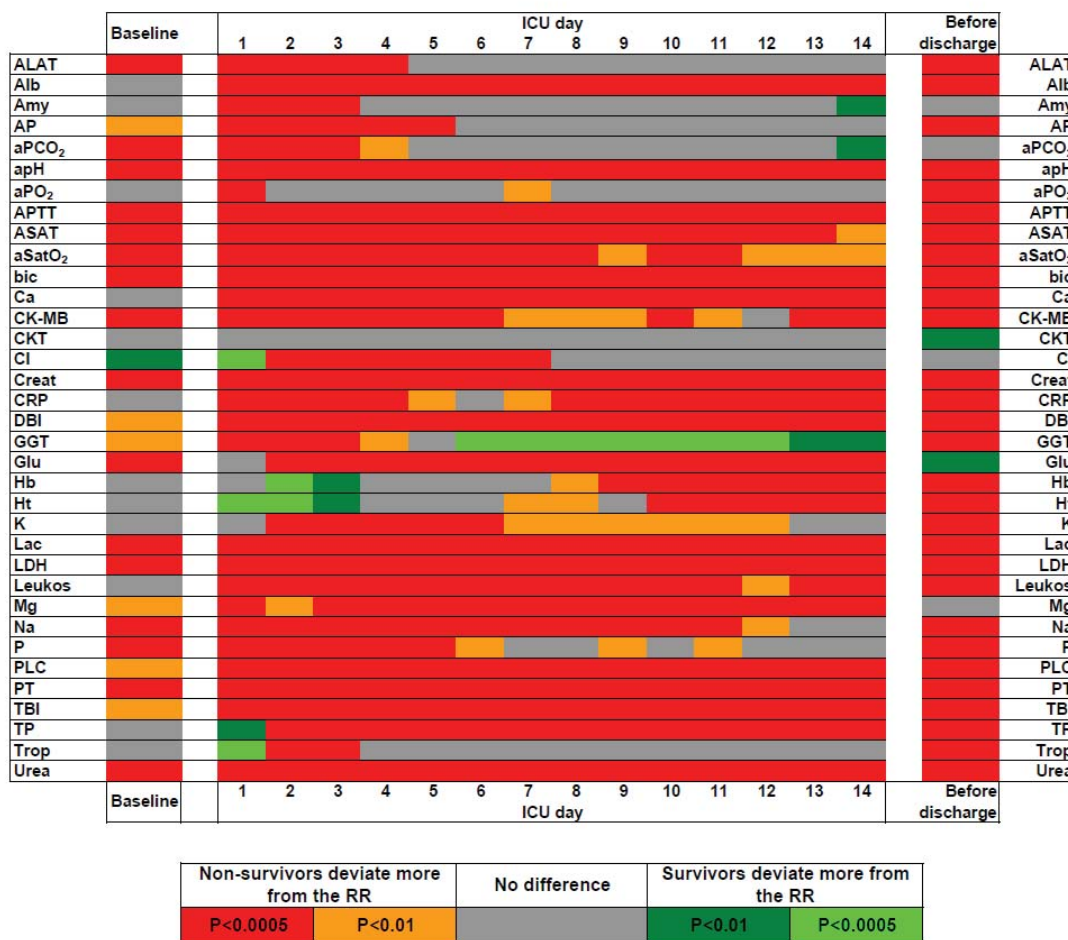


Figure 4. Heat map for the 35 parameters studied, red and orange in this heat-map indicate that derangements (i.e. distance from official reference values) for in-hospital non-survivors were larger than derangements for survivors (red: $P < 0.0005$; orange: $P < 0.01$). Gray indicates no significant difference between non-survivors and survivors. Green indicates a ‘paradoxically’ larger derangement for survivors than non-survivors (light green: $P < 0.0005$; dark green: $P < 0.01$). Arterial PCO₂ (aPCO₂) displays and a few other variables show an early paradoxical relation with outcome. During prolonged ICU stay, only GGT shows a consistently more deranged level in survivors.

TP and Trop) were outside the standard RI (Table 1). This underscores that many “abnormal” laboratory tests before the discharge from the ICU were not “abnormal” from the prognostic point of view. Time courses of all 35 parameters are shown in the supplementary material pages 15-50.

[J] HEAT-MAP TO SUMMARIZE RELATION OF DERANGEMENTS WITH OUTCOME

The heat-map (Fig. 4) summarizes all parameters whether non-survivors had more deranged values than survivors at baseline, ICU-day 1 through 14 and before discharge (underlying P-values are provided in supp. mat p 167). As might be expected, some parameters are

significantly more deranged (i.e. red color) across all time points in non-survivors (Alb, apH, APTT, Bic, Ca, Creat, Lac, PT and Urea) with underlying P-values as low as $<10^{-300}$ (supp. mat p 167).

Several parameters did not show differences at most time points, but few showed a 'paradoxical' difference (light and dark green) with a more deranged value. Between ICU-day 5 and 14 only GGT showed highly significantly more deranged values in survivors. This paradoxical relation persisted in subgroup analysis for the cardiothoracic surgery, miscellaneous surgery, trauma, and medical groups (supp. mat. 168).

DISCUSSION

In this comprehensive analysis of the most used blood-based laboratory measurements we found that 14 of the 35 parameters were out of the standard RI at ICU-discharge in patients who had a good outcome. Maybe unsurprisingly, our results underscore that early lactate has the strongest predictive value for in-hospital mortality compared to other laboratory variables. Furthermore, we found a U-shaped outcome relation in 13 variables.

Examination of the relation with outcome over the first 14 ICU-days showed a unique pattern of GGT compared to other laboratory variables. The levels of GGT were more deranged in the second week of ICU admission in survivors compared to non-survivors. This analysis of regularly performed lab measurements in our institution had no a priori assumptions about specific mechanisms. We hypothesized that the standard RI may not be a reliable tool in assessing critically ill patients since many patients have derangements upon the discharge from the ICU. In fact, it has been shown that adjusted RIs for the ICU population may decrease the false positive alerts up to 20% and increase the true negative results by 14%.¹² Many laboratory derangements in ICU setting may not endanger the patient and do not need further intervention. Thus it should not prevent the patient's discharge from the ICU. Obviously, if an observed value falls within the interquartile range in ICU-patients with a good outcome, it does not automatically imply that a specific value is associated with minimal risk. In order to assess the mortality risk associated with a specific laboratory parameter value, more advanced analyses are required.^{13,14}

Regarding lactate in critically ill patients, it has become evident that stress and not hypoxia is the most important driver of lactate elevations and explanation of its unique association with outcome.¹⁵ An early lactate-guided therapy trial demonstrated improved outcome in critically ill patients.¹⁶ Although many other laboratory variables of lesser predictive power are used in common scoring systems²⁻⁴ to predict mortality in ICU patients, lactate is not yet included. Yet the Sepsis-3 consensus recently incorporated lactate into the clinical definition

of septic shock.¹⁷ The ICU-based IQR for lactate of 0.8 to 1.4 mmol/L (Table 1) indicates that desirable lactate levels are in the lower part of the standard RI range (0.5 to 2.2 mmol/L; Table 1). In the past lactate was not always easy to measure routinely. With the current analytical equipment, we believe our results lend further support to both the routine use and the inclusion of lactate into future scoring systems.

The bivariate correlations showed that the (hemoglobin, hematocrit) and (total bilirubin, direct bilirubin) pairs were strongly correlated. This underscores that hematocrit is a redundant measure on top of hemoglobin, as has been in fact long been demonstrated.^{18,19} Likewise, the apparent unconditional performance of both the total bilirubin and direct bilirubin measurement does not provide additional information compared to the measurement of total bilirubin alone, at least for this overall patient group.

With regard to parameter variability we were surprised to find that variability was related with outcome for most parameters. Although there has been a strong focus on glucose variability as a therapeutic goal, it is remarkable that variability of, among others, several blood gas parameters or sodium or potassium had a stronger relation with outcome than the mean of these parameters (Table 1). To our judgment this strongly suggests that higher parameter variabilities in patients who do worse are a fundamental reflection of the clinical instability of such patients. Thus, unless specifically proven otherwise, a higher laboratory parameter instability should be considered a consequence and not a cause of a worse ICU outcome. With regard to the parameters that showed a U-shaped relation with outcome (Alb, aPCO₂, apH, aPO₂, Ca, Cl, glu, Hb, Ht, K, Na, PLC and TP; Table 1), all these parameters with the exception of albumin (Alb) and, to a lesser extent, total protein (TP) are known to manifest both pathological 'hypo' and 'hyper' states.

In our view the most surprising finding of our survey was the paradoxical relation of GGT with outcome. GGT is a key enzyme in modulating redox-sensitive (extra)cellular defenses²⁰⁻²² against toxins. GGT is constitutively expressed in several organs¹⁸ and it breaks down extracellular glutathione (GSH), which generates cysteine for intracellular de novo synthesis of GSH. Higher serum GGT plausibly reflects increased cellular GGT activity and serum GGT increases with chronic exposure to toxic metabolites.²⁰

Apart from its known association with the use of several drugs and ethanol consumption,²⁰ chronically elevated GGT in otherwise healthy persons has emerged as strong risk factor for cardiovascular disease.²³ Likewise in patients with liver disease elevated GGT is considered a marker of cholestasis together with indicators such as bilirubin and alkaline phosphatase. We observed earlier that secondarily elevated GGT was associated with increased survival rates after liver transplantation, liver resection and after surgical repair of a ruptured

abdominal aortic aneurysm.²⁴⁻²⁶ The current observation in a large cohort of critically ill patients and in subgroups without known primary liver disease (cardiovascular surgery, trauma and medical; supp. mat. p 168) supports the notion that transiently elevated GGT is crucially involved in some protective mechanisms leading to better outcome of patients admitted to the hospital.

One may also speculate interventions that increase GGT levels, such as GGT-inducing drugs²⁰ might also confer protection since the restoration of GSH levels with acetylcysteine is key in the management of patients with acetaminophen intoxication.^{27,28} Acetylcysteine provides cysteine for intracellular de novo synthesis of GSH. Apart from this indication, the benefit of acetylcysteine for related conditions is still unproven.²⁹ We believe this paradoxical relation of GGT might be observed in many existing ICU databases, but it has probably been overlooked because most studies focused on the first few ICU-days. At the very least, caregivers should realize that the development of an elevated GGT in the second ICU-week is not worrisome and should not automatically lead to investigations into its cause.

Another remarkable point about the heat map are the grey zones that reflect phases when abnormalities may be present but that do not discriminate outcome. With regard to the other parameters that are green on the heat-map, these occur all early during ICU-stay and reflect very small absolute differences (i.e. hemoglobin, hematocrit, chloride, total protein and troponin; supp. mat. p 15-50). The heat map shows that at discharge total creatine kinase and glucose were higher (dark green) in survivors than in non-survivors. For total creatine kinase activity it has been demonstrated earlier that lower enzyme activity levels reflect worse outcome. A confounder may also have been the large number of elective cardiothoracical surgery patients that have elevated post-operative total creatine kinase activity but have a lower mortality compared to other patients.

As already noted, a large body of ICU-literature concerns the association of deviating laboratory values and outcome.^{1-5,13,14} Our observations fully corroborate those observations since patients who did not survive the hospital admission, had more derangements of their laboratory variables. However, our results may also have some practical consequences as it clearly shows that the association of laboratory derangements with poor outcome may sometimes be time dependent and that some derangements might even predict good outcome such as the levels of GGT in the second week of ICU-admission. Thus, ICU care providers should realize that an abnormally high GGT may not necessarily be a cause for alarm or specific diagnostic procedures. In addition, our data show that some laboratory derangements in critically ill patients might not be considered "abnormal" from the prognostic point of view since derangements of 14 out of 35 laboratory variables were not associated with poor outcome (re-admission to the ICU and diseased within 1 year).

Our study has several limitations including the retrospective design and that we could not obtain the commonly used ICU severity scores such as APACHE or SOFA ^{2,5} since these were not available for most patients. Furthermore, we only performed univariate analysis of laboratory variables with outcome as it was not our aim to create predictive models. The study covered more than two decades, with many potentially influential changes in measurement or therapy. However, we surveyed the data exclusively for time effects and report these changes. The 1992-'2002 vs. 2003-2013 soccer plots (supp. mat. p 94-128) indicate that apart from the exceptions noted earlier, the behavior of most parameters has not dramatically changed. We also believe the extensive study period increases the robustness and external validity and reproducibility of many of our observations. Thus we think that our results represent clinically relevant information for the assessment of critically ill patients. Thus we are confident given that our observations can also be reproduced in other ICU cohorts. ICUs possessing large cohorts stored in integrated patient database management systems may be able to elucidate relations between medication or other therapies administered and later laboratory abnormalities, such as elevated GGT.

In conclusion, we believe that using ICU-based interquartile ranges instead of standard reference ranges will decrease the level of uncertainty in clinical decision making. The widespread association of parameter variability with outcome, makes it doubtful whether reducing variability of specific parameters is a useful therapeutic goal. Furthermore, even some derangements such as a late elevation in GGT apparently confer a good outcome.

Supplementary material can be viewed on:

http://www.ivcompatibility.org/documents/download_appendix.php?userid=nijstenmwn

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