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Intraday variability of albumin, ALT, AST, gamma-glutamyl transferase and lactate dehydrogenase in intensive care patients

Abstract

It is important to be able to separate the nonspecific variation of biomarkers from disease- or treatment-specific changes but there is limited information regarding intra-day variability of biomarkers for liver damage in intensive care patients. The aim of this study was to investigate the intra-day variability of frequently used liver markers in patients at an Intensive Care Unit (ICU). 26 patients in clinical steady state treated at two separate intensive care units at the Karolinska Hospital, Stockholm were included in the study. Blood samples were collected at time points 0, 5, 15, 30, 60, 90, 120, 150, 180, 210, 240, 270, 300 minutes and 24 hours and analyzed for albumin, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase and lactate dehydrogenase. The intra-day variation was calculated for each patient and marker. The 90th percentiles for the CV values for the study group were 6.6 % for albumin, 12.4 % for ALT, 11.2 % for AST, 10.2 % for GGT and 16.0% for LDH. Values deviating more than the 90th percentile of the CV values indicates a disease/treatment specific change.

Keywords: Intraday variability; Albumin; ALT; AST; Gamma-glutamyl transferase; Lactate dehydrogenase; Intensive care.

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Introduction

To minimize unnecessary treatments or failing to treat important conditions, it is essential to distinguish between changes of a biomarker due to the course of the disease and/or due to the treatment as opposed to change because of nonspecific variation to minimize unnecessary treatments or failing to treat important conditions. The random variation in the result of an analyte, not related to the disease/treatment is mainly due to preanalytical and analytical variation [1-3]. Analytical variation is a combination of analytical imprecision and bias [4]. Detection of analytical variation is an important task in the clinical laboratories for any clinical assay. The analytical imprecision is routinely monitored with internal control materials [5,6]. Most laboratories also participate in external quality assurance programs [7,8]. These programs provide information of bias in relation to other methods. Pre-analytical variation is much more complex and encompasses numerous factors related to the individual and the collection and handling of the sample. Individual factors include the time of sampling, food intake, exercise, medication, and posture [1,9]. The available information on the effects of these factors is usually based on healthy individuals or patients with much less severe conditions than encountered in ICU patients. Bilirubin is an example of this. We have previously shown that bilirubin has a strong diurnal variation with the highest values at 11 AM during the night-sleep condition and at 6 PM during the day-sleep condition and individual coefficients of variation between 12.8 to 42.5% [10]. This is valid for patients that have a regular sleeping pattern, but it is difficult to extrapolate these data to ICU patients that are sedated and in a respirator. Food intake, exercise, medication, and posture also differ in ICU patients as compared to patients in the ward or patients in walk-in-clinics.

The aim of the present study was to study the intra-day variation of frequently requested liver marker assays in ICU pa-

tients. We chose to only include individuals that were in a clinically stable condition to minimize the effects of changes due to improvements/deterioration of the underlying disease. Intensive care patients normally have short treatment periods in ICU. Most of the patients are moved to other units after 1-5 days and they are rarely in a stable condition during the entire stay in the ICU. The short treatment periods put a clear focus on the intra-day variation between different sampling times.

Materials and methods

Patients

Patients treated at the intensive care unit, Karolinska Hospital, Stockholm, and that were considered clinically to be in a steady state were eligible for this study. This study was approved by the regional ethical review board in Stockholm. Written informed consent was obtained from patients or their next of kin. Twenty-eighth patients were included in the study, but two of the patients were excluded as they had clear trends in their albumin values over time indicating that they were not in a steady state. Blood samples were collected from either an intravascular arterial catheter or a central venous catheter at time points 0, 5, 15, 30, 60, 90, 120, 150, 180, 210, 240, 270 and 300 minutes. An additional sample was collected 24 hours later. Serum samples were collected in Vacutainer tubes without additives. After clotting the tubes were centrifuged for 10 min at 2000 g at room temperature and the serum transferred to new tubes and frozen at -80C until analysis.

Assays

Albumin (reagent 7D54-21), Alanine aminotransferase (ALT; reagent 8L92-40), aspartate aminotransferase (AST; reagent 8L91-40), Gamma-Glutamyl Transferase (GGT; reagent 7D65-21) and Lactate Dehydrogenase (LDH; reagent 2P56-21) were analyzed with reagents from Abbott Laboratories, Abbott Park, IL, USA) on a BS380 instrument (Mindray, Shenzhen, China). The analytical total coefficients of variation were 0.5% at 32 g/L for albumin 1.6% at 0.5 µkat/L for ALT, 1.5% at 0.6 µkat/L for AST, 0.7% at 1.2 µkat/L for GGT and 1.0% at 2.5 µkat/L for LDH.

Statistical analysis

Calculation of coefficients of variations were performed with Statistica (StatSoft, Tulsa, OK, USA).

Results

Patient characteristics

Mean age of the study group was 62 years (range 26-82 years) with a mean weight of 69.5 kg (35-115) and a mean height of 169 cm (145-190). Most patients were admitted to ICU due to neurological/neurosurgical problems (n=11), respiratory failure (n=9) or trauma (n=4). Mean SOFA (Sequential Organ Failure Assessment) score was 11.2 (n=17). The mean time in the ICU for these patients was 25 days (17-31 days).

Variation in albumin, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase and lactate dehydrogenase

The median albumin concentration was 28.7 g/L (interquartile range 25.6-33.9 g/L). The median values for the enzymes were 0.58 µkat/L (0.41-1.07) for ALT, 0.81 µkat/L (0.50-1.22) for AST, 1.86 µkat/L (1.18-3.11) for GGT, and 2.90 µkat/L (2.23-3.53) for LDH. The median CV values were: Albumin 3.32% (IQR 2.6-4.8), ALT 8.1% (7.2-10.2), AST 8.4% (6.0-10.4), GGT 5.0% (4.3-8.0) and LDH 9.5% (8.4-10.9). The 90th percentiles for the CV values were 6.6 % for albumin, 12.4 % for ALT, 11.2 % for AST, 10.2 % for GGT and 16.0% for LDH.

CV in relation to the mean value for each patient

Only AST showed a significant Spearman rank correlation ($p<0.05$) between the concentration and CV ($r=-0.42$).

Table 1: Median CV and 90th percentiles for the studied analytes. The values are based on CV for each patient and 90th percentiles.

Analyte	Median value	Median CV	90th percentiles
Albumin	28.7 g/L	3.3% (IQR 2.6-4.8)	6.6%
ALT	0.58 µkat/L	8.1% (7.2-10.2)	12.4%
AST	0.81 µkat/L	8.4% (6.0-10.4)	11.2%
GGT	1.86 µkat/L	5.0% (4.3-8.0)	0.2%
LDH	2.90 µkat/L	9.5% (8.4-10.9)	16.0%

Discussion

It is important to be aware of the normal variation between two sampling times to be able to evaluate when a true change in the clinical status has occurred. Both false positive and false negative interpretations may lead to incorrect treatment. We chose to study the intra-day variability of albumin, ALT, AST, GGT and LDH in intensive care patients, as these patients differ from most other patient groups regarding factors that are known to influence the intra-day variability, e.g., sleep pattern, food intake, exercise, medication, and posture. Data from healthy individuals may thus not be representative for ICU patients. Liver damage is a problem that is common in the ICU [11-13]. Albumin, ALT, AST, GGT and LDH are often used as markers for liver damage [13]. Albumin can be used as a marker for the protein synthesis capacity of the liver and thus act as a marker for liver function [14,15]. Albumin is also used to monitor hydration/dehydration and as a marker for protein losses [16]. ALT and AST have a long tradition as routine markers for liver cell damage. LDH is often requested as part of “liver test panel” but it is present in the cytoplasm of all cells in the body and thus not particularly liver specific [17]. Even if LDH often is included in liver test panels, LDH should be considered an unspecific marker of tissue damage. For instance, hemolysis causes LDH elevation as the erythrocytes are rich in LDH [18]. A low degree of hemolysis could be a contributing factor to the slightly higher CV for LDH in this study than for the other liver markers. Even if the patients were in a steady state and did not receive blood transfusions there may be a low degree of hemolysis. Lippi et al. [19] using visual inspection to define hemolysis, reported 5.4% hemolyzed samples in the ICU which was higher than the 4% reported from surgical units and 0.1% for outpatients. GGT is often included in liver test panels and is increased mainly in patients with alcohol or drug abuse or gall obstructions [20,21].

Low-grade abnormalities of liver function tests are a significant entity in intensive care patients and are associated with mortality outcomes and clinical events [22]. It is therefore important that true changes in clinical status are interpreted correctly.

Conclusion

The 90th percentile means that one in ten results are outside the expected value due to normal variations. We consider this as an acceptable decision limit. This would mean that dif-

ferences larger than 6.6% for albumin, 12.4% for ALT, 11.2% for AST, 10.2% for GGT and 16.0% for LDH should be indications of clinical significance. Changes smaller than these values are at increased risk to be due to sample variation. An additional sample could be used when in doubt if the change is due to a clinical change or not.

Declarations

Author contributions: MB, JM, BR, AL: Conceptualization, data curation, formal analysis, methodology, resources, writing - original draft, writing - review & editing. MH: Writing - review & editing.

All authors approved the final version of the manuscript.

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Data availability: Data will be made available on request.

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