ESM. Appendix 1. Calculation of lactate-time integral and time-weighted mean lactate

We calculated the lactate-time integral by placing all the recorded lactate values on the y-axis and the time-points of lactate measurements on the x-axis for all patients, and then compared values between 90-day survivors and 90-day non-survivors. We calculated time-weighted mean lactate as total lactate-time integral divided by aggregate time of lactate measurements. The purpose of calculation of time-weighted lactate is to calculate a mean lactate value for a certain patient during a certain time period that takes the duration (time-weight) of each particular lactate level into account.

The lactate-time integral (time x lactate) depicts the "lactate burden" of each patient.
To give the reader a better appreciation of the differences between the lactate burdens of different patients, we calculated the time-weighted mean lactate, i.e. the lactate-time integral divided by the aggregate time of the observations. The time-weighted mean lactate may be interpreted as the mean lactate level during the ICU stay and used as on parameter for describing and comparing lactate levels in different patients.

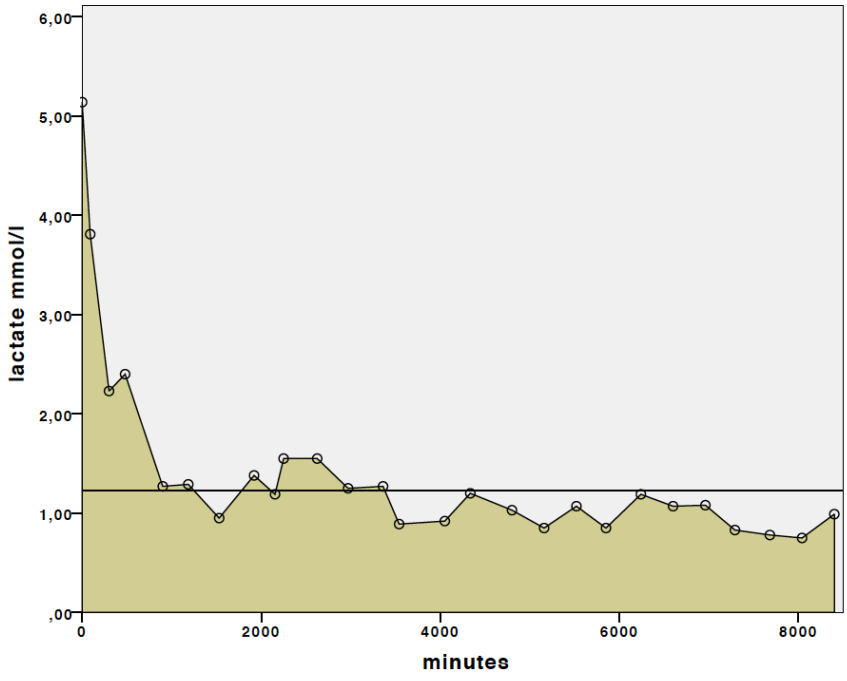

Fig. 1a: Lactate-time integral of a 90-day survivor (colored area = area under the curve). The reference line shows the *time-weighted mean lactate* of this patient (1.23 mmol/L) calculated as *the lactate-time integral / aggregate time of observations* (10304.4 min*mmol/L / 8400 min). The markers show each individual lactate measurement during the ICU-stay.

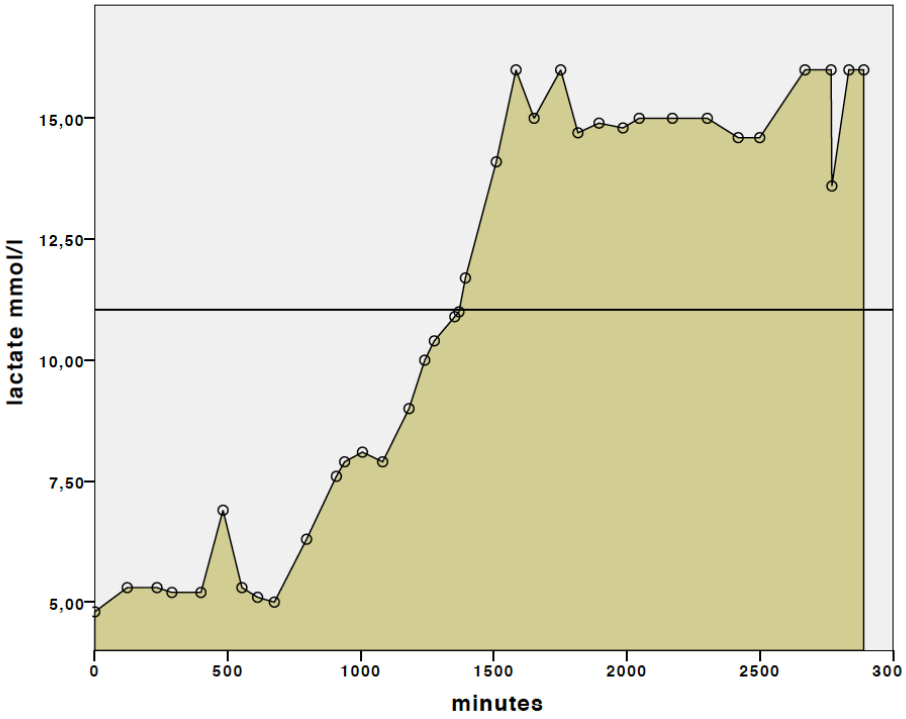

Fig. 1b: Lactate-time integral of a 90-day non-survivor. The reference line shows the time-weighted mean lactate (11.05 mmol/L).

To analyze the development of arterial lactate over time, we calculated the lactate-time integral for 6 hour intervals from 0 to 72 hours. All available lactate measurements were included. All patients and values were assessed, also those lacking observations for inclusion into calculation of change in lactate between different time-points as mentioned above. The values were then divided by the aggregate time of each observed time period for calculation of the time-weighted mean lactate per 6 hours. We also calculated the median values and the inter-quartile range for the lactate values for each 6 hour period from 0 to 72 hours using all available lactate values for 90-day survivors and non-survivors respectively.