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# Serum cholesterol and survival from acute inflammatory stress: African cows and UK citizens?

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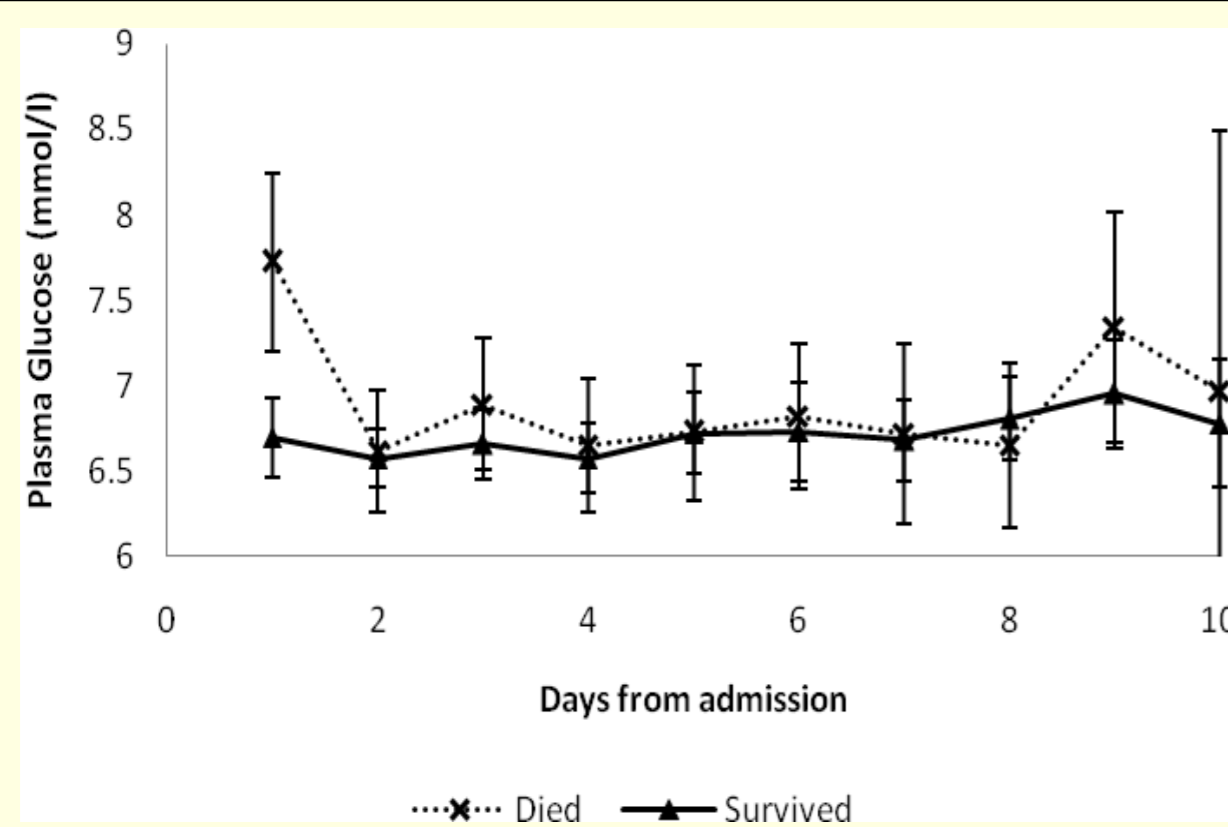
**Background:** This study demonstrates Informatics-based, e-Epidemiology knowledge-transfer between animal and human research: In 'omic studies with models of African cattle trypanosomiasis, we discovered important links between low cholesterol biosynthesis and susceptibility to infection, acute inflammation and death. In order to explore whether or not similar associations exist in humans, we chose intensive care as a setting for the study of people under severe inflammatory challenge. Human critical illness is associated with metabolic disturbances, with important links emerging between insulin resistance and lipid metabolism [1, 2]. Consistent lipid metabolic alterations, so called 'critical illness dyslipidemia', are characterised by increased levels of triglycerides (TGs), in association with decreases in high-density- (HDL) and low-density lipoprotein (LDL) cholesterol [1, 2]. However, in a recent subgroup of postoperative critical care patients receiving experimental tight glycaemic control, by intensive insulin treatment, there was evidence of insulin induced amelioration of critical illness dyslipidemia, which was associated with better clinical outcomes [3]. No studies have examined critical illness mortality in relation to the presence and pattern of critical illness dyslipidemia during routine therapeutic tight glycaemic control, which is a potential confounding factor in lipid metabolism.

**Setting and population:** We conducted a case-cohort study using patients admitted to the Intensive Care Unit at Salford Royal Hospitals NHS Foundation Trust between April 2006 and January 2007.

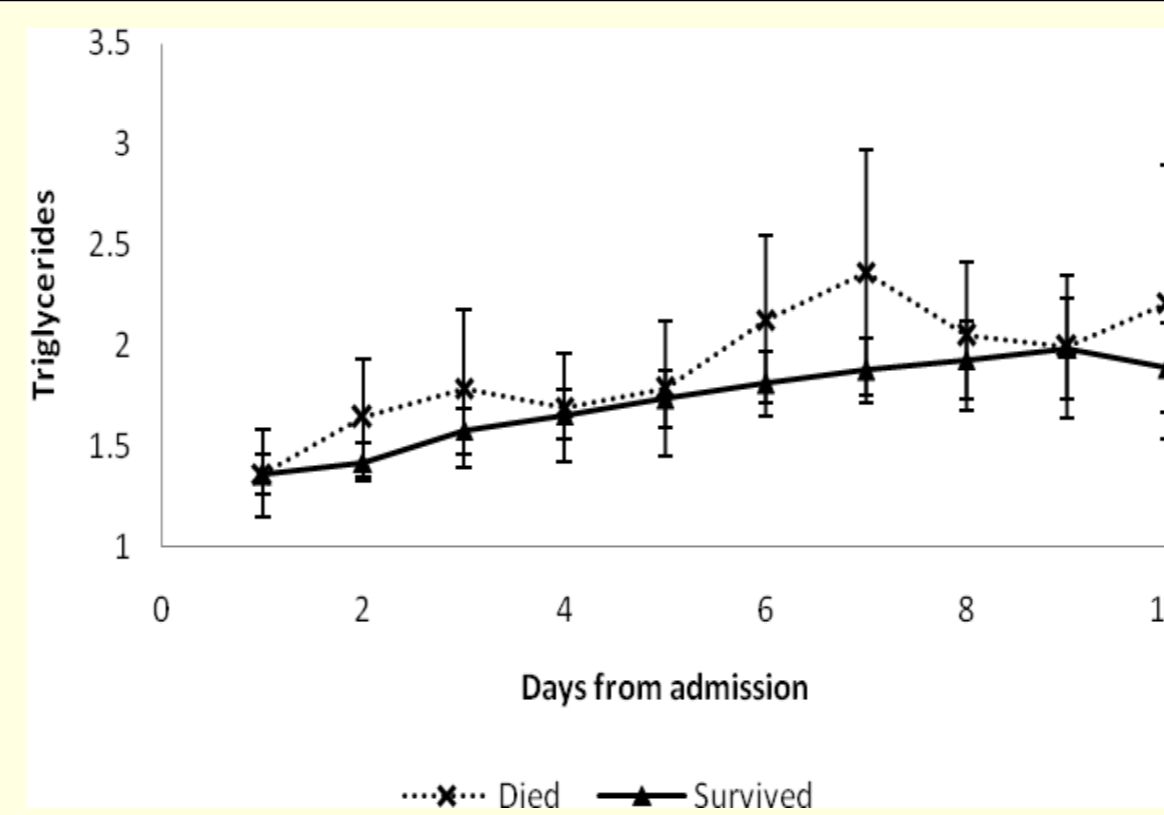
**Methods:** Biochemistry data, which are fed into the patient's health e-record, were extracted from the hospital's clinical information system, along with administrative data (admission/discharge data, demographics, and deaths), and managed using a prototype 'e-Lab' research query system built with Microsoft SQL server. The data were cleansed to remove data input errors and match data types, where necessary, in order that the data could be linked. Tables of data were constructed showing whether or not each patient was living or dead 28 days after the date of admission to the intensive care unit and lipid and glucose levels for the first 8 days in intensive care. The data were summarized as charts and descriptive statistics prior to univariate analysis and multivariate statistical modeling.

**Findings:** Patients who did not survive to 28 days had a total serum cholesterol on the first day of admission 0.31 (0.05–0.58) mmol/l lower than those who survived. There was no significant difference in HDL cholesterol ( $P = 0.4$ ) or triglycerides ( $P = 0.9$ ) by survival group. The prognostic value of total cholesterol on admission remained significant ( $P = 0.03$ ) if gender was added to a logistic model of death by 28-days, but did not remain significant with the addition of age, severe sepsis, or APACHE II score. While total serum cholesterol, HDL- and non-HDL cholesterol fall during the period of first to second ICU day, patients that subsequently survived to 28 days had significant mean increases in total cholesterol over the period day 2–3 (+0.13 mmol/l) compared with non-survivors (-0.10 mmol/l); 95% confidence interval for the difference = 0.10–0.37;  $P=0.001$ . This apparent switching in total serum cholesterol responses in survivors by ICU day 3 was significant in the non-HDL, with a difference of 0.17 (0.05–0.29). In a logistic regression model of death at 28-days, cholesterol and glucose at days 1, 2 and 3, APACHE II score, and severe sepsis, the most consistent predictors of death were cholesterol at day 3 ( $P = 0.005$ ), and day 2 ( $P = 0.01$ ), relative to baseline and each other, followed by APACHE II score ( $P = 0.04$ ).

**Discussion:** Our clinical observations add understanding to the links between lipid metabolism and host responses to severe tissue injury and infection. Furthermore, our study develops the concept that cholesterol may be protective during acute severe illnesses in humans, despite therapeutic tight glycemia, akin to our previous findings in African cattle trypanosomiasis, and that non-HDL cholesterol fraction responses (forward cholesterol transportation) may be associated a mortality susceptibility signal. The factor bringing the animal biology close to front-line clinical research here was Informatics. The e-Epidemiology relied not only on routinely-collected data but also enhanced collection of data (lipids), to reduce ascertainment bias. A key factor in the success of the project was having Informaticians embedded in clinical research environments for part of their time, which enabled the rapid shaping of the hypotheses, swift ethical approvals, and funding (within hospital resources) for additional laboratory sample processing.



**Figure 1:** Daily laboratory plasma glucose (mmol/l) for survivors and non-survivors (mean and 95% confidence interval)

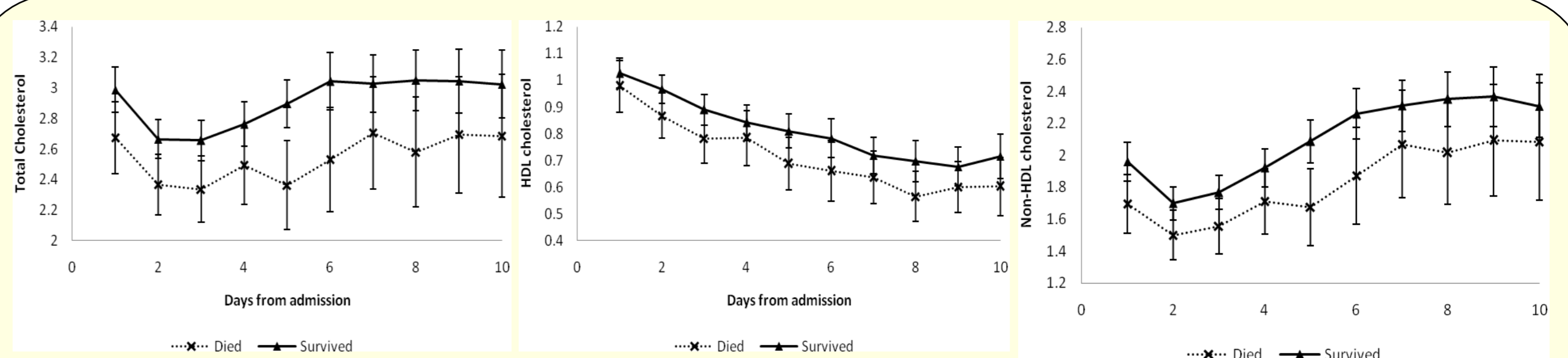


**Figure 2:** Daily serum triglycerides (mmol/l) for survivors and non-survivors (mean and 95% confidence interval)

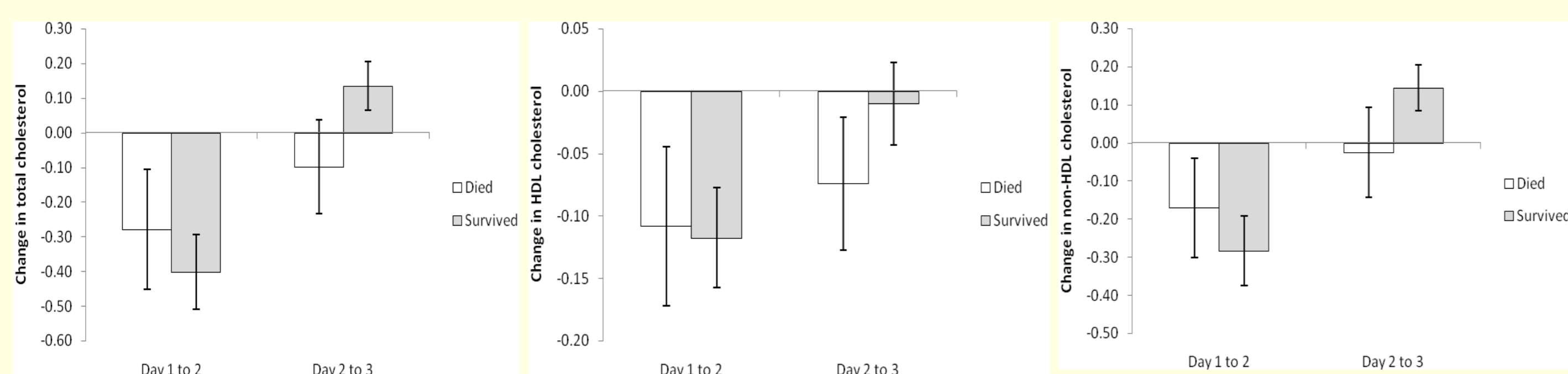
Figure 1 demonstrates the tight glycaemia control for survivors and non-survivors (at 28 days) within the first 10 days of admission to ICU.

Figure 2 shows that daily serum triglyceride levels for survivors and non-survivors remain at similar levels.

Figure 3 shows an initial decrease in serum cholesterol and non-HDL cholesterol followed by a recovery, for both survivors and non survivors. However, the total cholesterol on admission and the ability to recover cholesterol levels was higher in survivors than in non-survivors.



**Figure 3:** Total serum cholesterol, HDL- and non-HDL cholesterol (mmol/l) responses for survivors and non-survivors (mean and 95% confidence interval)



**Figure 4:** Changes in total, HDL- and non-HDL serum cholesterol (mean difference and 95% confidence interval mmol/l) during first three days of intensive care

Figure 4 shows that the average total cholesterol level in survivors increases from day 2 to day 3 in 28-day survivors but decreases in patients who died within 28 days. This effect was due to the non-HDL component of total serum cholesterol.

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