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The prognostic value of global haemostatic tests in the intensive care unit setting

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Background: Global haemostatic tests are often abnormal in critically ill patients, secondary to activation or consumption of coagulation factors or inhibitors. Methods for analysing plasma levels of these factors are, however, not widely available, and the predictive value of global tests is not known. We examined the clinical applicability to predict the outcome of the global haemostatic tests used at most hospitals.
Methods: Blood was collected from patients within 6 h of admission to an intensive care unit (ICU) and tested regarding platelet count, International Normalized Ratio (INR), and activated partial thromboplastin time (APTT). Ninety-two patients with platelet counts $<100\times10^{9}l^{-1}$, INR >1.36 and/or APTT >45 s were included in a study group, and an additional 92 patients with a comparable age and sex distribution, but not fulfilling these laboratory criteria, constituted a control group. The following data were recorded for each patient: number of days in the ICU and hospital; alive or deceased when released from the ICU and hospital; survival at 30 days and 180 days.
Results: Survival upon discharge from the ICU and hospital was significantly reduced in the study group. This was especially pronounced in patients with medical disorders, whereas the survival rate was slightly higher in surgery patients. Expressing the survival predicting ability of the screening tests as odds ratios for all patients (study and control groups together) indicated that prolonged APTT in particular foretold a lower survival rate at studied time-points after admission to the ICU.
Conclusions: The global haemostatic tests INR and APTT can predict survival in critically ill patients, and prolonged APTT in particular seems to be associated with a negative prognosis.

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Key words: anesthesiology; blood coagulation disorders; disseminated intravascular coagulation; intensive care; intensive care units; international normalized ratio; mortality; partial thromboplastin time; platelet count.

PATIENTS referred to intensive care units (ICU) often have coagulation disturbances. Accordingly, clinical manifestations such as thromboembolism or bleedings are common in these patients.

Global haemostatic tests such as platelet count, International Normalized Ratio (INR), and activated partial thromboplastin time (APTT) are widely available and simple to perform. The results of these tests are often abnormal in acquired coagulation disorders, which are commonly seen in patients admitted to intensive care units. There are also more sophisticated methods designed specifically for detecting alterations in the coagulation and fibrinolytic systems, including assays for soluble fibrin, thrombin-antithrombin complexes, prothrombin fragment $1+2$, antithrombin, fibrin D-dimers, and protein C. These analyses can facilitate the diagnosis of DIC (1–4), but, unfortunately, most of them are very expensive and are available only during office hours at a limited number of healthcare facilities specializing in coagulation disorders.

We investigated the correlation between global haemostatic tests and the outcome (survival and length of hospitalization) in critically ill patients in order to ascertain the clinical usefulness of the analyses that are available at most hospitals.

Methods

Study design and subjects

We conducted a prospective study at the main ICU, the Department of Anaesthesiology and the Department for Coagulation Disorders at Malmö University Hospital. Surgical and medical patients are treated at this ICU, but the hospital also has a coronary care unit, as well as a special intensive care unit for patients who have infectious disorders or burns and are in need of respiratory support. At the time the study

was performed, there was also a thoracic surgery ICU.

The patients admitted to the main ICU from March 1997 to April 1998 were included in the study.

Blood samples were taken within 6 h of admission. Platelet count (normal range 125–340 $\times 10^9 l^{-1}$), INR (normal value <1.2), and APTT (normal value 24–37 s) were determined. The haemoglobin concentration (Hb) was also analysed.

Patients were allocated to a study group and a control group. Inclusion in the former required one or more of the following screening results: platelet count $<100 \times 10^9 l^{-1}$, INR > 1.36 (PT < 50%), APTT > 45 s.

During the study period, 1114 patients were admitted to the ICU, some of them ($n = 88$) on more than one occasion (79 patients twice; six patients three times; two patients four times; one patient six times). Patients admitted fulfilling one or more of the following criteria were excluded: patients younger than 16 years ($n = 89$), stay in the ICU less than 6 h ($n = 38$), heparin given within 8 h prior to admittance ($n = 80$), peroral vitamin K-antagonist (warfarin sodium or dicumarol) taken within 7 days ($n = 25$), or any previously known haematological or coagulation deficiency ($n = 10$). We also excluded those who underwent any thrombolytic treatment ($n = 87$), acute treatment for rejection after transplantation (ATGAM, ATG, OKT 3, or Thymoglobulin; $n = 9$), preoperative treatment ($n = 2$), or isolated treatment for pain ($n = 7$), as well as patients referred directly from an ICU at another hospital ($n = 17$).

In all, 750 of the patients admitted to the ICU could be included for blood tests. However, for practical reasons, sampling was preferentially done during office hours, thus blood was collected from 494 of the 750 patients. Due to faulty blood sampling, the number was further reduced to 474. Ninety-two patients fulfilled the criteria for the study group. The same number of controls was accrued by selecting the next appropriate patient admitted to the ICU after each patient included in the study group, taking into account the sex of the individuals and allowing an age difference of less than 5 years. Based on diagnoses, the study group and the control group were each divided into two subgroups (Table 1), which were designated: 'medicine' (including patients who underwent only minor or no surgery) and 'surgery' (comprising those who did undergo major surgery as well as trauma patients). The aim of this study was to study the use of global haemostatic tests in an unselected ICU population, not to study the tests in certain groups of diagnoses. This is the reason why we split the groups into just medicine and surgery subgroups. The main diagnoses in the subgroups were as follows. Study medicine subgroup: nine patients with gastro-intestinal bleeding, four with cardiac diagnoses, two suffering from respiratory insufficiency, two with epilepsy, two intoxication patients, and five with infection disease. Corresponding numbers in the control medicine subgroup were 2, 13, 5, 1, 4, respective 4. In addition, three endocrinology patients were included. In the study surgery subgroup there were 27 patients who underwent abdominal surgery (23 intestine tract and four liver or pancreas), nine vascular surgery, five urology surgery, one ENT surgery, 13 orthopaedic surgery, and 11 were trauma cases. Corresponding numbers in the control surgery subgroup were 16 (11 and 5), 3, 1, 5, 5, respective 15. There were also three transplantation patients.

The study group and the control group were monitored in the same way. APACHE II-scores (5) were determined for the first 24 h. Briefly, this is a system to score the severity of the disease relevant to the ICU admittance. Moreover, we recorded the duration of mechanical ventilation, the time in the ICU and for all

Table 1

Demographic data and blood test results for the study group, the control group, and their respective subgroups (designated medicine and surgery).

	Study group			Control group		
	Total n = 92	Medicine n = 24	Surgery n = 68	Total n = 92	Medicine n = 38	Surgery n = 54
Age, years[1]	65.2 (17.1)	65.9 (14.0)	65.0 (18.1)	65.5 (16.9)	65.7 (14.1)	65.4 (18.8)
Gender, f/m	35/57	6/18	29/39	35/57	10/28	25/29
Platelet count, $10^9/L$[2,3]	92 (65, 160)	98 (68, 147)	91 (64, 167)	212 (157, 274)	216 (164, 278)	212 (154, 275)
INR[2,3]	1.48 (1.36, 1.64)	1.52 (1.40, 1.62)	1.48 (1.33, 1.66)	1.06 (1.00, 1.18)	1.01 (1.00, 1.15)	1.11 (1.01, 1.19)
APTT, s[2,3]	37 (33, 44)	35 (32, 43)	37 (34, 44)	29 (27, 31)	28 (27, 30)	30 (27, 32)
Haemoglobin, g/L[2]	110 (97, 122)	104 (88, 120)	111 (101, 122)	121 (104, 138)	133 (107, 146)	114 (102, 131)

[1]Mean and (±SD).
[2]Median (first and third quartiles within parentheses).
[3]Significant difference between the study and the control group (total and subgroups, respectively); $P < 0.001$.

hospitalization, as well as whether the patient was alive or deceased when released from the ICU and the hospital. Several patients were transferred to their local hospitals, and the length of stays there were included in the mentioned time data. We also recorded survival at 30 days and 180 days after the blood screening tests were done.

The study was approved by the Ethics Committee of the University of Lund.

Methods

The blood samples were analysed by standard methods at the Department of Clinical Chemistry, which is accredited according to EN 45001/ISO/IEC 17025 by SWEDAC (Swedish Board for Accreditation and Conformity Assessment). When the study was performed, the prothrombin complex (PT) was expressed as percent to measure the activity of factor II, VII and X (method according to Owren;6); and determined using SPA, Diagnostica Stago, Asnières, France. All calculations were performed using PT-values in percent, which was the way to express results when the study was carried out. The results were then converted to INR and this is the way they are presented in this paper.

The term respirator time refers to the amount of time for respirator-assisted breathing in the ICU. If a patient underwent surgery before arriving at the ICU, the length of time for the operation and for transportation to the ICU were not counted. Respirator time also included assisted ventilation given to a patient before admission to the ICU due to reasons other than surgery (e.g. respiratory arrest, cardiac arrest, and loss of consciousness).

Statistical methods

All statistical analyses were done using SPSS for Windows (SPSS Inc, Chicago, IL). The following statistical methods were used. Mann–Whitney *U*-test: comparing blood test results, APACHE II score, time on mechanical ventilation, and duration of stay in ICU and hospital. Pearson's chi-squared test and Fisher's exact test: comparing survival upon discharge from ICU and hospital. Log-rank test: comparing survival at 30 and 180 days. *P*-values of less than 0.05 were considered to be statistically significant.

Results

Demographic data and the results of the global haemostatic tests and the haemoglobin levels are presented in Table 1. The platelet count, INR, and APTT data differed significantly between the study group and the control group: the former patients had lower platelet count values and higher INR and APTT, as expected. We also found significant differences within the medicine and surgery subgroups. The haemoglobin level was significantly decreased in the study group compared to the controls (entire group and medicine subgroup; $P < 0.005$, respectively, $P < 0.006$), but not in the surgery subgroup ($P = 0.30$).

During the first 24 h in the ICU, APACHE II score was significantly higher ($P = 0.013$) in the surgery study subgroup [16 (12, 21); median (first and third quartiles)] compared to the surgery control subgroup [13 (10, 17)]. The corresponding numbers for the entire study group and medicine subgroup compared to the respective controls were [18 (13, 24) vs. 14 (11, 20); $P = 0.073$], respectively [24 (17, 31) vs. 18 (12, 34); $P = 0.54$]. There were no significant differences neither between the entire study and control group [5.0 (0.0, 36) vs. 2.8 (0.0, 15); $P = 0.12$] nor the subgroups when considering the time on mechanical ventilation.

Figure 1 illustrates the cumulative survival for the medicine and surgery subgroups of both the study and the control patients. It can be seen that the majority of deaths occurred early during the course of disease and that the prognosis was much poorer for the study medicine subgroup than for the other subgroups. There were significant differences in survival between the study and control group at 30 and 180 days after admission to the ICU ($P = 0.002$, respectively, $P < 0.001$) as well as between the subgroups.

There were also significant differences in survival between the study group and control group at the time of discharge from the ICU (74% vs. 97%; $P <$

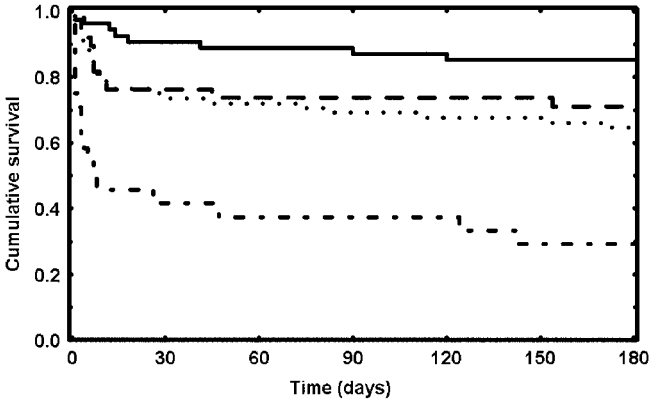

Fig. 1. Cumulative survival rates (Kaplan-Meier plot) for the investigated patient subgroups plotted as function of time. –·–·–·– Study, medicine; – – – – – Control, medicine; ····· Study, surgery; ——— Control, surgery. Statistics for equality of survival distributions at 30 and 180 days: significance level: control versus study (medicine subgroups) 0.002, <0.001; control versus study (surgery subgroups) 0.015, 0.009.

Table 2

Odds ratios (with 95% confidence interval) of screening parameters on survival rate in the total material (n = 184) at some different points of time (the odds ratios are adjusted for age and the other screening tests at multivariate logistic regression).

	Upon discharge from ICU	Upon discharge from hospital	30 days after admittance to ICU	180 days after admittance to ICU
Screening TPK	1.9 (0.64–5.5)	1.4 (0.54–3.4)	1.0 (0.41–2.6)	1.2 (0.52–2.9)
	0.25	0.52	0.94	0.64
Screening INR	0.38 (0.14–1.1)	0.56 (0.25–1.3)	0.54 (0.24–1.2)	0.43 (0.20–0.92)
	0.063	0.17	0.14	0.030
Screening APTT	0.068 (0.020–0.24)	0.062 (0.016–0.24)	0.062 (0.016–0.24)	0.10 (0.026–0.41)
	<0.001	<0.001	<0.001	0.001

New groups ('study group' and 'control group' first mixed) formed by splitting at the inclusion value of respective screening parameter. Significance levels are given.

0.001) and the hospital (64% vs. 86%; $P < 0.001$). The differences were also significant when comparing the subgroups. In contrast, there were no differences between survivors in the study and the control group in the length of either ICU care [1.0 (1.0, 3.0) vs. 1.0 (1.0, 2.0); $P = 0.52$; median (first and third quartiles)] or hospitalization [18 (10, 29) vs. 14 (8.0, 25); $P = 0.30$]. Neither were the differences significant when comparing the subgroups.

Table 2 shows the ability of the screening tests to predict survival rate at different times expressed as odds ratios for all the studied patients (study and control groups together). A prolonged APTT (>45 s; the inclusion criterion for the study group) prognosticated a significantly lower survival rate at all timepoints studied (upon discharge from ICU and from hospital and at 30 and 180 days after admittance to ICU). A high INR value (>1.36) predicted significantly decreased survival rate at 180 days. The INR value had no predictive power at the other points of time. The platelet count did not, however, predict survival rate at any of the four studied points of time.

Figure 2 illustrates the cumulative survival for the surgery and medicine subgroups when splitting all the 184 patients according to the inclusion criteria of this study. The most sinister outcomes were seen for survival depending on APTT (Fig. 2c) and INR (Fig. 2b). Regarding APTT, respectively, INR, there were significant differences in survival between the main groups ($P < 0.001$, respectively, $P < 0.001$) and the subgroups at 180 days after admission to the ICU. Such significant differences were not seen for the platelet count (Fig. 2a; $P = 0.12$).

Discussion

Our objective was to determine whether global haemostatic tests such as platelet count, INR and APTT can predict the clinical outcome for an unselected ICU population. We found that patients with platelet count $< 100 \times 10^9 l^{-1}$, INR > 1.36, and/or APTT > 45 s had lower survival rates than matched controls whose global haemostatic tests were close to normal. Prognoses appeared to be particularly poor for the medicine subgroup of the study patients. These simple tests are available at most hospitals, and, together with clinical manifestations such as bleeding or thrombosis, they often represent the only guidelines for coagulation therapy. We assigned patients to a study group and a control group on the basis of what are considered to be clinically important results of the indicated global tests (using the normal range of the tests to assign the groups would not have been productive as by definition only 95% of the healthy population are covered by the normal range). These two groups were comparable with regard to age, gender, and number of patients included. The haemoglobin levels were lower in the entire study group, as well as the medicine subgroup of these patients. This is not surprising and indicates that abnormal global haemostatic test results were caused by more severe disease, presumably to some extent increased bleeding. In the study group, the haemoglobin levels in the surgery subgroup did not differ significantly from controls, probably due to transfusion therapy.

We found that the study group showed a tendency toward higher APACHE II score. The survival rate was decreased in the study group compared to the control group, which implies that abnormal global haemostatic tests indicate a more sinister health situation. Our most important finding was that a prolonged APTT suggested shorter survival at all points of time studied. To some extent, this was also true for high INR (at 180 days), whereas the platelet count seemed to be less sensitive and was not useful in predicting survival in our study.

The APTT test measures most coagulation factors involved in the intrinsic plasma coagulation pathway,

but INR performed in our country detects merely factors II, VII, and X (method according to Owren; 6). Accordingly, APTT is the better one of these two tests at predicting survival, because prolonged APTT can reveal most abnormalities in plasma coagulation, whereas prolonged INR uncovers only a few specific disturbances. On the other hand, in many other countries, one uses the INR method according to Quick (7). In addition, this method mirrors the fibrinogen and factor V levels. Platelet count is a quantitative test that does not provide qualitative information about platelets, thus it is not a sensitive tool for measuring the function of primary haemostasis and therefore probably not a reliable predictor of ICU outcome. Also, the platelet count is influenced, e.g. by an inflammatory reaction, which consequently may have an impact on the predictive value.

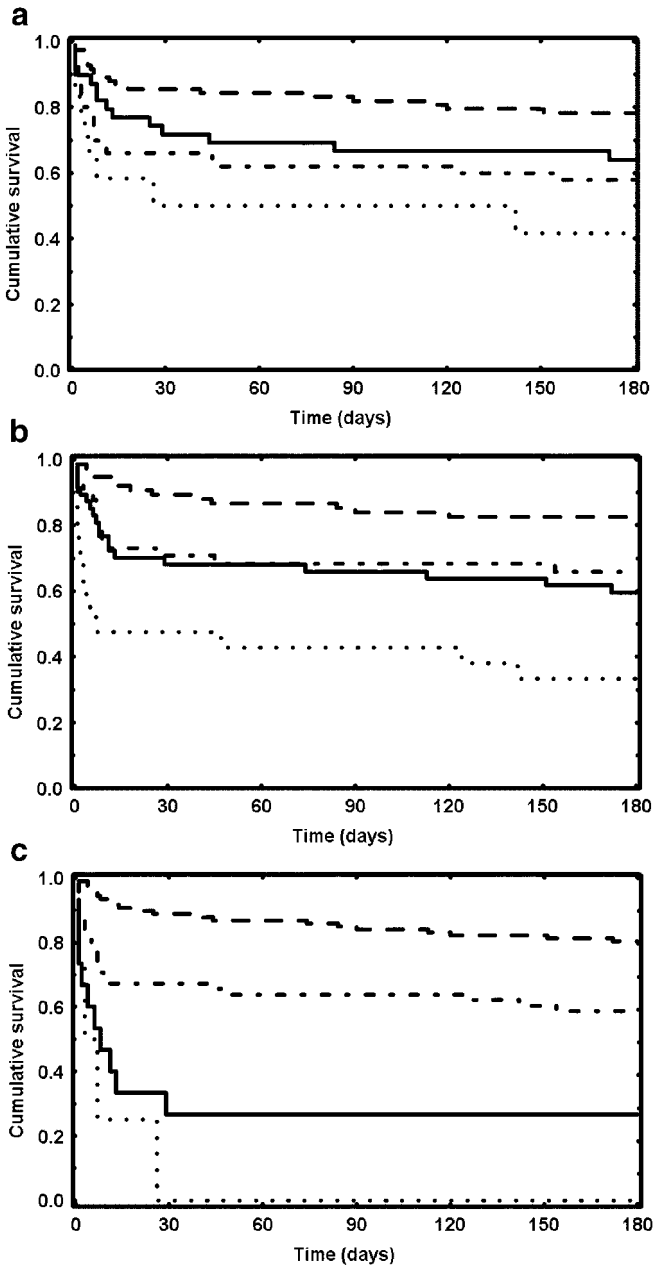

Fig. 2a–c. Cumulative survival rates (Kaplan-Meier plot) for the investigated patient subgroups plotted as function of time. (a) Splitting criterion is platelet count; (b) Splitting criterion is INR; (c) Splitting criterion is APTT. –·–·–·– Not fulfilling study inclusion criterion, medicine subgroup; ····· Fulfilling study inclusion criterion, medicine subgroup; ––––– Not fulfilling study inclusion criterion, surgery subgroup; ——— Fulfilling study inclusion criterion, surgery subgroup. Statistics for equality of survival distributions at 180 days: significance level: (a) between medicine subgroups: 0.30, between surgery subgroups: 0.086; (b) between medicine subgroups: 0.005, between surgery subgroups: 0.003; (c) between medicine subgroups: 0.004, between surgery subgroups: <0.001.

Lee and coworkers (8) studied medical ICU patients with sepsis and found thrombocytopenia ($<150\times10^9$ l^{-1}) but not disseminated intravascular coagulation (DIC) to be a risk factor for mortality. Nijsten and coworkers (9) reported that a blunted or absent rise in platelet count in critically ill patients was associated with increased mortality. Their study material comprised consecutive adult patients admitted to a surgical ICU of a university hospital. Stephan and coworkers (10) also studied surgical ICU patients and found thrombocytopenia patients to have higher mortality. Vanderschueren et al. (11) found both a low nadir platelet count ($<150\times10^9l^{-1}$) and a large fall of platelet count (to ≤50% of admission) to predict a poor vital outcome in adult predominantly medical ICU patients. Chakraverty and coworkers (12) found that increased prothrombin time (PT) ratio (probably according to Quick; 7) and low platelet count were common in patients admitted to an adult intensive care unit and both factors were predictive of excessive bleedings and poor outcome. Pixley et al. (13) studied medical ICU patients and found low or persistently low serial factor*V*-values to be associated with a poor prognosis, whereas high or increasing values correlated with a favourable outcome. The level of factor V is related to the INR value according to Quick (7) but not to the INR value according to Owren (6) as used in our study. McManus and Churchwell (14) found that APTT >50 s (or hypofibrinogenaemia) was superior to predict outcome of paediatric patients with meningococcal sepsis or the systemic inflammatory response syndrome (SIRS) with purpura.

Our study indicates that APTT is superior to both platelet count and INR (according to Owren; 6) as predictor of outcome in an adult ICU study cohort. To our knowledge, there are no reports on the predictive value of the combined tests used in our study applied to a main ICU taking care of both medicine and surgery adult patients. Even if our study material is

to a certain extent selected, it can be considered to be fairly representative for the common ICU patient.

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