SAHLGRENSKA ACADEMY

A Descriptive Study of Spontaneous Elevation of Activated Partial Thromboplastin Time in Critically Ill Patients

Degree Project in Medicine

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Gothenburg, Sweden 2019

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1. Abbreviations

APTT	Activated Partial Thromboplastin Time
PT	Prothrombin time
ICU	Intensive Care Unit
TF	Tissue Factor
HMWK	High-molecular weight kininogen
SAPS 3	Simplified Acute Physiology Score 3
APACHE II	Acute Physiology and Chronic Health Evaluation II
TEM	Thromboelastometry
TEG	Thromboelastography
ALAT	Alanine aminotransferase
ASAT	Aspartate aminotransferase
ALP	Alkaline phosphatase
CRP	C reactive protein
RASS	Richmond Agitation-Sedation Scale
GCS	Glasgow Coma Scale

2. Abstract

Title: A descriptive study of spontaneous elevation of activated partial thromboplastin time in critically ill patients

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Introduction: Coagulation abnormalities are common in intensive care patients and are associated with higher risk of mortality. Activated Partial Thromboplastin Time (APTT) is one of the most frequently used tests to illustrate the coagulation status of patients. According to earlier observations, APTT tends to increase spontaneously after admission to intensive care. However, the details and relevance regarding this issue remain unclear.

Objective: The purpose of this study was to investigate and describe how APTT evolves spontaneously in patients admitted to intensive care in order to improve their treatment and safety.

Methods: A prospective, observational study was conducted on patients admitted to the Intensive Care Unit (ICU) between January and April 2019. Patients with known diseases or treatments that elevated APTT were excluded. Blood samples were collected and analyzed on a daily basis from admission until APTT was normalized.

Results: 44 patients were included. APTT was significantly elevated on day 2 (p=0.01) and then subsequently normalized (APTT <32 seconds) from day 4-5. Median for the distance from lowest to highest point was 3.5sec (range 1.5-9.5) and maximum value, reached on average on day 2, was 33.5sec (range 29-52) which was 31% higher than the patient's individual baseline. A linear increase in APTT was observed in all studied patients

(p=0.00001), mean elevation of 15%, between the first two days of the first days of rising APTT.

Conclusion: A significant spontaneous elevation of APTT above normal was observed in the ICU patients during the first days after admission with normalization within five days. This could indicate that an invasive procedure that infers a risk of bleeding in critically ill should either be done as soon as possible or has to be postponed for the first days in the ICU.

Key words: Intensive care, Activated partial thromboplastin time, APTT, coagulation, critical illness

3. Background

3.1 Coagulation hemostasis

Maintained capacity for coagulation in case of injury as well as maintained balance between coagulation and fibrinolysis in normal homeostasis are central biophysical reactions that continuously prevent bleeding from minor injuries on blood vessel walls and protect against infections (1). The key purpose of the coagulation process is to build fibrin which interacts with blood platelets to seal an injured vessel in order to stop bleeding without strangling blood flow to other tissues (2). The modern view of the coagulation cascade is that it follows a Y-shaped pattern with two different parallel initiation mechanisms (2) which are called the intrinsic (contact activation) pathway and the extrinsic (tissue factor) pathway, respectively. Both are considered a zymogenic series of reactions from an inactive precursor molecule that is activated to become an active enzyme (3).

The extrinsic pathway, considered to be the primary reaction for the initiation of blood coagulation, is activated when the endothelium is traumatized and tissue factor (TF) from the vessel wall is exposed (4). This pathway is named after the fact that plasma needs to come into contact with an outer, extrinsic substance in order to initiate the cascade (3). Coagulation factor VII interacts with TF and builds a complex that activates factor X (2).

The intrinsic pathway occurs on activated platelets and starts with formation of a primary complex consisting of collagen, high-molecular-weight kininogen (HMWK), prekallikrein and factor XII. These together activate factors XI, IX and VIII. Eventually, both the extrinsic and intrinsic pathways coincide to activate factor X which then cleaves inactive prothrombin,

resulting in thrombin. Thrombin is needed to convert inactive fibrinogen into active fibrin, and the cascade ends with formation of a stable fibrin clot (2).

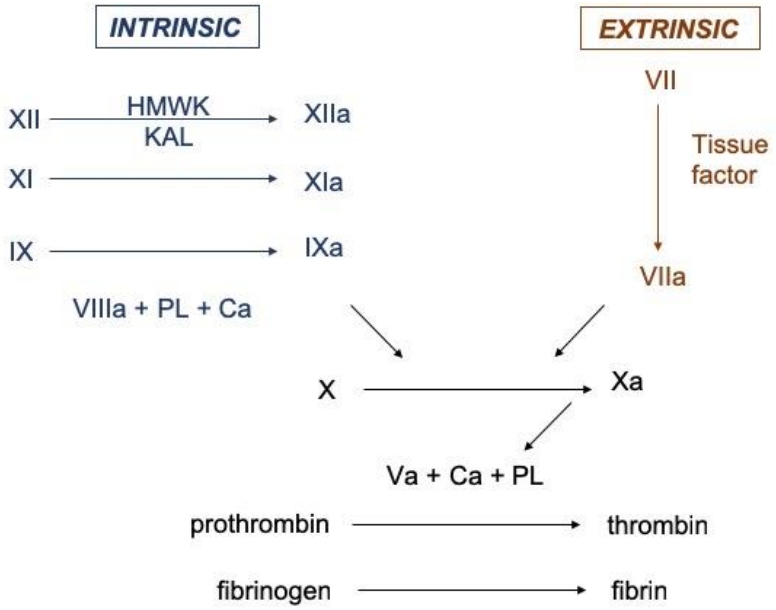

Figure 1 A schematic illustration of the coagulation cascade and its different pathways (5). The intrinsic pathway is illustrated in the left column and the extrinsic in the right. Activation of factor X leads to cleavage of inactive precursors to active molecules thrombin and fibrin.

HMWK, high molecular weight kininogen; KAL, kallikrein; PL, phospholipid; Ca, calcium ions. All of which are co-factors essential to the process.

The clot is broken down by fibrinolysis which requires participation of several receptors and cofactors (6). The process is initiated in the presence of fibrin and performed by a central lytic enzyme, plasmin (7). In order to maintain hemostasis in the blood stream, the fibrinolytic activity must be controlled which is done by using a variety of inhibiting enzymes (6).

3.2 Coagulation analysis

Activated Partial Thromboplastin Time (APTT) is a measure of the composite function of the intrinsic pathway (8), indicating the time it takes for blood to form a clot. The coagulation factors that APTT indirectly measures are prekallikrein, HMWK, fibrinogen and factors II, V, VIII, IX, X, XI and XII (9). As the APTT assay only engages the contact activation pathway, participation of the tissue factor in the reaction process is not needed; therefore, the test is named "partial" (9). To get a more complete view of the patient's coagulation status, APTT is tested together with prothrombin time (PT) which is a standardized test focused on function in the extrinsic pathway (8, 9).

The APTT test has been available since 1953 and was originally designed to detect hemophilia and increased bleeding tendency (10). Today, there are over 300 different analysis methods in use (11) which is why standardization of the test has not been possible (9). The specific elements in each method influence the hemostatic measurements which is why it is crucial to know which analysis method is being used (8, 12). Each method reports APTT results in seconds, but the normal interval varies depending on the exact method (13). At the Sahlgrenska Hospital, the normal interval today lies between 24 and 32 seconds (14), and is based on recommendations from the producer and locally performed controls on healthy people with assumed normal distribution (15).

The APTT assay is sensitive as it can be affected by several factors (9, 13, 16). Table1 summarizes the most important sources of false APTT results and their effect on the test.

Table 1 Factors that lead to false APTT results. The table shows in which direction APTT is shifting in presence of different confounders and how excessive their effect is estimated to be in relation to each other (16).

Confounders to false APTT	**APTT direction**
Incorrect sample collection	+ / -
Pediatric population	+
Liver dysfunction	+++
Heparin	+++
Anticoagulants	+
Lupus anticoagulans	+
Specific antibodies (inhibitors)	++
Coagulation factor deficiency (hereditary, DIC or massive bleeding)	++

Note: + prolongation, - shortening

The sample collection must be done correctly which means avoiding both over- and underfilled collection tubes that can lead to falsely prolonged or shortened APTT (9). According to a study made in Utah, there is no clinically significant difference whether the sample is taken from a peripheral arterial catheter or a peripheral venipuncture (17). Routine venipuncture, however, minimizes sample activation and is therefore considered the most optimal collection procedure for APTT (9).

The APTT test is frequently used in adult populations, and the same reference interval is used throughout adulthood without any age-related adjustments. As infants have unique properties specific to their coagulation system, the reference interval is different for them (18).

The liver plays a key role in the coagulation process through its synthesis of coagulation factors II, V, VII, VIII, X, XI, XII, XIII and fibrinogen, all of which have a primary procoagulant function, as well as antithrombin which is primarily an anticoagulant factor (19). In chronic liver disease, the concentration of these factors is markedly altered (20), often

manifesting with decreased levels, except for fibrinogen which is an acute phase protein and often elevated in case of an end-stage liver disease (19). Both APTT and PT become significantly increased due to the general effect that the liver has on coagulation (20). These tests are reflecting two different parts of the coagulation cascade and are linked together by the liver which means that a mutual elevation of APTT and PT is most likely due to hepatic failure. An isolated elevation of APTT strongly indicates a condition that does not involve the liver.

Treatment with heparin or multiple anticoagulants leads to prolonged APTT but is not always associated with increased bleeding tendency (13). Heparin influences the clot formation by inhibiting thrombin and factor Xa in the intrinsic pathway (21). Repeated samples for APTT are used to monitor heparin dosage but must be critically evaluated due to APTT's sensitivity to confounders (13).

Testing for APTT is important in the clinic and is often used in surgery and anesthesia to determine the patient's bleeding tendency (13). To consider it safe to undergo an invasive operative procedure, e.g. lumbar puncture, the test results must lie within normal range. A prolonged APTT of unknown cause is a direct contraindication to a such procedure (14). However, because of the APTT test's sensitivity to confounders, it is debatable whether or not it should be used in this context at all. It is a convenient method for the physician, but a proper medical history, however, has shown to give much more valid information regarding the patient's potential coagulation defects (13, 22). Unfortunately, the history is not always easy to obtain from the patient, especially if critically ill, such as during intensive care.

Thromboelastometry (TEM) is a method for coagulation analysis that has recently become an important tool within intensive care (23). However, the assay being rather expensive, it is not in widespread use. The assay uses the gradual change in viscoelastic properties during clot formation in a sample of whole blood, either with or without supplementary substances or dynamic activation (24). The test, which in most respects is comparable to thromboelastography (TEG), is based on the clot forming between the inside of a cup and a centrally placed oscillating pin (24). The *in vitro* coagulation process is presented by a graphical and numerical illustration over time (25). It determines different modalities such as reaction time (R value or Clotting Time) which represents how many seconds it takes to detect the first evidence of a clot formation (26, 27). Clotting time, clot firmness and how fast the clot is broken down by fibrinolysis are graphically illustrated (Fig.2). Depending on the choice of added reactants, different profiles are obtained. For instance, a graph called INTEM uses phospholipids, whereas EXTEM uses tissue factor as reactant in the analysis (26).

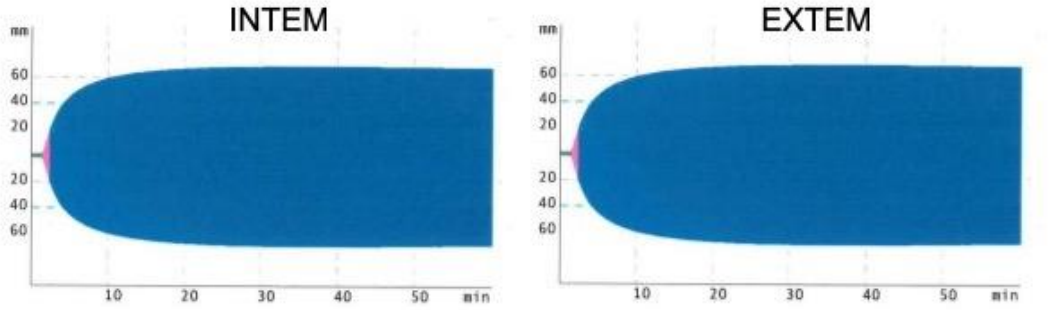

Figure 2 Two of four coagulation graphs used in thromboelastometry at Sahlgrenska ICU. The aim with this figure is to exemplify a normal coagulation status analyzed in the same patient at the same time, which is why the illustrated graphs appear identical. Time is illustrated on x-axis and clot thickness on y-axis. The initiation phase (clotting time) is shown in green, clot formation time in pink and clot stability in blue. On the left, INTEM is showing

the function in the contact activation pathway. EXTEM on the right is used to illustrate function in the tissue factor pathway.

TEG provides the user with a readily available summary of the coagulation status but requires insight into its different components by the treating physician. The APTT is a simpler and low-priced alternative and is therefore dominating clinical practice. However, it is important to understand the limitations of APTT which takes neither the function of the different components of the coagulation system nor the coagulation status *in vivo* into consideration (27, 28). Even though there is evidence showing a positive correlation between APTT and TEM (23, 29), they should not be used as substitutes for each other. The basic idea with TEM is to analyze the consistency of blood in patients with hepatic dysfunction or bleeding in order to guide transfusion therapy (24). By combining the TEM assay with APTT, it can be determined if the abnormal APTT has an unknown primary origin (often associated with normal TEM (30)) or if it can be explained by some identifiable pathophysiological reaction.

3.3 Coagulation abnormalities in the critically ill

Coagulation abnormalities are common in patients admitted to the ICU (31-33) and correlate with significantly higher mortality (34). Marcel Levi et al have in their recent study shown that prolongation of APTT and PT are found in 14-28% of the ICU patients (31). It seems that prolonged APTT in the critically ill is associated with higher mortality rates independent of illness severity (35).

There are several reasons as to why coagulation abnormalities are frequently observed within intensive care. The ICU patients are often treated with anticoagulants which cause an

abnormal coagulation status. Furthermore, the observed coagulopathy is in most cases acquired due to general pathophysiological reactions in severe illness (33). The most common causes that disturb the coagulation in the ICU patients are disruptions of homeostasis, e.g. acidosis that inhibits the enzymatic activity central to the coagulation (36), thrombocytopenia, thrombocytopathy secondary to liver or renal failure, disseminated intravasal coagulation (DIC) and enhanced fibrinolysis (33).

Thrombocytopenia, defined as platelet counts <150 x 10^9/L, is often present in the ICU patients, manifesting typically during the first days after the admission (31). Half of the patients admitted to the ICU develop thrombocytopenia at some point of their stay due to failure of regulatory mechanisms which results in a disturbed balance among platelet production, pooling and consumption (34). The most common underlying causes to thrombocytopenia in critically ill are sepsis, DIC and diverse medication (31). It is possible to draw conclusions about the most probable underlying cause by investigating the development of thrombocytopenia (34). DIC is a syndrome that is caused by a systemic activation of coagulation which causes a formation of microvascular thrombi and results in organ dysfunction and increased risk of bleeding (37). It is a life-threatening condition that can emerge as a complication to an underlying disease like sepsis or trauma (31).

Fibrinolysis is counteracting blood clotting and its activity is strictly controlled in normal circumstances (6). Enhanced fibrinolysis is rare in critically ill patients but can be caused by some cancer forms and thrombolytic treatments (31).

3.4 APTT in the critically ill

There is no earlier data showing in which manner APTT is expected to react spontaneously in critically ill patients. There are three theoretical alternatives for how APTT could develop during the most acute period of illness: direct elevation, delayed elevation and constantly normal APTT (Appendix A). The interest in APTT as an interesting but rather controversial coagulation parameter in this patient category is based on clinical observations in the ICU. To get an idea of which APTT course can be expected in the ICU patients and to reinforce the hypothesis of APTT elevation, a pilot set of retrospective data was collected from 21 patients in Sahlgrenska ICU over a period between December 2018 and January 2019. The following variables were registered: APTT, PT, age, gender and Simplified Acute Physiology Score 3 (SAPS3), a score used to estimate illness severity. When all of the registered APTT values were plotted on the same chart by using a regression analysis, we could see an explicit trend showing that APTT seems to be elevated in the beginning of an acute illness to then successively decrease over time (Fig.3).

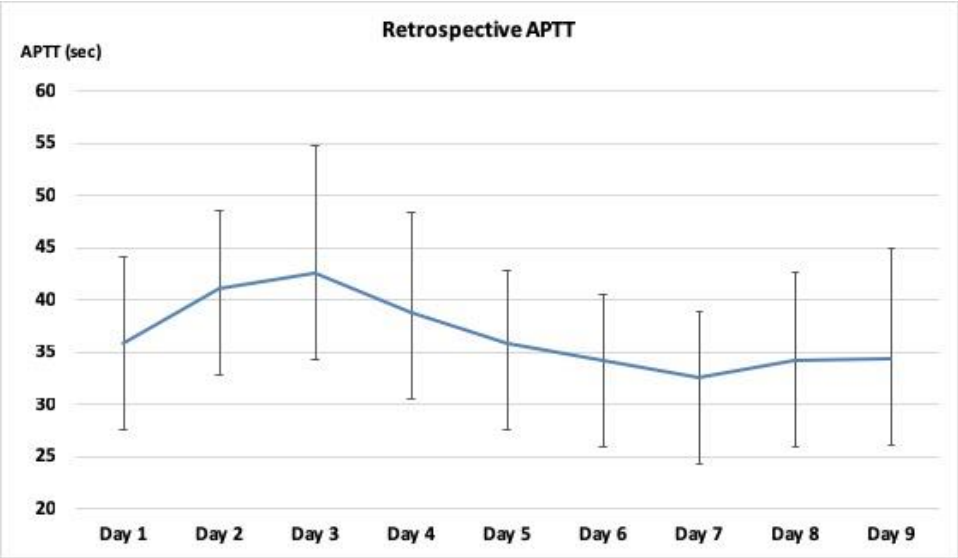

Figure 3 Activated partial thromboplastin time (APTT) over time, measured retrospectively in intensive care patients. This graphical illustration indicates an initial increase that is followed by a successive decrease after a couple of days.

4. Aim

There is an ongoing debate on whether or not APTT should be used to decide which patients can undergo an invasive operative procedure, e.g. lumbar puncture. In antithrombotic treatment with heparin, like during continuous renal replacement therapy, an elevated APTT is aimed for and monitored for correct dosage. However, the APTT is a test that is affected by many different factors unrelated to coagulation which makes it quite unreliable as a coagulation assay. Based on earlier data, it seems that the ICU patients manifest with prolonged APTT without a significant clinical bleeding tendency which has awoken the question of if the critical illness itself could lead to falsely abnormal test results. The hypothesis of this study is that APTT is going to increase spontaneously under the most acute disease course and will then be normalized after a couple days of intensive care without clinical evidence of increased bleeding.

The aim of this study is to describe how APTT spontaneously evolves in critically ill and how long it takes for elevated values to decrease to normal. If we succeed to identify how APTT acts over the most acute period of critical illness, this knowledge can be used to improve routine procedures that depend on APTT along with increasing patient safety in the ICU.

5. Material and methods

5.1 Study design and screening

A prospective, observational study was conducted in the central ICU at Sahlgrenska University Hospital between January 31, 2019 and April 5, 2019. All adult patients were eligible and screened for inclusion on a daily basis, except weekends.

5.1.1 Inclusion criteria

Those who were included in the study were patients admitted to the ICU due to either circulatory or respiratory failure. This was defined as some of the following: need of any respiratory support including mechanical invasive ventilation, non-invasive ventilation, continuous positive air pressure, high flow oxygen treatment or if the positive end expiratory pressure has been increased by 2 cm H2O, usage of aortic pump, usage of inotropic drugs (dopamine, dobutamine, noradrenaline, phenylephrine, adrenaline), usage of milrinone or vasopressin plus one of the inotropic drugs above, or, either suspected or diagnosed infection together with hypotension plus treatment above.

5.1.2 Exclusion criteria

The exclusion was made after following criteria: age under 18, suspected or diagnosed coagulopathy of known cause, treatment with anticoagulation therapy, secondary coagulopathy due to hepatic failure, or, continuous renal replacement therapy (treatment including heparin).

5.2 Collecting blood samples and clinical data

The daily sampling routine was initiated as soon as the consent was given for the participation. The following blood samples were taken every morning at the same time (5 a.m.): APTT, PK, ALAT, ASAT, ALP, bilirubin, CRP, white blood cell count (WBC), thrombocyte platelet count (TPC), creatinine (CREA), albumin, fibrinogen, antithrombin III and anti-Xa.

These specific blood samples were chosen in order to highlight the patients' renal and hepatic function, inflammatory reactions as well as coagulation and function in blood. The main objective was to collect all of the given samples under a period of 7 days or until APTT was normalized again. The sampling period was discontinued in case of discharge from hospitalization, transfer to other hospitals or death.

To be able to describe the study population, clinical data was collected on each patient on a daily basis. These registrations included mean arterial pressure (MAP), heart rate, respiratory

rate, saturation, core temperature, Glasgow Coma Scale (GCS) and Richmond Agitation-Sedation Scale (RASS). Vital parameters were needed for evaluation of illness severity score in the ICU patients.

To get a full, momentary view on coagulation when APTT was abnormal, the sampling kit was completed with TEM in some of the patients who were randomly selected for the analysis. In those patients, TEM was analyzed in a double-sequenced manner; the first test was done on the first day of sampling when APTT still was prolonged and the second when APTT had been normalized again. To narrow down this part of the analysis, the graphical illustration of INTEM was used exclusively, as it focuses on showing details of the contact activation pathway similarly to APTT. Only three numerical parameters were registered describing clotting time and clot stability.

5.3 Coagulation analysis and laboratory methods

All of the study samples were analyzed in the central laboratory of Sahlgrenska University Hospital. At the time of the study, a coagulation instrument called Sysmex-CS5100 was being used which is based on analyzing the clotting time. This method is validated in comparison to other valid coagulation measurement methods (38). The blood sample is collected in a citrate tube by using regular clinical practice and analyzed with a specific method. The method starts with an activation of factor XIa via contact (surface) activation (8). When the contact activation has been initiated for 3 minutes in citrate plasma, calcium chloride and negatively charged phospholipids are added which leads to fibrin building. To avoid a misleading variation depending on the platelet count, functional thrombocyte activation or activation via

the glass walls of the sample tube, standardized phospholipids are being used. Plasma is then mixed with Actin FSL, a specific reagent ordered from Siemens, incubated and then subsequently mixed with calcium chloride. The coagulation process begins, and fibrin building is registered by using a standard wavelength 660 nm. After adding calcium chloride, a baseline (0%) is defined and the analysis continues until a specific endpoint is reached (100%). This endpoint is predefined and dependent on the method. Between these measured values from 0 to 100%, 50% is registered and used as a predictor for clotting time. The clinically relevant outcome, clotting time, is reported as p-APTT in seconds (8, 15).

Analysis of APTT at Sahlgrenska Hospital is accredited which means that the laboratory maintains suitable standards and analyzes all of the incoming samples by always using the method described above. Of all the different producers, the Region of Västra Götaland has chosen to use Siemens because this company is the one that has succeeded to meet the requirements set for the coagulation analysis. In fact, the whole Region including hospitals outside Gothenburg, that is e.g. Trollhättan and Borås, use the same method so that the sample results can be compared with each other regardless of where they were taken in the first place.

5.4 Evaluation of disease severity in the ICU

To predict morbidity and mortality of patients in the ICU and to get information on prognosis, different kinds of scoring systems have been developed. The most common ones are Acute Physiology and Chronic Health Evaluation II (APACHE II) and the Simplified Acute Physiology Score II (SAPS II) (39), recently replaced by SAPS3 which is basically the same

as its forerunner, but is only based on values from the first hour in the ICU (40). SAPS takes into account several different variables including physiological factors, age, type of admission, and some variables regarding underlying disease (40, 41).

The APACHE II score is slightly more difficult to calculate as it requires registration of a number of variables during the initial 24 hours in the ICU. This score is calculated in the beginning of the ICU admission to help determine the patient's mortality risk for the admission. It is only calculated once and not aimed to illustrate any kind of improvement under patient's stay (42). The variables that are relevant for APACHE II are displayed in the calculation template (Appendix B). For instance, vital parameters as well as serum creatinine, age and presence of chronic health problems are taken into consideration. In the Sahlgrenska ICU there is no common routine of registration of APACHE; thus, the score must be manually calculated.

Both SAPS and APACHE are equally adequate scoring systems (43, 44). Considering their equal standing, SAPS3 was chosen to be used in this study as it is user-friendly and easily taken from a digitalized registration system, PasIva.

5.5 Co-operation with delirium study

To simplify logistical and ethical planning, this study was imbedded in an ongoing study in the Sahlgrenska ICU with primary focus on delirium in the critically ill. Patients with critical illness tend to suffer from delirium when they are in the most acute phase of their illness and admitted to ICU. Of patients that are hospitalized in general, signs of delirium are shown in

approximately 20% of cases whereas patients admitted to intensive care are afflicted in over 60% of cases (45). To study the prevalence of this phenomenon, the ICU patients were screened on a daily basis to detect the potential candidates, then examined using the Confusion Assessment Method for ICU (46) and a lumbar puncture to detect any associated alternations in composition of cerebrospinal fluid while in state of delirium. To be able to perform a lumbar puncture, APTT must be within the normal range of 24-32 seconds; thus, prolonged APTT is considered a definite contraindication to this procedure. For the safety of the participating patients in the delirium study, these routines are strictly followed which is why registrations of APTT have been done on a daily basis. While doing so, some inexplicable alternations in coagulation have appeared and evoked an interest in this phenomenon leading to a hypothesis and an interest to conduct this APTT study specifically on ICU patients.

5.6 Statistical methods

Analyzing and management of data was performed in Excel and SPSS (version 25.0.0.0). The study was constructed as a pure descriptive study which is why complicated statistical analysis was not needed. The data was analyzed in three sections using different statistical methods. The first section is focused on description of demographics, the second analyzes the main study (APTT day 1 to 5) and the third analyzes the sub-study (APTT day 1 to 2), respectively.

When describing the population demographics, simple calculations of median and range (min/max) were done.

In the main study which describes APTT during the first 5 days, calculations of median and range were done. To test if the group values on each day significantly diverged from the starting point, Wilcoxon signed-rank test was used. This test was chosen instead of regular two-tailed paired t-test because the sample size was limited and because there was no evidence that the samples were normally distributed. To compare median, max and min values between two groups (based on sex, morbidity and ICU diagnosis, respectively), Mann-Whitney u-test was used.

In the third section, Wilcoxon signed-rank test was used in order to determine whether the observed differences in APTT between the first two days were significant. To find out if there was a correlation between the different subgroups in regard to illness severity and age, respectively, Mann-Whitney u-test was used as a test method. To evaluate a possible relation between the two observed subgroups (increasing vs decreasing APTT) and different kinds of categorical variables (sex, morbidities and ICU diagnoses), the patients were sorted into different subpopulations. Their relations were analyzed by using Mann-Whitney u-test. This test was used instead of Chi-square in order to get more power to the analysis.

6. Ethics

The APTT study was imbedded into the delirium study that already had a complete and authorized ethics application pursuant to The Helsinki Declaration regarding ethical principles for medical research involving human study material (no. 564-16). The APTT study protocol was amended to the Regional Research Ethics Committee of Gothenburg in December 2018 and approved on February 28th, 2019.

As an additional blood sampling without any connection to the patient's diagnosis or medical treatment was needed on a daily basis, some ethical considerations were necessary. Collection of study material did not infer primary benefit to the patient. It was specified in the ethics application that a verbal and written consent was required in each case, always before exposing the patient to excessive blood sampling. If the patient was alert, he would receive the information and approve the study. In case of a sedated patient or a patient otherwise incompetent of taking a stand, the closest relative was informed and consulted about the patient's most probable attitude towards clinical studies. When the patient was considered adequate, he was informed and given an own chance to approve or disapprove to the study. The patient's will was always respected, regardless of the view given by the relatives.

The introductory information was preferably addressed to the relatives because of the fact that ICU patients often suffer from fatigue and delirium which temporarily impairs their ability to understand complex information. The information was given face-to-face in order to ensure understanding and reflection before answering.

Information on both APTT and delirium studies were often given simultaneously. It was emphasized that giving consent to the APTT study would not indicate approval of the delirium study and vice versa. Moreover, the patient was informed that being included in the study was fully optional and completely separated from the care given in the ICU and that there always was a chance of withdrawal.

7. Results

There were totally 277 admissions during the screening period whereof 89 were postoperative patients and 188 intensive care patients. The postoperative patients received neither circulatory nor respiratory support; thus, they did not qualify for the study. After the enrollment period, a total of 44 patients were included and 144 excluded. The most common reason for exclusion was treatment with potent anticoagulation. Due to short ICU stay, transportation to another facility or death, it was not possible to manage to finalize five consecutive days of sampling in all of these patients. The sample series allowed complete analysis in only 18 patients which is why a sub-study was performed focusing on APTT in day 1-2 in 38 patients. Figure4 displays enrollment numbers.

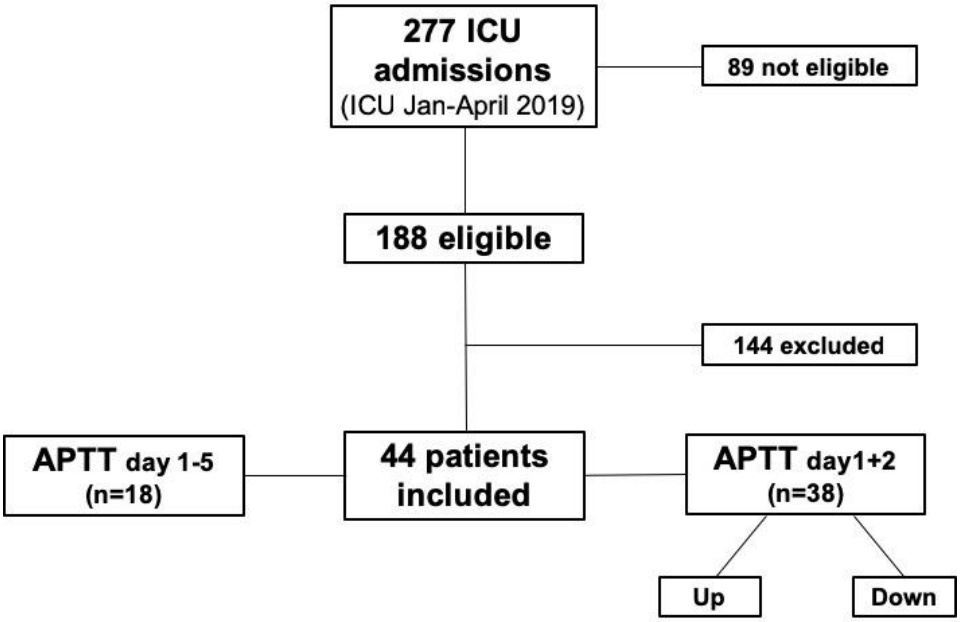

Figure 4 Consort diagram. The main study focused on observing APTT on day 1-5. The patients in the main study were also included in a sub-study where APTT dynamics were analyzed day 1-2 in patients lost to sampling after day 2.

7.1 Patient demographics

The patient demographics are described in Table1. Forty-four patients were included consisting of 11 women and 33 men. Eighteen patients had complete sampling days 1-5 and were included in the main analysis. 38 patients were analyzed for APTT dynamics day 1-2 in the sub-study (Fig.4). There were no significant differences between the sexes regarding age or SAPS3. Table1 also includes morbidity and reasons for need of intensive care. The most common co-morbidity was cardiovascular sickness, and the most frequent ICU diagnoses were infection and circulatory failure.

Table1 Patient demographics. The table consists of three levels: general description of the entire study population, population in the main study describing the dynamics in the ICU on day 1-5 and lastly, population in a sub-study focusing on days 1 and 2.

Population demographics		
Entire population (n=44)		**n (%)**
Age (yrs), median (min;max)		64 (21;89)
Female		11 (25%)
Male		33 (75%)
SAPS3 (admission severity scoring); median (min;max)		57 (21;92)
Morbidity		
	Cardiovascular	18 (41%)
	Pulmonary	7 (16%)
	Renal	8 (18%)
	CNS	11 (25%)
ICU reason for admission		
	Circulatory failure	20 (45%)
	Respiratory failure	19 (43%)
	Renal dysfunction	8 (18%)
	CNS	12 (27%)
	Infection	25 (57%)
Main study		
APTT day 1–5 (n=18)		
Age (yrs), median (min;max)		60.5 (25;89)
Female		6 (33%)
Male		12 (67%)

SAPS3		53 (23;74)
Morbidity		
	Cardiovascular	10 (56%)
	Pulmonary	4 (22%)
	Renal	6 (33%)
	CNS	4 (22%)
ICU reason for admission		
	Circulatory failure	8 (44%)
	Respiratory failure	6 (33%)
	Renal dysfunction	4 (22%)
	CNS	4 (22%)
	Infection	10 (56%)
Sub-study		
APTT day 1+2 (n=38)		
Age (yrs), median (min;max)		64 (21;89)
Female		10 (26%)
Male		28 (74%)
SAPS3		57 (21;92)
Morbidity		
	Cardiovascular	17 (45%)
	Pulmonary	7 (18%)
	Renal	7 (18%)
	CNS	9 (24%)
ICU reason for admission		
	Circulatory failure	18 (47%)
	Respiratory failure	16 (42%)
	Renal dysfunction	7 (18%)
	CNS	9 (24%)
	Infection	21 (55%)

7.2 Main study: APTT evolution day one to five

APTT course was studied between days one to five. All of the patients that had been followed for at least five days were included in this analysis. A total number of 18 patients fulfilled the criteria of valid observations during the first five days. Patients in this group had on average one known prehospital morbidity and two ICU admission diagnoses per patient.

The main question was how APTT evolves over time during intensive care. For a visual overview, individual values were plotted first (Fig.5). There were three distinct outliers that did not match with the common trend. These are shown as dotted and hatched lines in Fig.5. After their medical history was penetrated, two of them were excluded post hoc, shown as dotted lines in Fig.5. The patient illustrated with a hatched line was retained in the cohort.

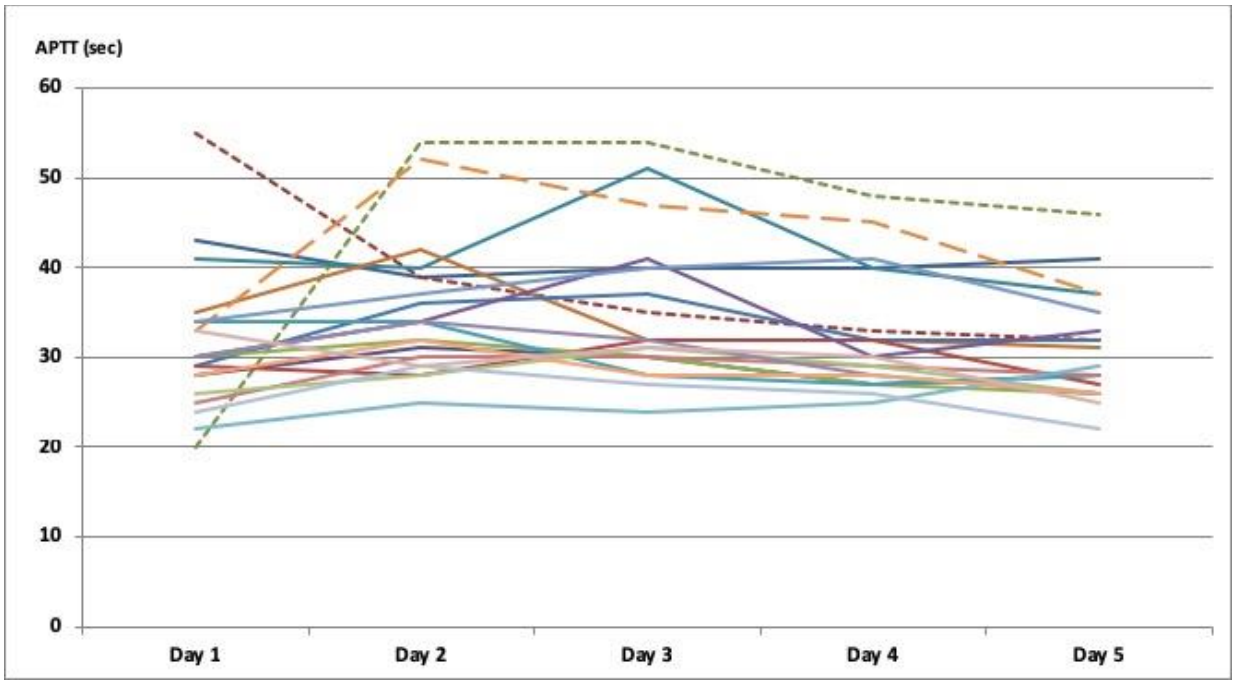

Figure 5 All daily observations registered over five days (n=18). The dotted and hatched lines indicate outliers that were identified first after the enrollment.

In the next step, the individual values were averaged. The results show that APTT follows a typical hill-shaped course with a light elevation on day 2-3 and is then decreased on day 4-5 (Fig.6). The elevation between measurements on day 1 and 2 was statistically significant (p=0.01). When the group values on day 1 were compared to days 4 and 5, respectively, the observed difference was no longer statistically significant (p=0.495 and p=0.298).

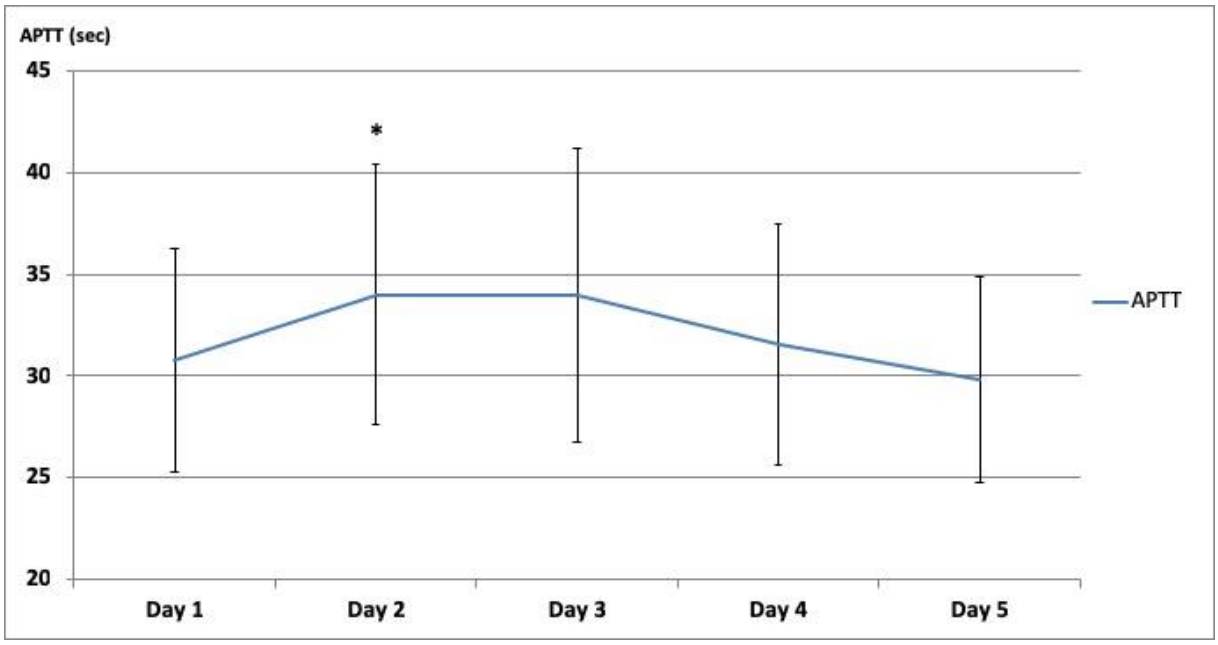

Figure 6 APTT course (mean) during the first five days of observation. The staples indicate standard deviation. Outliers no. 1 and 2 are ignored in this graph. The graphics show that APTT is initially elevated, reaching the maximum height on day 2-3 and subsequently normalizing 4-5 days after admission.
*significant elevation compared to day 1

During the observation period of five days, a median as well as maximum and minimum values were registered. Median for this period was 3.5 seconds (range 1.5-9.5). Maximum value attained a median of 33.5 seconds (range 29-52) and was reached on average on day 2. The APTT peak value was on average 31% higher than the patients' individual baseline values. The lowest value during the sampling period was 28 seconds (range 22-37). Normalization, meaning APTT under 32 seconds, was reached on average on day 4.

The identified characteristics in APTT development regarding median, maximum and minimum values as well as time until maximum and normalization were tested in different subdivisions. The analyses were performed on each subdivision, respectively, based on sex,

cardiovascular morbidity and presence of infection as ICU diagnosis. None of the subgroups showed a significant difference in APTT development.

Values of APTT on the first day of ICU admission were compared with vital parameters on day 1. There was no association between APTT and MAP, POX, heart rate, respiratory rate, core temperature, GCS or RASS, respectively.

Coagulation was analyzed by using TEM in eleven randomly selected patients with elevated APTT and was controlled twice during the study period. The viscoelastic coagulation assay showed no obvious abnormalities associated with prolonged APTT in any of the studied patients. The test was normal both before and after normalization of APTT in all of the cases.

7.3 Sub-study: APTT dynamics between day one and two

7.3.1 Entire group

The change in APTT between day one and two in the ICU was analyzed in 38 patients, corresponding to 86% of the whole study population. Details of the study population are shown in Table1. Those who were excluded from this analysis were patients who were discharged from the intensive care within one day; thus, impossible to follow. The study population consisted of 10 women (26%) and 28 men (74%). The two earlier acknowledged outliers were similarly identified in this sub-study and excluded from the final analysis. Individual plots (Fig.7) revealed two main directions of APTT change under the first two days in the ICU. Of the total number of 36 patients, outliers ignored, six of them (17%) developed

a descending trend and 30 (83%) an ascending trend. All of the observations were gathered around the same interval.

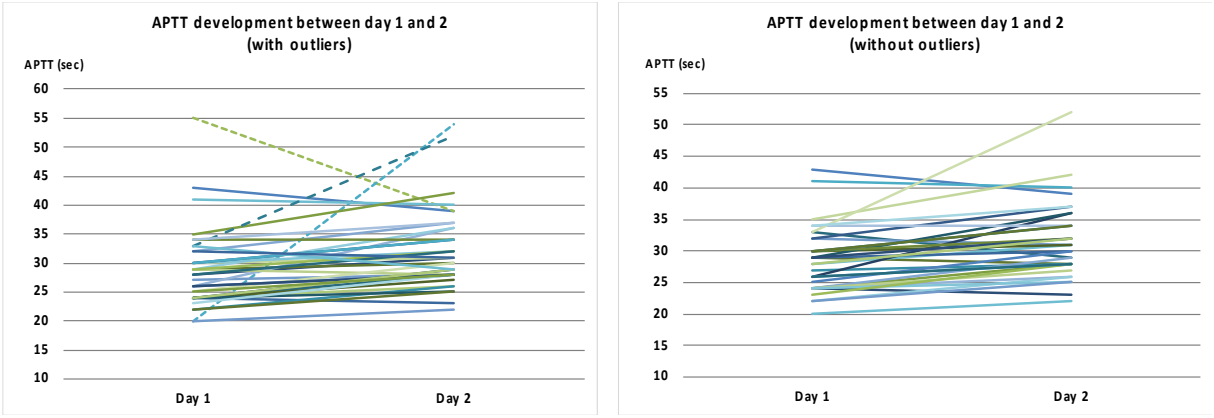

Figure 7 Individual APTT on day 1 and 2 in the ICU (n=38). The graph on the left illustrates all the patients that were included, outliers marked with dotted and hatched lines. The corresponding graph on the right leaves out the two outliers (dotted lines) that did not qualify for the analysis. The majority of patients seem to manifest with an increasing trend.

7.3.2 Comparing subgroups of descending and ascending APTT

With an exploratory approach, the patients were compared based on their direction of initial APTT change. An ascending trend seemed to be much more common than a descending one, dominating the statistics with 82% of the cases. Individual APTT values on day 1 and 2 in the respective subgroup are shown in Figure 8.

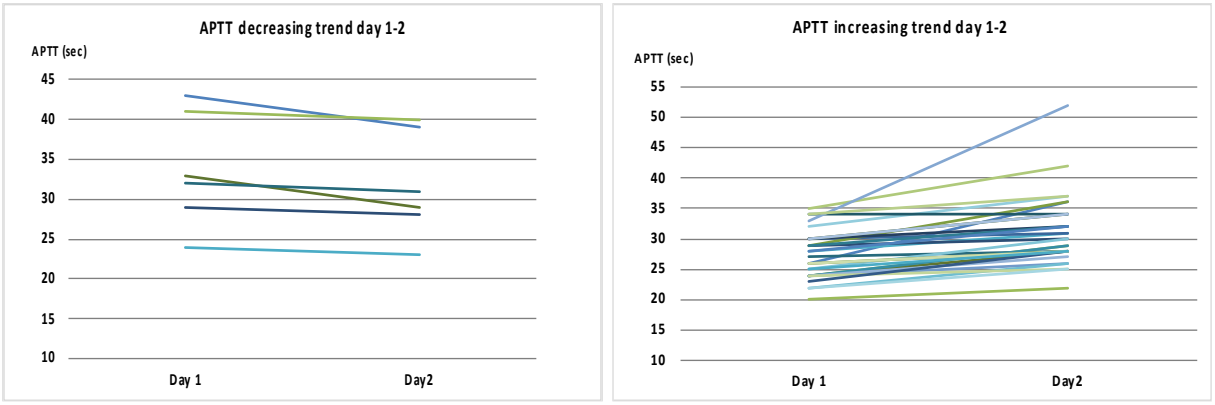

Figure 8 Evolution of APTT during the first two days after admission to the ICU (n=36). All of the observations with descending course (n=6) are separated and illustrated in the graph on the left. All of the observations with ascending course (n=30) are illustrated on the right. In this analysis, the increasing trend seems to be more common. Only six patients had a manifest decreasing APTT.

The group with increasing APTT was larger with a total amount of 30 patients, whereof 8 (27%) were women and 22 (73%) men. They had a median SAPS3 of 57 (21;92), median age 65.5 (21;89) and mean slope 4.0, the positive value indicating an ascending course. The group with decreasing APTT consisted of 2 women (33%) and 4 men (67%). This group had median SAPS3 of 50 (24;71) and median age at 54.5 (34;73). Mean slope for this group was -2.0, the negative value indicating a descending course. When these values from each group were compared, the observations regarding lower SAPS3 and lower median age in the group with descending APTT-trend were not statistically significant. Demographics are displayed in Table 2.

Table 2 Demographics of the subgroups in the sub-study (n=36) after elimination of outliers. The division of these groups was based on their initial APTT development. Several modalities were compared between the groups in order to find significant differences, p-values of these comparisons are shown in the right column.

Sub-study				
APTT day 1+2		**APTT down**	**APTT up**	***p-value***
Number of patients		6 (17%)	30 (83%)	
Age (yrs), median (min;max)		56 (34;56)	65 (21;89)	0.362
Female		2 (33%)	8 (27%)	
Male		4 (67%)	22 (73%)	
SAPS3		52 (21;81)	56 (21;92)	0.472
Morbidity				
	Cardiovascular	4 (57%)	12 (41%)	0.379
	Pulmonary	2 (29%)	5 (17%)	0.168
	Renal	1 (14%)	5 (17%)	0.984
	CNS	3 (43%)	6 (21%)	0.535
ICU diagnosis				
	Circulatory failure	3 (43%)	14 (48%)	0.389
	Respiratory failure	4 (57%)	11 (38%)	0.159
	Renal dysfunction	1 (14%)	5 (17%)	0.834
	CNS	2 (29%)	7 (24%)	0.660
	Infection	2 (29%)	17 (59%)	0.631

The subgroups with either increasing or decreasing APTT were compared as to sex, morbidity and ICU diagnosis by using Mann-Whitney test with 95% significance level. There were no significant differences between the groups (Table 2).

Ultimately, the group with descending APTT was examined for changes after day 2. Out of the six patients, five had been surgically treated before admission and one patient was admitted to the ICU after intoxication. Fig.9 illustrates the observations made on these patients during the first three days showing an abrupt shift from the decreasing to increasing APTT between day 2 and 3.

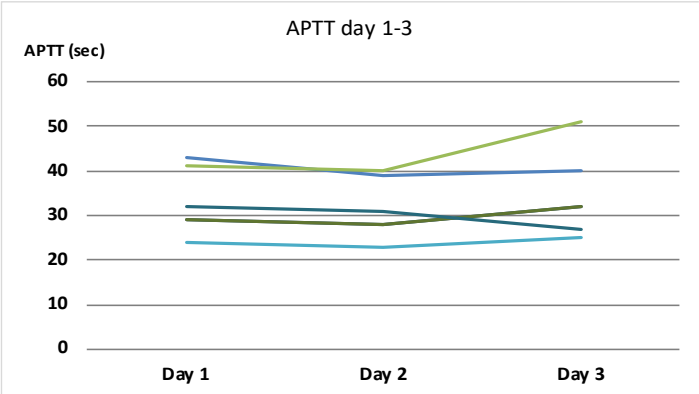

Figure 9 Development of APTT in those with initially descending course. Note that two patients had the exact same APTT values which is why only five lines are visible in the graphical illustration. In five of six patients there was a shift in trend between day 2 and 3. Five of the patients were surgically treated on the same day as the sampling period was initiated and 1 was admitted to the ICU after intoxication.

To be able to identify the amplitude of the observed APTT increase in this cohort, it was considered crucial that all of the samples would be collected from the start of the real ICU period which is why the starting point was defined individually in each patient. The analysis of APTT dynamics between day 1 and 2 was repeated in the entire group with 36 patients using APTT evolution between day 2 and 3 in the six cases with initially decreasing APTT. The trends were now unanimously increasing between the first and the second measurement, except for one outlier that was identified but ignored after a review of the patient's medical record.

In this final analysis, the group of 35 patients showed a highly significant increase in APTT between the first two measuremets (p=0.00001). Mean elevation of APTT in this group was 15%. Figure 10 displays the individual course of APTT between the first two measurements with the first values substituted as described.

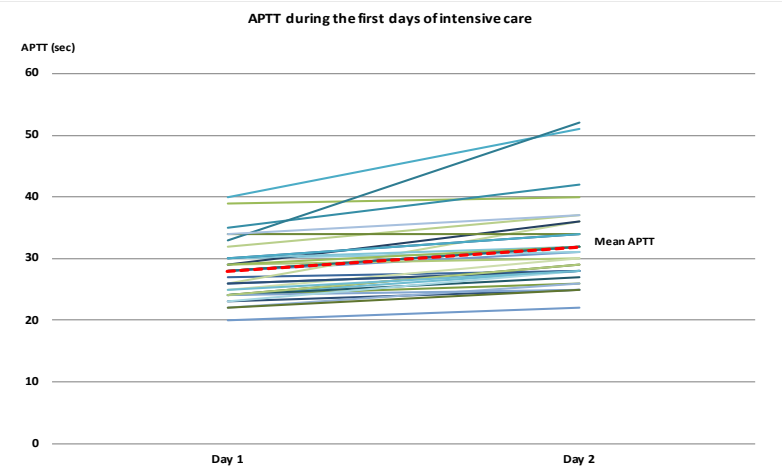

Figure 10 Observations of APTT during the initial rise (n=35). For six patients, the value for day 2 and 3, being the first increase after admission, were used. The red dotted line is showing mean value in this cohort. The results show that an ascending trend is present in all of the studied patients. The increase of APTT was highly significant (p=0.00001) reaching a mean of 15% from baseline values.

8. Discussion

8.1 Main findings

8.1.1 Main study

The results in this study suggest that APTT in critically ill patients has an initially increasing course with its peak on day 2-3 and spontaneous normalization within five days from admission. The peak (maximum value) is on average elevated 31% from the baseline. There is only a small amount of earlier studies which describe APTT in critically ill patients. The existing data indicates that APTT elevation is in fact quite common in the ICU, as it is present in 14-28% of the ICU patients (31), which is supporting the findings in the APTT study.

The hypothesis of this study was that APTT would be elevated in the ICU patients without signs of clinically significant bleeding tendency. In order to identify the right patients with primary APTT abnormality without some other known underlying cause, TEM was analyzed on randomly selected study patients with elevated APTT. TEG is mainly used to illustrate coagulation abnormalities secondary to bleeding or liver failure (26), and has shown to be superior to the conventional coagulation assays in regard to predicting clinical bleeding tendency (23). Conditions which exclusively prolong the APTT test can be present without affecting the TEG assay (30). There were no significant abnormal findings in the performed viscoelastic assays which strengthens the assumption of the population being representative and valid in order to answer the current research question.

Abnormal coagulation status with prolonged APTT is common in the critically ill (31). However, it is known that APTT is a sensitive parameter that is affected by many factors without clinically significant increased bleeding tendency (13). It is not fully understood if the observed APTT elevation is caused by a true coagulation abnormality or if the test results are falsely prolonged due to other factors. Possible reasons to both outcomes could be the acute severe sickness itself or the extensive treatment routines characteristic to the intensive care.

Some evidence indicate that a few other blood samples, which are often collected in the critically ill by routine, can interact with the APTT by falsely prolonging the test results (47). Furthermore, incorrect sampling routine is known to be associated with falsely elevated APTT values by either shortening or prolonging the test results (9). As the ICU patients are frequently tested with several simultaneous blood samples within a short period of time, there might be a slightly increased risk that some of the samples are taken incorrectly.

An additional possible explanation to the high incidence of abnormal coagulation parameters in ICU patients is the extensive life-supporting therapy they are often receiving. A great number of ICU patients suffer from organ dysfunction and are instantly treated with inotropes, mechanical ventilation and/or external fluids (48). There is evidence showing that certain heavy life support in the ICU is affecting the coagulation system (49). For instance, extracorporeal membrane oxygenation, which is used in case of severe respiratory failure, affects the coagulation system by inducing both thrombotic and hemorrhagic events (50). To understand the effect of each treatment given in the ICU, it would be interesting to compare the coagulation between ICU patients receiving different kinds of life support.

In summary, the observed APTT prolongation in the critically ill might in fact be secondary to a combination of physiological and sample analytical issues specific to intensive care patients. This could mean that the APTT elevation is caused by the critical illness itself, with or without true coagulation abnormality. However, the present study material is not enough to express an opinion on if the APTT test should be ignored in the clinic or if it still is valid to be used with specific caution. The results in this study could indicate that the physicians should have a slightly skeptical attitude towards APTT as a coagulation parameter in the critically ill. On the other hand, if the physician chooses to follow the current clinical routines and use APTT before a planned minor invasive procedure, the observations done in this study could indicate that it is wise to perform the procedure either directly in connection with the admission or a couple of days later. Postponing the procedure to the day following ICU admission increases the risk of APTT rising above the upper limit of its normal interval.

8.1.2 Sub-study

In the main study, it was observed that statistically significant findings only appeared during the initial two days of sample taking, which is why the focus was narrowed down to this specific part of the APTT process. The results of this sub-study initially indicated that the patients followed either an increasing or decreasing linear APTT trend. The increasing course seemed more common which supports the theory of critically ill patients having a primary coagulation abnormality that is detected with the coagulation tests. However, as the groups with varied initial APTT directions were almost identical when tested for different variables, skepticism towards the relevance of this division was evoked. The groups were the same in terms of age and SAPS3. Furthermore, no significant differences were detected between the divisions based on sex, cardiovascular morbidity or infection, respectively. These three qualities were specifically chosen as they all are considered, based on earlier knowledge, to have an impact on coagulation.

The female sex is known to have a procoagulant effect, increasing the risk for venous thromboembolisms (51). However, as the clientele in the ICU is dominated by men (52), gender-based analyses are strongly inhibited in this patient category. Male dominance was present even in this study which included only 28% and 29% women in each respective subgroup, explaining why the lack of gender-differences is not surprising. In this study, cardiovascular morbidity dominated in the study population and was therefore relevant to investigate further. Moreover, there is some evidence from earlier studies which show an association between diabetes mellitus type 2 and shortened APTT, indicating hypercoagulability (53), which might also apply to other cardiovascular diseases. Finally, sepsis is a condition caused by an infection which activates the coagulation system,

contributing to a prothrombotic state (54). The findings in this section of the APTT-study are interesting because they strengthen the assumption that dividing the study population in two based on the initial APTT course might actually be irrelevant. Furthermore, the effect of an individual is substantial when measuring coagulation parameters (55), which explains why extended variation can be seen in both groups despite lack of significant differences in terms of categorical variables.

When looking closer at the observations in the group with decreasing APTT, the trend was only present between the first and second measurement points (between day 1 and 2) and then shifted direction to an increasing course on day 3. Moreover, 83% of these patients were admitted to the ICU after a major surgery and were included in the study on the same day as they had been operated on. It is known that general anesthesia and major surgery induce a perioperational stress reaction contributing to a postoperative hypercoagulability (56) which could explain why the coagulation system seems to react with a delay in these patients. The initial decrease could be caused by the postoperative reactions in the body meaning that the actual ICU period in these patients begins on day 2 of sampling. The same assumption could even apply to intoxication which strains the patient's body with the metabolism of the drug overdose before the actual ICU stage is initiated. However, the ratio between the number of surgically treated patients in each APTT group was not analyzed in this study which is why the discussed assumption is uncertain. To verify the validity of this issue, such comparison is needed.

When the analysis was corrected by adjusting the start of the study period individually, the APTT in all of the study patients became ascendant, with the exception of one outlier with persistent ongoing decrease. This patient was treated in the ICU for a diabetic ketoacidosis

due to immunomodulation for metastatic malignant melanoma. There is evidence that both the cancer and the treatment can induce a hypercoagulable state (57) which explains why this patient did not follow the expected trend and can thus be excluded as an outlier.

APTT was observed to increase on average by 15% after the first day in the ICU. However, the initial rise being so limited, its clinical importance can be questioned. The current normal interval at Sahlgrenska Hospital is based on normal distributed population (15) and frequently used in local treatment recommendations considering invasive procedures (14). Even though APTT can be prolonged without increased bleeding tendency (13, 15), the upper limit is generally respected by the physicians. As the defined limits strictly forbid all invasive procedures in case of abnormal APTT, the risk of even a slightest elevation should be considered clinically relevant.

All in all, the subdivision of the initial APTT into groups of increasing and decreasing values, respectively, undeniably turned out to lack clinical significance. Regardless of this, the analysis was valuable as it contributed to deeper understanding of the study material and correction of the final results.

8.2 Methodological considerations

In this study, three outliers were identified when analyzing the statistics. Outlier no.1 was admitted to the ICU due to acute hepatic failure. When APTT was compared with other parameters in this patient, a significant correlation was found between APTT and PT; both of them equally increased. A mutual increase of these tests is in the majority of cases caused by hepatic dysfunction resulting in coagulation abnormality (20). Outlier no.2 suffered from a

multi-organ failure during the ICU residency and passed away within a couple of days from the start of the study period. Similar to outlier1, a significant co-variation was registered between APTT and PT, caused, most likely, by the liver failure. The study was aimed to investigate unclear coagulation abnormalities in the critically ill that were not caused by hepatic dysfunction. Therefore, in order to get correct results, these two outliers were excluded from the final analysis.

The third outlier had a more abrupt increase in APTT that could not be explained by hepatic failure. This patient was admitted to the ICU because of septic shock secondary to pneumonia. As discussed above, sepsis can itself affect the hemostasis by causing severe coagulation abnormalities (54). Moreover, C-reactive protein, a test for detecting bacterial infection that was included in the sampling kit in this study, can interact with the APTT assay causing prolonged APTT values (47). However, the exact reason for this patient's variance from the rest of the population could not be explained with absolute certainty which is why his participation was still considered adequate.

The primary plan with this study was to manage to collect data from at least 80 patients. However, the final cohort was much smaller; mainly caused by the problems on an organizational level at the hospital. During the enrollment period there was a shortage of personnel in the postoperative unit which was taken over by the central ICU. Consequently, a greater number than usual of postoperative patients were found in the central ICU, inhibiting the enrollment of suitable candidates. The postoperative patients did not qualify for the study in the first place; thus, they were automatically ignored during the screening process.

This study was constructed as a daily follow-up study requiring daily registrations on each patient. To minimize analytical failure in observational studies with regular blood sampling, it is usually recommended to collect and refrigerate the samples and then analyze all of them simultaneously, using the same method. If the samples are collected and analyzed separately on each day of the study period, there is a risk that the current priming method is suddenly shifted, causing a skew in the results. When consulting the central laboratory and biomedical analytics at Sahlgrenska University Hospital, they did not consider this an issue in this minor project with short duration. For greater studies that run for several years, this source of error must be taken into account.

Despite detailed planning of the sampling routine, it turned out to be difficult to carry out correctly. There was an unexpected amount of blood sampling not performed, mostly concerning the samples with unusual character; that is, albumin, fibrinogen, antithrombin and anti-Xa. The amount of these samples that were successfully collected was so limited that they could not be analyzed. The reason for this insufficiency was, above all, difficulty in flow of information. The Sahlgrenska ICU is a major clinic with many co-workers which makes it nearly impossible for information to reach all of them. This problem was identified early on in the data collection phase and in order to counteract this, the study was introduced on several occasions, both verbally and via internet. To make the information easier to notice and recall, yellow information forms were used to point out which patients were included, and which samples were needed. Unfortunately, this information could only reach a few of the active personnel in the ICU and was very dependent on the information transfer between the nurses in the ward room.

8.3 Limitations

There are several limitations to this study. First, the number of patients in the final analysis was low contributing to uncertain results. Therefore, it can be challenging to express any true difference between the measurements by using such a small cohort which also makes it harder to draw greater conclusions.

Secondly, this is a clinical study conducted in the ICU, a department with rapid daily turn-over of patients. Many patients who are admitted to the intensive care do not stay in the ICU as long as it takes for APTT to normalize. This is both a logistical issue when planning the study and a risk for selection bias because the follow-up is done properly on only the sickest patients who are bound to stay in the ICU a little longer. These patients stay in the ICU long enough so that the sampling routine is finished before losing the patient to another ward.

All the participating patients were followed while hospitalized which meant that the sampling routine was still continued after that the patient was discharged from the ICU and was taken care of in another unit. However, due to difficulties with the sampling routine in other departments, there is a chance that the results mostly represent the patients with more severe illnesses and those who were lost in the follow-up are actually those with milder disease with less impact on coagulation.

This was a prospective but purely observational study which can complicate the correct following of the protocol in the case that unexpected events emerge, e.g. if the patient passes away or suddenly transfers to another hospital. The results are also much more dependent on the researcher and his or her ability to put in effort on the study. In this study, the screening was done under working hours on weekdays which may have led to an unknown number of

missed patients. In the ICU, rapid changes and general frailty in patients are quite regular which is why collection of samples once a day might be a little too long of a time-interval. There is a risk that some small but crucial changes in coagulation are missed.

Thirdly, the study suffered a loss of sampling results mainly due to the difficulties with the protocol routine. Not all of the wanted samples were routinely taken which is why they were easily missed. The number of patients in the study population was prioritized before the quantity of different samples. Because of lacking data and risk of false results, some of the samples cannot be used in the analysis.

Fourthly, due to lacking statistical support, simple descriptive analyses were applied. By using a mixed model, the study would have gained more powerful results, taking into account the number of patients in each measurement point. The graphical illustrations are now slightly misleading which can be seen by observing the length of the error bars. However, using that kind of statistical analysis would have required the assistance of a statistical professional.

8.4 Conclusion

This study shows that an elevated APTT, which could signal a coagulation abnormality, is often present in critically ill. In this study with a limited sample size, an increase in APTT was observed with a subsequent normalization of the test within five days from ICU admission. A delay in APTT elevation is expected in patients treated with major surgery and is caused by the perioperative stress that takes some time to recover from. These findings support the hypothesis that APTT is affected by the critical illness itself and that there is a

typical trend for how the test can be expected to develop in the ICU patients. However, the study does not provide an answer whether or not the observed prolongation of the APTT assay is associated with increased bleeding tendency, or what the underlying cause to the prolongation might be. To get a better insight into the clinical significance of the APTT tests behavior and to be able to draw actual conclusions which help us improve the clinical recommendations, further research with a larger study population and better practical planning should be done.

9. Populärvetenskaplig sammanfattning

Utvärdering av ett koagulationsprov under intensivvård

Intensivvårdspatienter drabbas ofta av koagulationsrubbningar, vilket innebär störningar i blodets förmåga att bilda proppar. Koagulation är ett komplext och strikt reglerat system som kräver ett samspel mellan olika komponenter i blodet. För att en blodpropp ska formas krävs det ett samspel mellan blodplättar och små molekyler som kallas koagulationsfaktorer. Dessa faktorer aktiveras i samband med skada i ett blodkärl och behövs för att den bildade proppen ska bli lagom stark. För att mäta funktionen i koagulationssystemet har ett antal olika blodprover utvecklats. Aktiverad partiell tromboplastin tid (APTT) är ett av de mest använda proven och mäter hur många sekunder det tar för en stabil blodpropp att formas. Det finns många olika metoder som kan användas för att mäta APTT. Man behöver emellertid vara medveten om att vad som anses vara ett normalt resultat beror på den metod som används. På

Sahlgrenska Universitetssjukhuset ligger normalintervallet på 24–32 sekunder. Inom intensivvård används testet ofta för att kartlägga patientens blödningsrisk innan kirurgiska ingrepp genomförs, som till exempel vid ryggmärgsvätskeprov. Testet är dock väldigt känsligt och kan bli falskt förhöjt av olika orsaker som exempelvis fel provhantering, organsvikt och bruk av vissa läkemedel. En teori är att även den svåra sjukdomen som intensivvårdspatienter drabbas av skulle kunna leda till falskt påverkade APTT-värden, men detaljerna kring denna teori är ännu relativt okända.

Syftet med den här studien var att observera och beskriva förloppet hos APTT under den mest akuta sjukdomsperioden. Studien gjordes på vuxna intensivvårdspatienter på Sahlgrenska Universitetssjukhuset under perioden januari - april 2019. De patienter som deltog i studien följdes under sju dagar eller till dess att APTT normaliserades. Under provperioden registrerades resultat dagligen från såväl blodproverna som patientens vitala tecken.

Studien visar att man ofta kan se en APTT-förhöjning efter 2–3 dagars intensivvård oberoende av sjukdomens svårighetsgrad samt en efterföljande normalisering av provet inom fem dagar från inskrivningstillfället. De allra flesta kan förväntas ha en snabb stegring av APTT. Hos de patienter som genomgått ett större kirurgiskt ingrepp måste kroppen återhämta sig under det första dygnet, vilket är orsaken till att en liten fördröjning kan observeras innan APTT börjar stiga.

Den här studien kan öka förståelsen för provtagning i denna speciella patientgrupp, vilket kan vara till hjälp vid planering av den kliniska handläggningen av patienterna inom intensivvården. Mot bakgrund av att onormala APTT-värden utan tydlig klinisk signifikans ofta förekommer hos intensivvårdspatienter måste provresultaten hanteras med kritisk

inställning. Om man trots detta väljer att använda testet inför ett kirurgiskt ingrepp kan observationerna i den här studien tyda på att sådana procedurer helst ska genomföras i direkt anslutning till inskrivningstillfället eller ett par dagar senare då spontan normalisering av provet kan förväntas. Då ett APTT-värde utanför normalintervallets gränser strikt förbjuder alla operativa ingrepp är ett snabbt agerande att rekommendera.

10. Acknowledgements

I would like to thank Christian Rylander for all the support and guidance with my project. Thank you for having the faith in me and aiming high from the beginning. Thank you for all the inspiration you have given me for my future carrier.

I would like to thank Erik Belfrage for co-operation. It has been an honor and a pleasure working with you, and I'm grateful for all the help with my thesis.

I would also like to thank all the co-workers in the Sahlgrenska ICU. Doctors, nurses and nursing assistants: thank you all for your valuable work and assistance with my project. It has been a pleasure working with all of you. I would not have managed to contribute this project without your help.

A huge thank you to Shahrzad Rahimi and Alexa Tjornhom for helping me with my thesis and adding the final touch. Thank you to my boyfriend for all the valuable feedback, love and support on the way. You are amazing!

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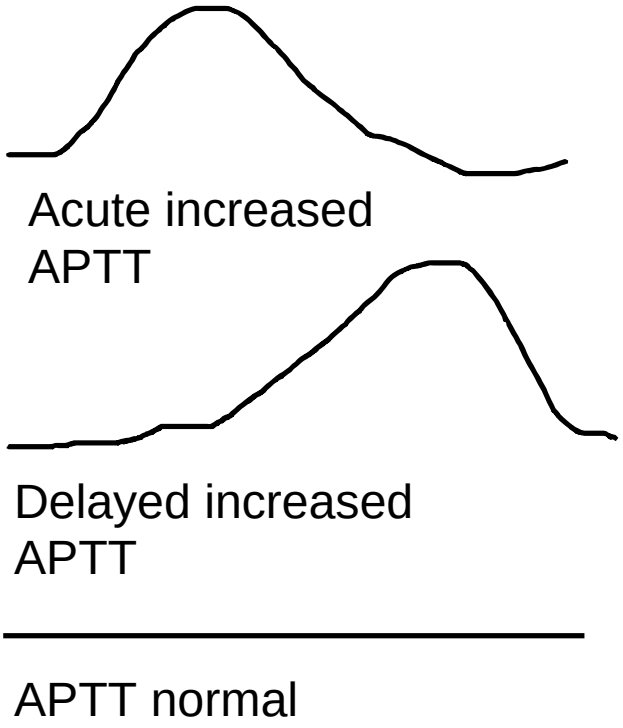
12. Appendix

12.1 Appendix A



Appendix A The possible, theoretical courses of APTT found in the ICU patients

12.2 Appendix B: APACHE II

POÄNG **Parameter**	**4**	**3**	**2**	**1**	**0**	**1**	**2**	**3**	**4**
Rektal temp. (°C)	≥41	39-40,9		38,5-38.9	36-38,4	34-35,9	32-33,9	30-31,9	≤29,9
MAP (mm Hg)	≥160	130-159	110-129		70-109		50-69		≤49
Hjärtfrekv. (min^{-1})	≥180	140-179	110-139		70-109		55-69	40-54	≤39
Andningsfrekv. (min^{-1})	≥50	35-49		25-34	12-24	10-11	6-9		≤5
Oxygenering									

Om FIO2 ≥0,5 Beräkna AaDO2 (kPa)	≥67	47-66	27-46		<27				
Om FIO2 < 0,5 Registrera PaO2 (kPa)					>9,3	8,1-9,3		7,3-8,0	<7,3
aB-pH	≥7,7	7,6-7,69		7,5-7,59	7,33-7,49		7,25-7,32	7,15-7,24	<7,15
S-Na (mmol/l)	≥180	160-179	155-159	150-154	130-149		120-129	111-119	≤110
S-K (mmol/l)	≥7	6-6,9		5,5-5,9	3,5-5,4	3-3,4	2,5-2,9		<2,5
S-kreatinin (µmol/l) *	≥600	300-599	180-299	130-179	50-129		≤49		
B-Hb (g/l)	≥180		150-179	140-149	90-139		61-89		≤60
B-LPK (x 10^9/l)	≥40		20-39,9	15-19,9	3-14,9		1-2,9		<1
GCS 15-GCS									

Chronic Health Evaluation (CHE) (0-5 poäng)

Kronisk organsvikt eller nedsatt immunförsvar som föreligger innan inskrivning på sjukhus definieras enligt nedan:

- **LEVER:** Biopsiverifierad cirrhos och dokumenterad portahypertension; episoder av övre gastrointestinal blödning på grund av portal hypertension, eller tidigare episoder av leversvikt/encefalopati/koma.
- **CIRKULATION:** New York Heart Association klass IV, dvs. angina eller andra kardiella symptom i vila eller vid minimal ansträngning.
- **RESPIRATION:** Kronisk restriktiv, obstruktiv eller kärlsjukdom som leder till allvarligt nedsatt arbetsförmåga, t.ex. oförmåga att gå i trappor eller att utföra hushållssysslor; eller dokumenterad kronisk hypoxi, hyperkapné, sekundär polycytemi, allvarlig pulmonell hypertension (> 40 mm Hg) eller respiratorberoende.
- **NJURFUNKTION:** Beroende av kronisk dialys (hemo- eller peritoneal)
- **IMMUNSYSTEMET:** Patienten har erhållit behandling som nedsätter infektionsförsvaret, t.ex. immunosuppression, kemoterapi, strålning, långtids- eller nyligen högdos- steroidbehandling, eller har en sjukdom som är tillräckligt avancerad för att dämpa immunförsvaret, t.ex. leukemi, lymfom eller AIDS.

Om patienten har någon av ovanstående kroniska organsvikter eller nedsatt immunförsvar så adderas poäng enligt följande:

- 2 poäng vid elektiv kirurgi
- 5 poäng vid icke elektiv kirurgi eller icke opererad

Ålder	Poäng
≤44	0
45-54	2
55-64	3
65-74	5
≥75	6

Reference: SIR (Svenska Intensivvårdsregistret)