RISK FACTORS OF SEVERE COMPLICATIONS ASSOCIATED WITH CENTRAL VENOUS LINES IN CHILDREN TREATED FOR MALIGNANT DISEASE – PREDICTION IN RISK ANALYSIS

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A b s t r a c t

Central venous lines (CVL) are a necessary condition in the modern treatment of malignant disease. In children, the need for permanent venous access is even more important. However, CVL can also be the reason for severe and life-threatening complication. These complications may even lead to serious problems and delays in the treatment of the main disease and thus worsening the patient's prognosis. Septic complications and complications due to thrombosis/microthrombosis associated with CVL belong to the most serious ones. Moreover, they probably influence each other.

The risk of such complications is individual and influenced not only by main diagnosis and the therapeutical protocol used, but also by epidemiological circumstances, by the immune status of the patient, and his/her tendency to thrombosis (thrombophilia). The possibility of predicting the risk of serious CVL-associated complications before the beginning of the treatment and before insertion of the first CVL could increase the chance of successful treatment and even prevention of such complications. This work is targeted on creating a model for the prediction of the risk of thrombotic and/or septic CVL complication based on several haemocoagulation parameters examined at the time of diagnosis in children with malignant disease.

The model was created based on a retrospective analysis of 410 episodes/complications leading to extraction of CVL in 168 children. With the help of probabilistic risk scoring of CVL complications and analysis of the time to extraction (TTE) of CVL, we identified coagulation parameters mentioned below. The positivity of these parameters at the time of diagnosis is associated with the increased risk of CVL complications during oncology treatment:
 – decreased plasmatic level of Protein C (PC) at the time of diagnosis
 – decreased plasmatic level of Protein S (PS) at the time of diagnosis
 – positivity of Pro C Global test at the time of diagnosis
 – increased D dimmers at the time of diagnosis
 – increased plasmatic level of Lipoprotein (a) (Lp(a)) at the time of diagnosis
This predictive model will have to undergo further validation and introduction of more parameters (e.g. pathogens causing sepsis, type of CVL, and place of its insertion), but our pilot data may be a first step toward further prospective analyses and may also become the cornerstone for a different and "tailored" preventive and therapeutic care of severe complications associated with CVL in children with malignancy.

INTRODUCTION

Central venous lines are a necessary condition in the modern treatment of malignant disease. In children, the need for permanent venous access is even more important. However, CVL can also be the reason for severe and life-threatening complication. These complications may even lead to serious problems and delays in the treatment of the main disease and thus worsening of the patient's prognosis. Septic complications and complications due to thrombosis/microthrombosis associated with CVL belong to the most serious ones. Moreover, they probably influence each other. It has been proven that using heparin-coated CVL with a reduced risk of thrombus formation also decreases the number of infectious complications associated with CVL (1). On the other hand, adding antibiotics to the heparin solution used for CVL flushes and locks leads not only to a reduction of septic complications but also reduces the number of episodes with catheter occlusion (2).

Inherited prothrombotic risk factors play an important role in the pathophysiology of thrombosis in children and increase the incidence of such events, especially in children with combined prothrombotic risk factors, if one of them is F V Leiden. This is also the case in patients treated for malignancy with indwelling CVL (3). However, some authors point out that CVL alone is a reason sufficient enough for thrombus formation and thus other risk factors, including hereditary prothrombotic factors, do not have any serious impact (4). But, not only the artificial surface of CVL or inherited thrombotic risk factors are responsible for thrombotic complications associated with central venous catheters. Malignant disease and its treatment can also increase the risk of the event. The increased incidence of thrombotic complications in children during initial treatment of acute lymphoblastic leukaemia (ALL) with a combination of prednisone and L-asparaginase (5) is well-known.

However, the typical fully developed deep vein thrombosis is not the only thrombotic complication of CVL. During the time of using certain CVL, one can frequently experience episodes of malfunction and/or obturation of one or more lumens of the catheter. Some of these problems may be caused by malposition of the catheter or by a mechanical failure of CVL, but mostly it is the first sign of developing thrombosis/microthrombosis or fibrin sheath related to catheter. This clot then prevents the proper use of CVL and, moreover, it is the ideal place for growth of infection, especially in immunocompromised children under treatment for ma-

lignancy. Both of these conditions – thrombus/microthrombus formation and an infectious focus – can result in severe life-threatening complication and, of course, CVL extraction. All of them worsen the prognosis of the child.

If we could predict, with the help of certain laboratory tests performed at the time of diagnosis, the risk level of complications mentioned above, we could probably prevent or, at least, treat these complications better. It could lead to improvement of the patient's prognosis. This was the reason for the development of the STON project (Survey on Thrombotic Complication in Oncology). STON belongs to the GANDALF project – an integral part of the project Health Technology Assessment in Oncology, supported by the Czech Ministry of Health and by the research grant of the Czech Ministry of Education (project No. MŠMT J07/98 – 141100003).

METHODS AND PATIENTS

As described above, thrombotic and septic complications of CVL influence each other. We suppose that if we can predict the excessive risk of thrombotic/microthrombotic complication of CVL, we will probably be able to prevent it or at least decrease its incidence, and thus we will also be able to influence septic complications associated with CVL. The objectives of this work are the following:

1) To stratify individual episodes of septic and thrombotic/microthrombotic complications associated with CVL in children with malignancy regarding their risk level. This stratification then must be validated towards single episodes as well as towards individual patients.
2) To prove whether hereditary prothrombotic risk factors FV Leiden and mutation of FII G20210A are related to the increased number and/or severity of CVL-related complications in children with malignancy.
3) To prove, with the help of mathematic modelling, whether examination of selected haemocoagulation parameters at the time of diagnosis can be used for prediction of the severity and/or frequency of septic and thrombotic/microthrombotic complications in children treated for malignant disease.
4) To find a possible relationship between the severity and frequency of septic and thrombotic/microthrombotic CVL complications and diagnoses or diagnostic groups in children treated for malignant disease.

The relationship between the risk of CVL-associated complication and the results of laboratory testing that we performed at the time of diagnosis would enable us to tailor the actual preventive and/or therapeutical care in patients according to the different level of risk of complication.

PATIENTS

We retrospectively evaluated the data of all 228 patients with newly diagnosed malignant diseases (solid tumours and leukaemia) treated at the Department of Paediatric Oncology, University Hospital Brno, CZ, from October 1999 to December 2002. The age of our patients varied from 1 month to 24 years. 127 (55.7%) of the patients were male and 101 (44.3%) female (*Fig. 1*). All of them belonged to white Caucasian population. During the time of the follow-up (median 12.2 months) 410 CVLs were inserted in 186 patients.(*Fig. 2*). Forty-two (18.4%) of our patients were treated without insertion of any CVL. These patients were not included in further analyses. Only 100 CVLs (23.9%) remained "in situ" during the follow-up period (*Fig. 3*).

The Department of Paediatric Oncology, University Hospital in Brno, is a tertiary referral centre for more than 4 million population. It provides diagnosis and therapy of all malignant diseases for children and young adults. The relative representation of diagnosis in our cohort is shown in *Fig. 1*.
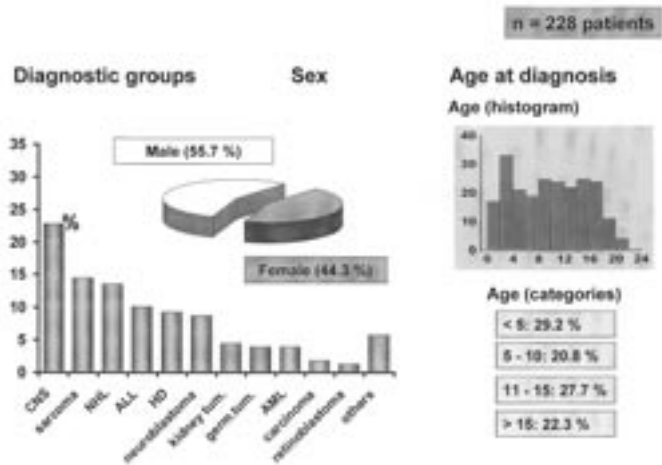
Fig. 1
Description of analyzed dataset. Overview of patients´ characteristics (Age, sex, diagnostic groups)
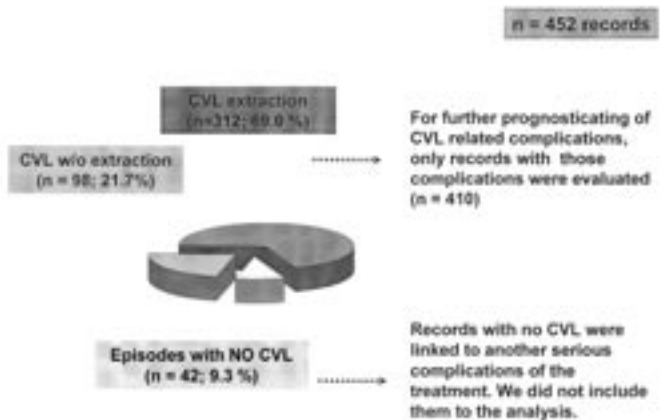

Fig. 2
Description of analyzed dataset. Each patient has at least one record. In this project each record represents one central venous line (CVL). Patients without CVL were excluded from the analyses.

The most frequent were tumours of the central nervous system (CNS) (52 patients, 22.8 %), sarcomas (33 patients, 14.5 %), NHL (31 patients, 13.6 %), ALL (23 patients, 10.09 %), Hodgkin's disease (21 patients, 9.2 %), and neuroblastoma (20 patients, 8.8 %). Other diagnoses were treated in less than 5% of all patients during the follow-up period. Protocols valid at the time of the actual follow-up at the Department of Paediatric Oncology, University Hospital in Brno, were used for the treatment.

During the diagnostic process all patients at the department were examined routinely also for the following laboratory tests:

– assessment of plasmatic level of AT (Coamatic LR Antithrombin, Chromogenix, USA)
– assessment of plasmatic level of D dimmers (STA Liatest D-Di, Diagnostica STAGO, France)
– assessment of plasmatic level of fibrinogen (Thrombin reagent for Fibrinogen assay, Helena Biosciences, United Kingdom)
– assessment of plasmatic level of homocysteine (HPLC, Chromosystem Instruments & Chemicals GmbH, Germany)
– assessment of plasmatic level of FXII (PTT-automate 10, Diagnostica STAGO, France)
– assessment of FV Leiden mutation in homo/heterozygous form – PCR (East-Port Prague, Czech Republic)
– assessment of FII G20210A mutation in homo/heterozygous form – PCR (East-Port Prague, Czech Republic)
– assessment of plasmatic level of lipoprotein (a) (RANDOX Lipoprotein(a), RX Daytona, RANDOX Laboratories Ltd., United Kingdom)
– examination of Pro C Global test (ProC Global Test, Dade-Behring, Germany)

The numbers of patients tested for certain parameters and normative values are described in *Fig 4.*

Central venous lines were inserted in 186 consecutive patients. "Tunnelled" CVLs were applied in most cases; however, implantable ports and non-tunnelled short-time CVLs were also used in some patients. However, CVL complications were evaluated regardless of the type of CVL used. CVL was always inserted by the surgeon in anaesthesia at the operating room under aseptic condition. Doppler ultrasound examination was performed prior to the insertion to avoid thrombotic occlusion at the site of future insertion of CVL. All catheters were placed in the upper venous system. The way of choice was via the left subclavian vein. If this was not possible, then the right subclavian vein or jugular veins were used. This technique was chosen by the surgeon despite the evidence that insertion of CVL via the right subclavian vein is probably the best as far as future thrombotic complication is concerned (*6*) The surgical procedure was not covered by any prophylactic antibiotic or antithrombotic medication. The patients were not given any preventive antithrombotic treatment during their further therapy of the main disease, either.

At the time of CVL extraction, the reason for such extraction was recorded with special interest if septic complication and/or catheter obturation were the reasons for the extraction. Sepsis was characterised in accordance with the definition of The American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference (1992). In patients with severe sepsis, septic shock or MOFS (multi-organ failure syndrome), CVL was extracted even prior to the known result of microbiology evaluation of blood-stream infection. In infection and/or SIRS (systemic inflammatory response syndrome) CVL was extracted after a proven or at least highly suspicious CVL infection (*7*). To prove a catheter-related infection the same infectious agent had to be found in a blood sample taken from CVL as well as from a peripheral vein. CVL was also removed when a pathogen typical of a CVL-related infection (Staphylococcus epidermidis, Candida sp., Staphylococcus aureus) was cultured (*8*). However, it is possible that some CVL were extracted only due to the patient's severe clinical status and from this retrospective study we had not enough information to exclude that the primary infectious focus was elsewhere (not in CVL) or that the cultured pathogen was influenced by contamination during sampling. This was the reason why we were unable to introduce the type of pathogen into our scoring system.

Any problems with catheter patency were recorded into the patient's documentation. If a tissue plasminogen activator (tPA) (Actilyse, Boehringer Ingelheim International GmbH, Ingelheim am
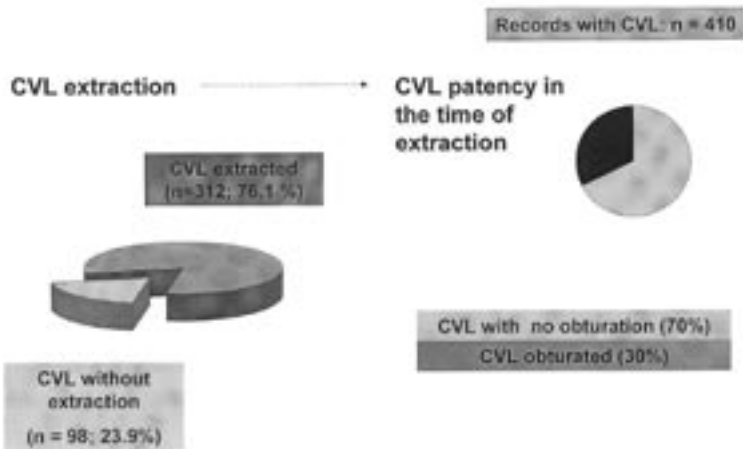
Records with CVL: n = 410

CVL extraction ⟶ CVL patency in the time of extraction

CVL extracted
(n=312; 76,1 %)

CVL without extraction
(n = 98; 23,9%)

CVL with no obturation (70%)
CVL obturated (30%)

Fig. 3
Description of analyzed dataset. Significant number of CVLs had to be extracted (76, 1%). Only 70% of extracted CVLs were not obturated at the time of extraction.

Parameter	NORMAL INTERVAL	n = 228 patients SAMPLE SIZE
AT	80 – 120 %	N = 221
PC	70 - 140	N = 198
PS	65 - 140	N = 200
ProC Global	< 0.76	N = 184
LP(a)	0 - 300	N = 199
Homocystein	0 - 15	N = 183
Fibrinogen	1,6 – 4,2	N = 223
F XII	> 70	N = 180
D Dimers	0 – 0.5	N = 182
FV Leiden FII G20210A	Negative	N = 195

Fig. 4
Parameters mentioned in this figure are connected to the risk of thrombotic events, when out of normal range. These parameters were measured at the time of diagnosis in 228 patients included in our study.

Rhein, Germany) was used to restore the patency, a special form was filled out by the person applying the drug. Two millilitres of Actilyse solution (1 mg/1ml) were used for each lumen of CVL.

Statistical analysis

DESIGN OF THE STUDY

The data on potential risk factors of the severe CVL-related complications in children cancer patients were retrospectively obtained from clinical databases. This approach gave us a retrospective view of problems connected not only with thrombosis but also with other risk situations concerning CVC during malignancy treatment. The results of the analysis enable us to design a study for continuous collecting of clinically relevant risk data; these long-term observations will make case-control studies possible in the future (9). The sample size of the data is sufficient to detect +/- 5 % differences from the total mean (10).

ANALYSIS OF PRIMARY DATA

Frequencies of events (binomial data) are the most common variables within our dataset. The relative frequency estimates were compared by a standard binomial test for paired data or multiple comparisons. Associations of categorical variables were analysed using contingency table analysis; McNemar test with Yates correction (11, 12) was adopted for paired data. Continuous data were compared by a two sample t-test or one-way ANOVA after verification of these test assumptions (12, 13). Non-parametric methods (Mann-Whitney test, Kruskal-Wallis test) were adopted for data which did not fulfil the prerequisites of parametric tests.

Multiple comparisons of binomial data suffered from non-homogeneity of the data and occurrence of rare events. The confidence intervals for extreme values of binomial data and multiple comparisons were computed using F statistics (12). Relative frequencies were normalised by arcsine transformation combined with the square root of the binomial parameter p (15, 12) prior to their cross-comparisons; Bonferroni correction was applied to multiple cross-comparisons.

ANALYSIS OF TIME TO EXTRACTION (TTE) OF CATHETER

An alternative method for evaluation of risk event incidence is the analysis of time to extraction (TTE) of the catheter. The standard Kaplan-Meier technique and the log-rank (13) test for comparison of two groups' TTE were adopted. The survival curves were characterised by the median survival time; the confidence intervals were computed according to the following equation:

$$SE(p_j) = p_j \cdot \sqrt{\sum_{i=1}^{j} \left[\frac{f_i}{r_i(r_i - f_i)} \right]}.$$

where p_j – proportion of survivals in given time
r_i – number of living (event-free) patients at the beginning of evaluated time interval
f_i – number of events during evaluated time interval

RISK SCORE OF COMPLICATIONS RELATED TO CVL

The analysis revealed the necessity of an inseparable evaluation of the thrombosis/microthrombosis risk and other problems (sepsis, etc.), as they often coincided with the thrombophilic state or interchanged with it. A combined risk score was thus developed. The score has the following properties:
    – combined score evaluating all types of problems connected with CVL
    – additive property of score reflects complications in patients in the past
    – the score is replicable, i.e., its variables and formulae are well defined

– score range (0–100 % of maximal risk) provides clear interpretation
– the score could be interpreted on the level of individual patients

Although the risk score development was influenced by empirical inputs due to the pilot stage of our project, its results were statistically validated by both univariate and multivariate analyses. The complications related to CVL were first empirically ordered according to their seriousness (mechanical disturbances, "therapeutical" reasons for intervention, obturation, thrombosis/microthrombosis, sepsis, and other complications). Extraction of CVL (1/0) (1=event) and the risk of its repetition in further treatment were adopted for validation purposes and evaluated in connection with the above-mentioned problems by univariate logistic regression.

The risk scores were assigned to events in the following order: CVL with no problems (RS: 0 %) <= CVL extraction due to "therapeutical" intervention (RS: 11 %) < tPA application and no subsequent problems (RS: 33 %) < tPA application and subsequent extraction, no sepsis (RS: 50 %) << sepsis and subsequent extraction of CVL, without prior tPA application (RS: 82 %) < unsuccessful application of tPA, subsequent extraction due to sepsis (RS: 92 %).

The risk score values reflect the amount of patients risk on a relative scale and incorporate the risk of CVL extraction and other complications during subsequent treatment. The value of the risk score could be connected to episodes of CVL usage and summarised (mean, confidence interval) for individual patients or their groups.

The risk score was validated and we proved its ability to distinguish among patients with repeated complications, patients with sepsis, etc. Differences in risk score values were also found among patients according to their primary diagnosis. The validation process contained the following steps:

Cross-validation of the risk score development; two groups were used for cross-validation and the results noted above were confirmed;

ROC (Receiver Operating Characteristic) curves; risk score values show satisfactory values of specificity and sensitivity (> 0.711), which promise further successful development of risk score.

It is to be noted that it is almost impossible to find a universal and exact continuous parameter suitable for application in clinical practice during a single study. The variability of patients with low or medium stress defines areas where the test results are accompanied with frequent errors, i.e. inconclusive areas. These inconclusive areas should be defined for any test used in clinical practice besides the sensitivity and specificity of tests commonly applied; the proposed risk score should be applied onto other independent datasets to strictly prove its efficiency and define its value for clinical practice.

RESULTS

Two hundred and twenty-eight patients were diagnosed for malignant disease during the time period from October 1999 to December 2002 at the Department of Paediatric Oncology, University Hospital in Brno, Czech Republic. All of these patients were examined for potential risk factors. The results of the testing are described in *Fig. 5.* At least one positive risk factor was found in 84.2 % of our patients (*Fig. 6*).

In 186 (81.6 %) of these patients 410 central venous lines were inserted during the time of follow-up. Only patients with CVL were included in further analyses. However, 312 (76.1 %) catheters had to be removed due to various reasons. Some of the extractions were, of course, not related to severe CVL complications, but rather to "mechanical" problems with CVL (rupture, mechanical obturation, spontaneous extraction, etc. in 99 CVLs, 31.7 %), or had other "therapy-related" reasons (44 CVLs, 14.1 %). CVL was extracted in 13.8 % (43 CVLs) at the end of the therapy
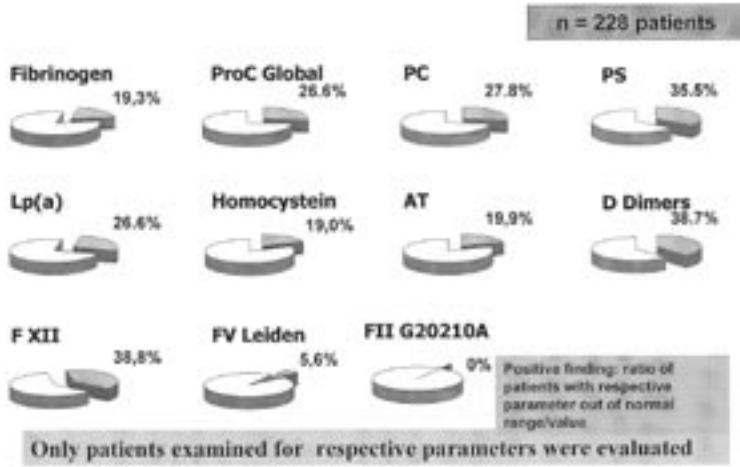
Fig. 5
Parameters connected to the increased risk of thrombotic event and/or complication might be used
as potential predicators of such a risk. This figure shows percentage of positive (risk-associated) find-
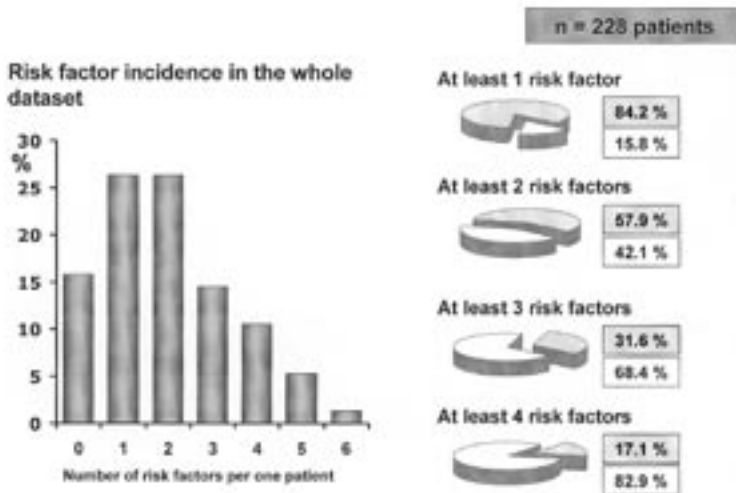ings in respective parameters in our patients.

Fig. 6
Incidence of risk factors (potential predicators) in all 228 patients. Stratification according to the
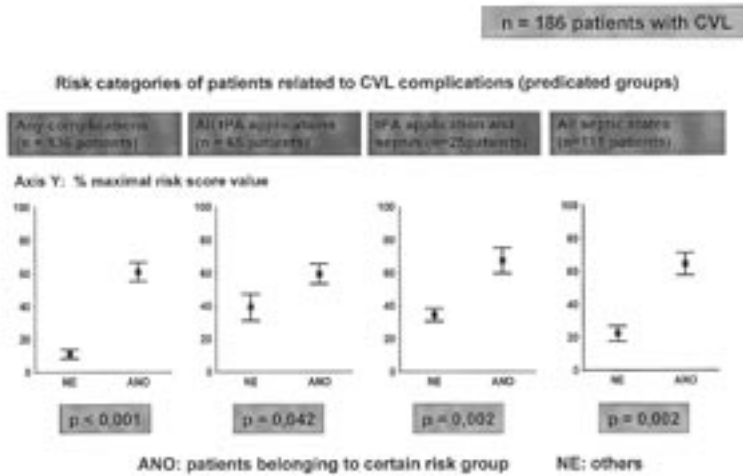number of risk factors.

Fig. 7
Risk score validation. Patients were divided in four groups related to their CVL complication characteristics. Patients belonging to certain risk group had significantly lower maximal risk score value than other patients.
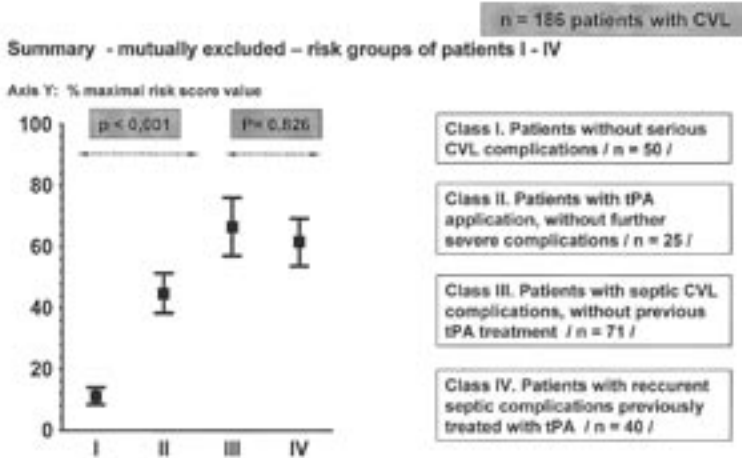

Fig. 8
Risk score validation. Patients were divided in four mutually excluded groups according to presence of septic complications of CVL and also according to the need for the need of tPA administration for restoring CVL patency. Maximal risk score value is significantly different between classes I–III.

154

with no complication, and in 10 CVLs (3.2 %) the reason for extraction was the death of the patient not related to CVL complication. Septic complications were the reason for 116 (37.2 % of all CVL inserted) extractions and 30 % of all removed catheters were obturated at the time of extraction (*Fig. 3*). The need for tPA treatment to restore the patency of CVL was recorded in 65 out of 186 (34.9 %) of patients with inserted CVL.

Risk score validation

Four groups of patients were created with respect to their complications associated with CVL. These groups are not mutually excluding. They are as follows:
patients with any complication associated with CVL;
patients with the need for tPA treatment for restoring the patency of CVL;
patients with the need for tPA treatment and further septic complication of CVL;
patients with any septic complication of CVL (irrespective of tPA treatment).

The maximum value of risk score of patients belonging to the respective risk groups was related to the maximum risk score value of patients who did not carry such a risk. We found statistically significant differences in all of the risk groups (p ranging from 0.042 to < 0.001) (*Fig. 7*).

The risk score was also validated on mutually excluding risk classes of patients mentioned below:
Class I patients with no severe complication of CVL;
Class II patients with the need for tPA treatment to recover patency of CVL, without further complication (no sepsis, no extraction of CVL);
Class III patients with septic complication (leading to CVL removal) without previous need for tPA treatment;
Class IV patients with repeated septic complications despite previous tPA treatment for restoring patency of CVL.
There was a statistically significant difference in the maximum risk score value between individual classes (p < 0.001) except for the difference between classes III and IV. This can be explained probably by two reasons. Firstly, a septic complication itself leads to a high increment in risk score and thus further risk factors do not have sufficient influence on risk scoring; secondly, there is a different approach to patients with repeated septic CVL complications (different first-line antibiotics, empirical treatment with antifungal drugs, more aggressive supportive therapy, etc.). Especially the second reason would explain why the risk score of class IV is slightly lower than that in class III. This difference is, however, not statistically significant (p=0. 86). For a graphical outcome (*Fig 8*).
To exclude that the risk score is influenced by criteria not related to any real risk, we compared the maximum risk score value in dependence on the patients' sex

and age. We found no significant difference of the risk score value between these categories (*Fig. 9*).

What we found very interesting was a significant difference of the maximum risk score value in our patients in relation to the diagnosis of malignant disease ($p < 0.001$). The highest risk score value was in patients suffering from AML and Hodgkin's disease and the lowest score level could be seen in patients with the diagnosis of retinoblastoma. However, because of the varying and, in some diagnostic groups, very small number of patients in the respective categories, further validation of this interesting finding should be done.

The validity of our risk score is also supported by the finding that, with increasing number of CVL-related complications in one patient, the risk score for such a patient is increasing ($p=0.037$). In other words, patients with more CVL-related complications are of higher risk.

Analysis of the laboratory parameters studied – potential risk predictors – by risk score

The aim of this analysis was to find out if patients with positive laboratory parameters examined at the time of diagnosis showed increased risk and/or frequency of CVL-related complications, and thus if these parameters could be used as potential risk predictors. We found a statistically significant difference between the maximum level of our risk score in patients with decreased plasmatic levels of PC at the time of diagnosis ($p=0.047$), decreased plasmatic levels of PS at the time of diagnosis ($p=0.022$) increased D dimmers at the time of diagnosis ($p=0.033$), and patients with normal findings in these parameters. The differences in other monitored parameters were not statistically significant (*Figs 10, 11*).

When we compared the maximum risk score value in patients regarding the number of positive risk factors at the time of diagnosis, we found a statistically significant difference only between the patients with no risk factor present and the other patients ($p= 0.037$). The number of positive risk factors found at the time of diagnosis did not further influence the risk score significantly (*Fig. 12*). In other words, the presence of at least one risk factor leads to an increased risk of CVL-related septic and/or thrombotic/microthrombotic complications.

Risk analysis of Time to Extraction (TTE) of CVL

Time to extraction of CVL is a very important clinical parameter. It can inform not only about the risk of CVL complication but also about problems caused by time periods, when a child does not have proper venous access, and it also mirrors problems with replacement of CVL. Predicting TTE at the time of diagnosis could give us information about events, which might seriously influence the timing and scheduling of chemotherapy and could help us with the planning of supportive therapy measures.
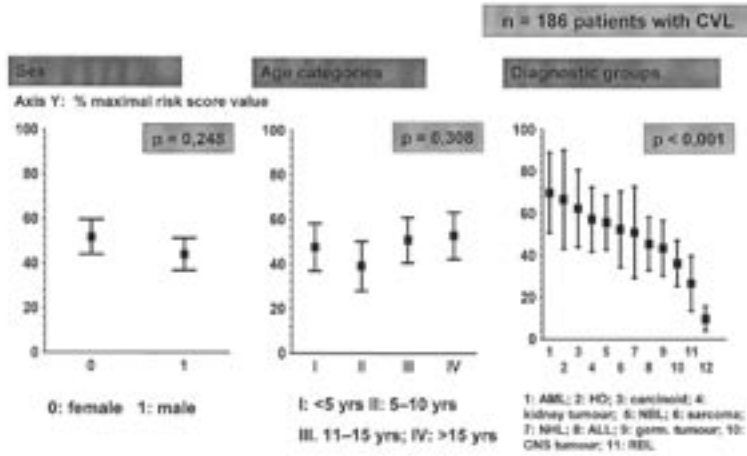
156

Fig. 9
Risk score validation. Risk score value is not influenced by the age and/or sex of the patient. There is significant difference in maximal risk score value in dependence on diagnostic groups. Highest risk score value was found in patients with acute myeloid leukaemia (AML) and lowest in patients with retinoblastoma (RBL)
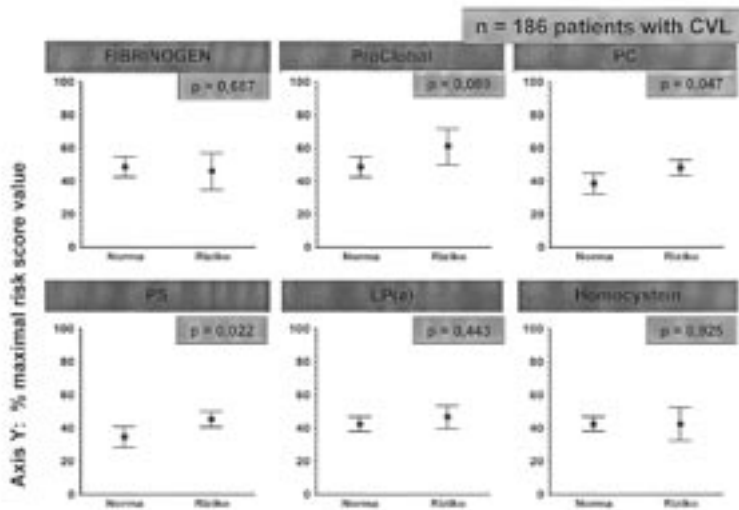

Fig. 10
Analysis of potential risk predictors by the risk score. Patients with decreased plasmatic level of protein C (PC) and protein S (PS) had significantly higher maximal risk score value than patients with normal findings in these parameters at the time of diagnosis of malignant disease. Other parameters did not show statistically significant difference.
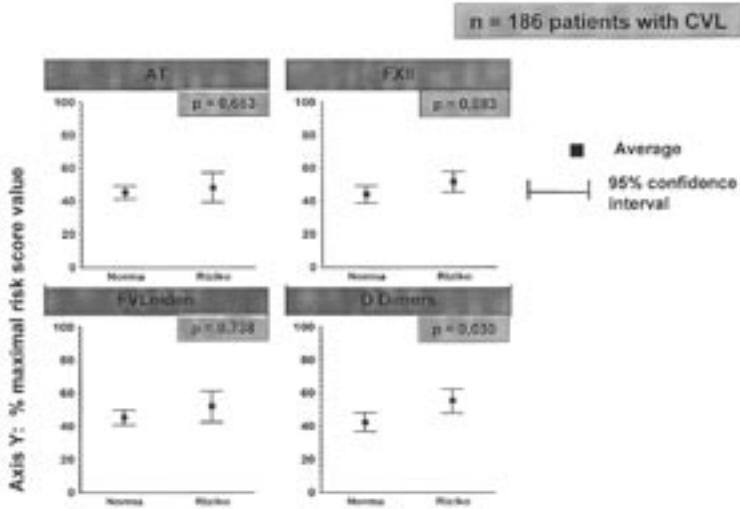
Fig. 11
Analysis of potential risk predictors by the risk score. Patients with increased plasmatic level of D dimmers had significantly higher maximal risk score value than patient with normal findings in these parameters at the time of diagnosis of malignant disease. Other parameters did not show statistically significant difference.
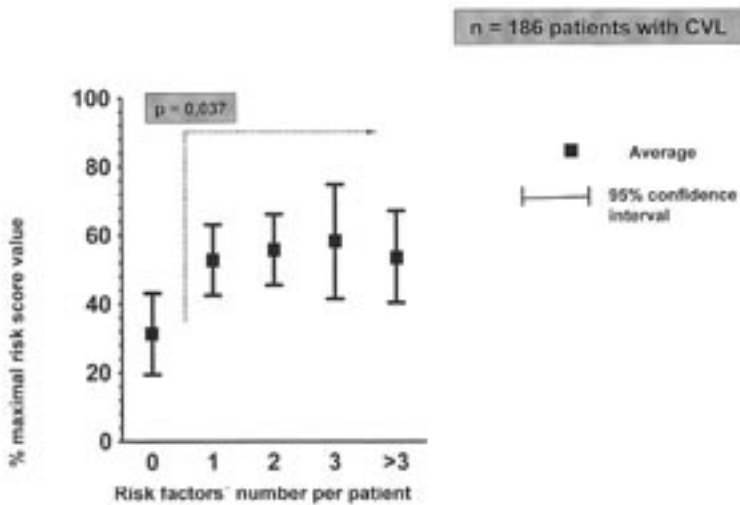

Fig. 12
Analysis of potential risk predictors by the risk score. We found significant difference in maximal risk score value between patients without any risk factor and patients with at least one risk factor. The number of these factors positive in the patient had no significant influence on maximal risk score value.

158

When comparing TTE in patients with at least one risk factor to TTE in patients with no positivity in the studied parameters (risk factors) at the time of diagnosis, we found a statistically significant difference (p=0.038), although the median of TTE had not been reached during our follow-up (*Figs. 13, 14*). The number of risk factors present in the patient did not further influence TTE significantly. This finding correlates with the risk score analysis.

We also found a statistically significant shortening of TTE in patients with a positive ProC Global test at the time of diagnosis (p=0.017), decreased plasmatic levels of PC at the time of diagnosis (p=0.002), increased plasmatic levels of Lp(a) at the time of diagnosis (p=0.001), and in patients with increased D dimmers at the time of diagnosis (p=0.041). Other monitored parameters did not significantly influence TTE in our patients (*Figs. 15, 16*).

By means of risk scoring and analysis of TTE we were able to:

distinguish diagnostic groups with different risk of severe CVL complications. This difference is probably not only due to diagnosis itself, but mainly due to the therapeutical protocol used; confirm that the risk level of CVL complications increases in patients with repeated events and that successfully treated CVL episodes (with no need for CVL removal) appear later after CVL insertion and in patients without repeated CVL-related complications; prove that the risk of CVL-related septic and/or thrombotic/microthrombotic complications is higher in patients with at least one of the risk factors monitored in this work. The number of risk factors does not have any further significant influence on the risk score or TTE; identify a set of coagulation-related risk factors. Positivity in these risk factors at the time of diagnosis of malignant disease is related to the increased risk of CVL-associated septic and/or thrombotic/microthrombotic complications. These risk factors include: decreased PS and PC plasmatic level, increased D dimmers, increased plasmatic level of Lp(a), and a positive ProC Global test.

DISCUSSION

The aim of this work was to assess and possibly predict the risk of CVL-related (mainly septic and thrombotic) complications from the viewpoint of haematology. It is true that CVL-related complications may also be caused by completely different reasons and problems, e.g. location and insertion of CVL (*6*), the type of CVL; however, thrombotic risks are also of clinical importance (*3*).

Thrombosis/microthrombosis is not the only serious complication of CVL. Septic complications also play a very important clinical role, and this role is accented especially in children treated for cancer in the course of febrile neutropenia. We suppose that the relation between sepsis and thrombus formation in association with CVL (*16*) enables us to formulate the hypothesis that prediction of thrombotic risk in a patient can help us identify a patient prone also to more severe septic

complications of CVL. The risk we are talking about might not be inherited only. It can be the result of a combination of malignant disease itself and its influence on coagulation and the immune system on the background of possible inherited thrombophilia. It is almost impossible to recognize these respective reasons at the time of diagnosis. This is why, irrespective of the haematological background of this work, it has ambition to help in the evaluation and possibly prediction of not only thrombotic/microthrombotic, but also other severe complications of CVL.

The principal outcome of this work is the development of risk score. The whole project is now only in its pilot phase, but our model is able to quantify the risk of single CVL-related episodes as well as the risk value for the individual patient in a continuous range. Together with TTE it can categorise this risk and relate it to separate risk factors monitored in this work.

It is clear from our data that mainly the impaired protein C pathway at the time of diagnosis is associated with an increased risk of CVL complication during further treatment for malignant disease. The presence of FV Leiden mutation paradoxically did not influence the severity of the CVL-related complication risk significantly (p=0.738). No mutation of FII G20210A was assessed, as it was not present in any of our patients. Another factor, which was in significant correlation with the risk level of CVL complications, was the increased D-dimmer level. It is well known that malignant disease has a high influence on the coagulation system, mainly through its activation via TF receptors expressed on malignant cells. Increased D dimmers might be the only sign of future malignant disease, sometimes even many years before the diagnosis. The last factor with a significant influence on the CVL-related complication risk was the plasmatic level of Lp(a) at the time of diagnosis. Thrombosis and Lp(a) in children with malignancy is often reported, mainly in context with ALL (17, 18).

The finding that certain diagnoses are associated with a higher risk of CVL complications is also interesting. The highest risk is associated with AML. It is well known that AML may cause severe impairment of haemocoagulation and the protocols used in our department (AML BFM -98 at the time of this study) lead to severe and long-time febrile neutropenias in children. Both of these reasons are sufficient to increase the risk of CVL-related thrombotic and/or septic complications. The risk of CVL-related thrombotic complication is, however, often increased also in patients with ALL, mainly during the induction therapy with concomitant medication with corticosteroids and L-asparaginase (5). However, in our patients ALL was not associated with a higher risk of CVL complication. The reason might be seen in the recommendation of the BFM group to insert CVL preferably after chemotherapy courses with concomitant corticosteroid/L-asparaginase administration. This supports our assumption that not only the diagnosis but also the therapy used is important for the risk level of CVL-related complications.

It is clear that it is very difficult – if possible at all – to distinguish the influence of the underlying disease from the influence of the therapeutical protocol,
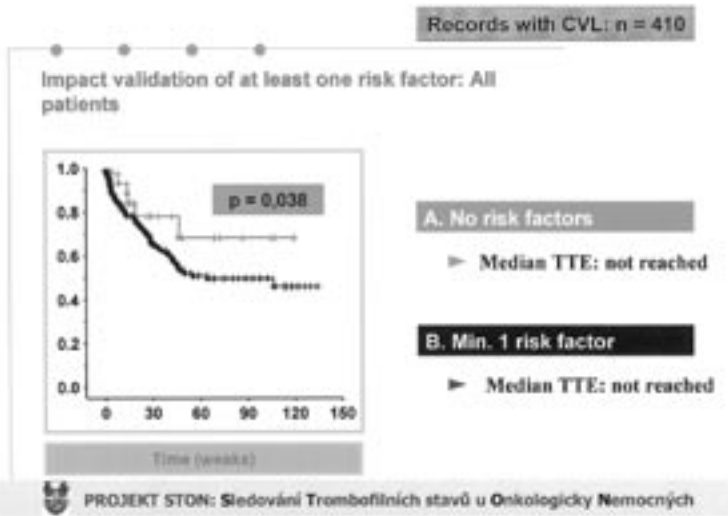
Fig. 13
Time to extraction (TTE) of CVL. Positivity of at least one risk factor led to significant shortening of TTE in our patients.
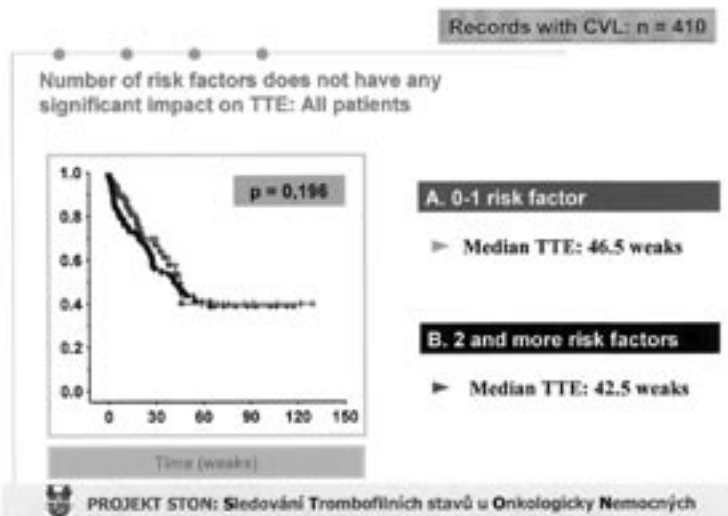

Fig. 14
Time to extraction (TTE) of CVL. Number of positive risk factors in our patients had no further significant influence on TTE.
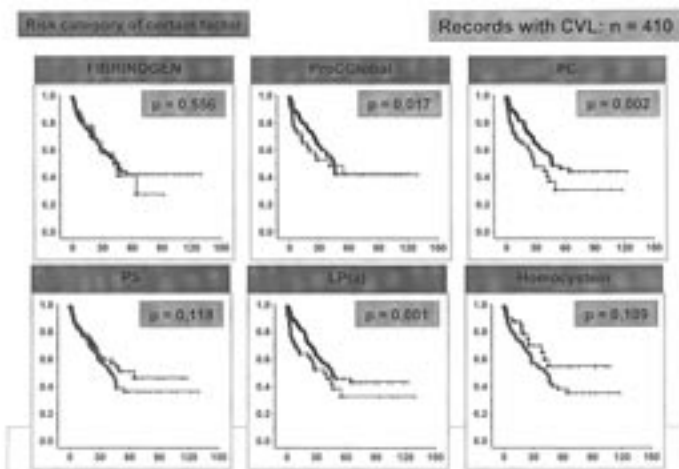
Fig. 15
Analysis of TTE related to individual risk factors. Patients with positive Pro C Global test, decreased protein C (PC) plasmatic level and increased plasmatic level of Lipoprotein(a) at the time of diagnosis had significantly shorter time to extraction (TTE) of CVL than patients with normal findings in these parameters.
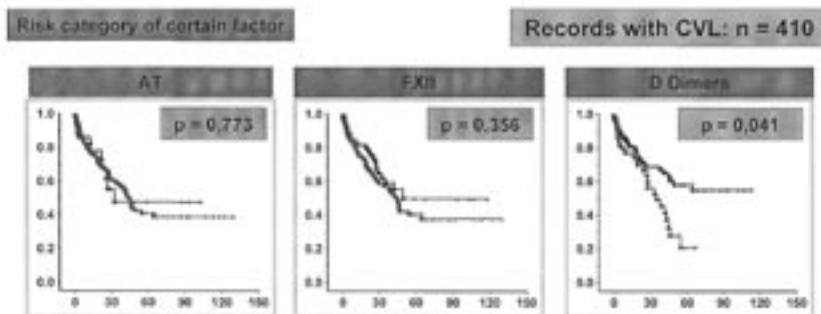

Fig. 16
Analysis of TTE related to individual risk factors. Patients with increased plasmatic level of D dimmers at the time of diagnosis had significantly shorter time to extraction (TTE) of CVL than patients with normal findings in these parameters.

162

site and technique of CVL insertion, the type of inserted CVL from the influence of hereditary thrombophilia, and other impairment of the coagulation system and the immune system on the severity and frequency of a CVL-related complication, as these different mechanisms influence one another. However, it is probably possible to assess the whole system at the beginning of treatment and – with the help of mathematic modelling – predict the risk of CVL-related complications based on these data. We believe that we have identified some of the parameters suitable for this prediction. To identify patients with a higher risk of thrombotic/microthrombotic and/or septic complications associated with CVL enables us to offer different preventive and/or therapeutical approaches to these patients.

CONCLUSION

With respect to the aims of our project we can conclude:

Ad (1): We have developed a probabilistic risk score. This score enables us to stratify the risk of CVL-related complications in children treated for malignant disease. The score was validated for individual episodes (CVL complications) as well as for individual patients.

Ad (2): We have not been able to prove a significant influence of the FV Leiden mutation and the mutation of FII G20210A on the risk of CVL-related septic and/or thrombotic /microthrombotic complications. In our patients, there was no carrier of FII G20210A mutation. The influence of FV Leiden was not significant enough (p= 0.738).

Ad (3): We have identified coagulation-related parameters associated with the increased risk of CVL-related septic and/or thrombotic/microthrombotic complications, and they might be probably used as predictors of such a risk. They are as follows:

decreased plasmatic level of PC at the time of diagnosis;
decreased plasmatic level of PS at the time of diagnosis;
positive ProC Global test at the time of diagnosis;
increased D dimmers at the time of diagnosis;
increased plasmatic level of Lp(a) at the time of diagnosis.

Ad (4): We have proposed a possible influence of certain diagnoses or diagnostic groups of malignant diseases on the severity and frequency of CVL-related septic and/or thrombotic /microthrombotic complications. Despite a high statistical significance (p < 0.001), this finding should be further validated.

This work provides some answers regarding a very complicated area of supportive treatment in paediatric oncology, but it also raises many new questions. As such, it may help in delivering different and "tailored" care to the patient.

Mathematical modelling and risk prediction is an unambiguous contribution to clinical practice. In our view, this is the way to follow. As every model can be improved, further categories should be implemented. Examples of such categories are:

quantification of the risk related to certain diagnoses and its treatment;

type and technique of inserted CVL;

severity of febrile neutropenia and the algorithm of its treatment;

a more precise definition of CVL-related sepsis and pathogens causing it.

These are the main reasons why we plan to continue with the STON project in the form of a prospective study. It will enable us to get more information than we get from retrospective data analyses.

This work is only an initial step on our long way to improving the quality of life and prognosis of children with malignancy. However, each step forward on this way is helpful.

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RIZIKOVÉ FAKTORY VÁŽNÝCH KOMPLIKACÍ CENTRÁLNÍCH ŽILNÍCH KATÉTRŮ
U DĚTÍ S MALIGNÍM ONEMOCNĚNÍM – PREDIKCE V RIZIKOVÉ ANALÝZE

S o u h r n

Centrální žilní katétr (CŽK) je v současné době ve většině případů nezbytnou podmínkou umožňující moderní léčbu maligních onemocnění. U dětí je potřeba kvalitního permanentního žilního přístupu ještě výraznější. S CŽK však mohou být asociovány i závažné komplikace, které mohou ohrožovat život pacienta a/nebo znesnadňovat vlastní onkologickou léčbu. Mezi nejzávažnější patří komplikace septické a komplikace spojené s tvorbou trombu či mikrotrombu souvisejícího s CŽK. Trombotické a septické komplikace se pravděpodobně navzájem ovlivňují.

Riziko takových komplikací je individuální a závisí nejen na základní diagnóze a použitém léčebném protokolu, ale i na imunologickém profilu pacienta, okolních, např. epidemiologických vlivech, ale také na sklonu jednotlivých pacientů k nadměrné tvorbě krevní sraženiny. Predikce alespoň některých z těchto rizik na počátku léčby by umožnila diferencovaný přístup k jednotlivým pacientům a zvýšila tak šanci na úspěšnou léčbu či dokonce prevenci výše uvedených komplikací. Cílem práce bylo vytvořit prediktivní model, který by zejména na základě hemokoagulačních parametrů vyšetřovaných při diagnóze, před zahájením jakékoli léčby a před implantací CŽK, umožnil prognózovat rizikovost komplikací spojených s CŽK v průběhu léčby onkologicky nemocných dětí.

Na základě retrospektivní analýzy 410 epizod komplikací vedoucích k extrakci CŽK u 186 pacientů léčených pro nově diagnostikované maligní onemocnění na Klinice dětské onkologie Fakultní nemocnice Brno v období 10/1999–12/2002 bylo možno vytvořit model umožňující pomocí pravděpodobnostního rizikového skóre a analýzy doby do extrakce katétru (Time to extraction: TTE) stanovit parametry, jejichž pozitivita při stanovení diagnózy je spojena se zvýšeným rizikem - daným

tíží a četností – komplikací CŽK. Jedná se o tyto parametry:
- snížená plazmatická hladina PC v době diagnózy
- snížená plazmatická hladina PS v době diagnózy
- pozitivní test ProC Global v době diagnózy
- pozitivita D dimerů v době diagnózy
- zvýšená plazmatická hladina Lp(a) v době diagnózy

Pozitivní nález v těchto parametrech není pravděpodobně daný jen hereditární trombofilií, je ovlivněn i základní diagnózou. Avšak právě proto umožňuje zohlednit výchozí stav u jednotlivého pacienta a může být informativním a alespoň částečně validním predikátorem budoucích komplikací. Vytvořený prediktivní model bude třeba dále validovat a upřesňovat vyhodnocováním dat dalších epizod pacientů léčených pro maligní onemocnění. Avšak již tato pilotní data se mohou stát základem pro v budoucnu prováděné prospektivní analýzy a jsou prvním podkladem pro poskytování diferencované léčebné a preventivní péče při zvládnutí vážných komplikací spojených s užíváním CŽK u dětí s malignitou.

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166