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Dynamic reference intervals for coagulation parameters from infancy to adolescence

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ABSTRACT

Introduction: Practical and ethical challenges as well as time and costs have restricted the generation of pediatric reference intervals. Therefore, pediatric reference intervals on coagulation parameters based on solid evidence are still scarce. Furthermore, reference intervals by age-group cannot reflect the dynamics of age and sex specific coagulation values during childhood. This study is the first to close this gap and provide continuous age and sex dependent reference intervals during childhood in hemostasis.

Methods: We used an innovative indirect method for providing continuous reference intervals for five common coagulation parameters: Activated partial thromboplastin time (aPTT), prothrombin time (PT), thrombin clotting time (TT), fibrinogen (FIB) and antithrombin (AT). Calculations were performed using retrospective laboratory data from pediatric patients between 2005 and 2015 of two major Austrian hospitals, resulting in a total of 195.360 measurements (aPTT: 55,100; PT: 35,492; TT: 35,295; FIB: 49,789; AT: 19,684).

Results: This multicenter study provides calculations of continuous reference intervals for five common coagulation parameters in a large pediatric cohort, accounting for age and gender.

Conclusion: To the best of our knowledge, this is the first multicenter study, determining continuous pediatric coagulation reference intervals based on a large retrospective dataset.

1. Introduction

Laboratory reference intervals (RIs) are fundamental for an accurate clinical decision-making processes and therefore have an important impact on the overall quality of patients' healthcare. Especially in children, reference ranges may vary dramatically by age from infancy to adolescence due to continuous changes of biological development. Gender as well as ethnic differences are further factors which can lead to additional variations in RIs [1]. In addition, the analytical setting of each laboratory complicates the situation further. This is why organizations such as the Subcommittee of the Scientific and Standardization Committee of the International Society on Thrombosis and Hemostasis (ISTH) recommend that laboratories define their own age-dependent reference ranges [2]. According to current guidelines, variations such as age, gender, assays etc. that determine RI-ranges must comprise results of at least 120 verifiably healthy reference individuals [3]. Hence, establishing RIs is quite challenging and almost impossible for single laboratories. The identification and recruitment of a sufficient number of healthy children is time-consuming and analytical costs are substantial. But most importantly, collecting blood from children without benefit to their personal health is ethically problematic [1,4]. Consequently, most laboratories refer to published RIs or to those provided by the manufacturer. This, however, may lead to misinterpretations and inadequate clinical decisions due to differences in reference populations and analytical methods.

In the past years, several nation-wide multi-center collaborative projects in Canada, Germany, the US and Scandinavia have been initiated, aiming to establish pediatric reference intervals based on a large amount of data [5–11]. However, all these investigations leave three problems still unsolved: 1) Due to the variable of combinations of patient population and

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assays used in clinical laboratories around the world, the proposed RIs may not properly reflect every possible health care setting. 2) In all the mentioned RI projects, arbitrary age groups were defined. Consequently, RIs may change abrupt on the pediatric patients' birthday leading to two different RIs in just two days and the question, which of the two reflects the patients' laboratory RI-values correctly. In analogy with other developmental quantities routinely specified in relation to age (e.g., weight- and height-for-age charts), a continuous description would seem to be more appropriate [12–17]. 3) Unfortunately, all these large RI projects focused mainly on clinical chemistry or hematological parameters, while RIs on coagulation parameters are lacking in these studies. Therefore, the only source of pediatric RIs are even smaller studies with < 120 healthy individuals per subgroup with still same limitations as the above mentioned studies [11,18–24].

In our study, we therefore aimed to establish continuous pediatric RIs for coagulation parameters from large laboratory databases using a retrospective indirect approach according to Arzideh et al. [25–28] and Zierk et al. [16,29,30] and to compare these with existing RIs. To the best of our knowledge, this is the first large multicenter study investigating pediatric RIs on coagulation parameters using an indirect approach and presenting these findings as continuous RIs for routine coagulation parameters.

2. Methods

2.1. Study population

Data for the coagulation parameters: activated Partial Thromboplastin Time (aPTT), Prothrombin time (PT), Thrombin Clotting Time (TT), Fibrinogen activity (FIB) and Antithrombin activity (AT) were collected from laboratory information systems (LIS) of the Medical University Hospitals of Vienna and Salzburg over a time period of ten years (2005–2015). Laboratory results from patients aged 18 years or less taken during routine clinical care of patients were taken in account. The dataset contained information on the unit ordering the tests, the date of request, the gender and age of the patient, the laboratory test results and an anonymized identification number. Subjects with incomplete information were excluded from further statistical analyses. To minimize distortion in the calculation of RIs via indirect approach, analyses from critical ill patients (intensive care and emergency units) as well as multiple observations obtained from an individual subject if available were excluded. Based on these criteria we obtained 55.101 aPTT, 35.492 PT, 35.295 TT, 49.789 FIB and 19.684 AT laboratory results of patients. The population was equally distributed between male and female patients for all parameters.

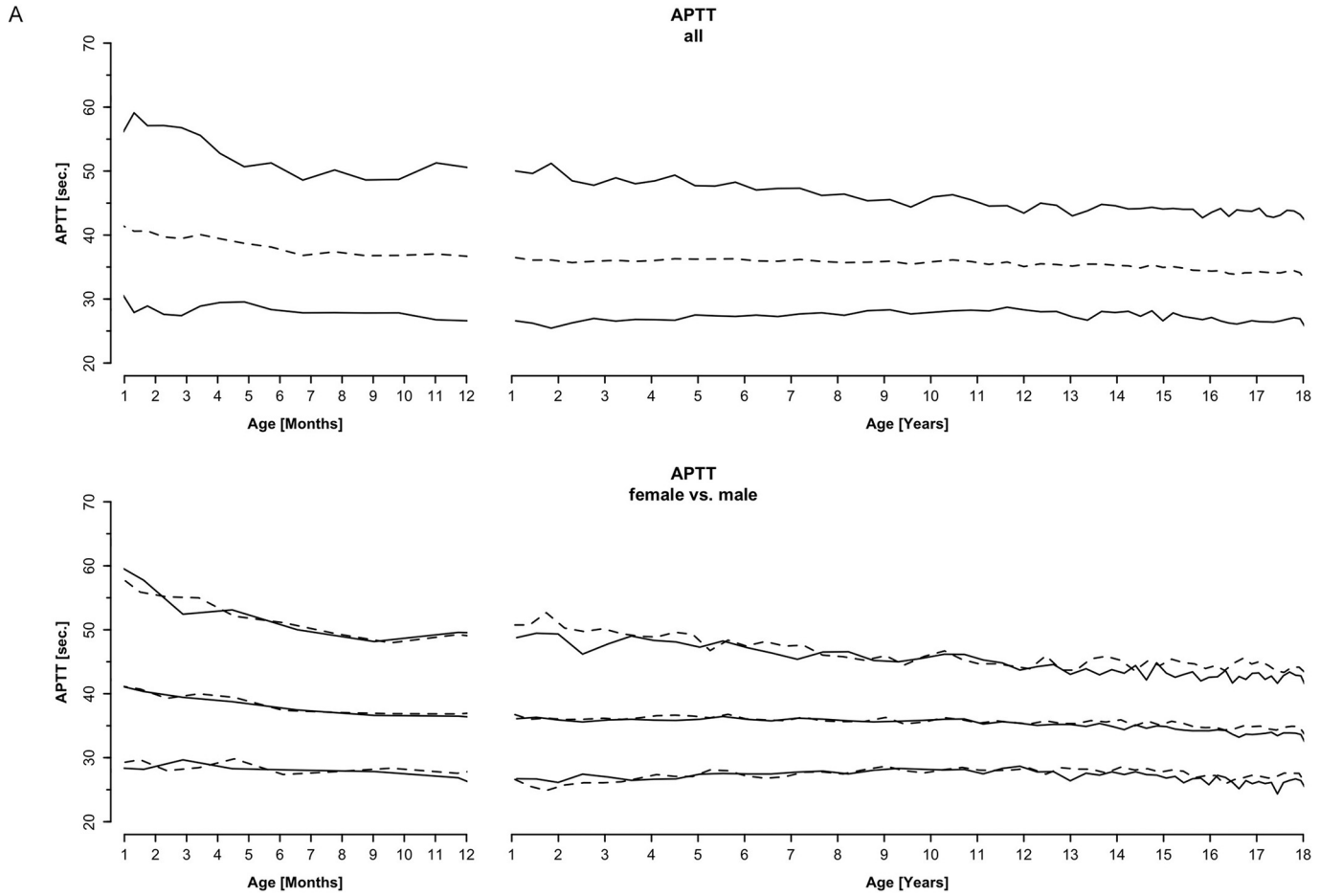

Fig. 1. Continuous reference intervals for APTT (A), PT (B), TT (C), FIB (D) and AT (E), overall and stratified by gender.
Upper, median and lower curves denote the 97.5th, 50th and 2.5th percentiles. Dashed lines denote female values, solid lines denote male values. Values at 12 months and 1 year slightly differ from one another due to separate calculation.