

Calculate the Range of Bleeding Assessment Tool Score in Healthy Volunteers (Male and Female) in the State of Uttarakhand

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Abstract

The essential step in the assessment of patients for a probable bleeding disorder is to evaluate the severity of bleeding symptoms. To improve the compilation and precision of the patients with history of bleeding symptoms, several Bleeding Assessment Tools (BAT) have been anticipated. A structured questionnaire was approved by the ISTH/SSC-BAT together in year 2010. In our study, data from 99 normal adults (42 females and 57 males) from Uttarakhand were analysed this score (ISTH/SSC- BAT). Mean age of the adult population was 29 year. Normal range obtained were 0–3, 0–5 for males and female respectively after removing the outliers. The median BAT score was 0 in adult males and 1 in adult females. This information may now be used to evaluate the history of bleeding symptoms as a normal or abnormal in the state of Uttarakhand. We aim to standardize this score system in the population of Uttarakhand in our study and improve diagnostic accuracy at a low cost and grass root level.

Keywords: BAT score, Bleeding disorder, Uttarakhand.

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INTRODUCTION

Inherited bleeding disorders are conditions that draws low concern to public health in India, even though they cause noteworthy morbidity to the patients, their families and society [1, 2]. These disorders are not only inherited but may arise spontaneously. Our country has the second largest global population and a high birth rate [3]. According to World Federation of hemophilia, India has 1.38 cases of hemophilia, 0.04 cases of Von Willebrand disease (VWD) and 0.02 cases of other bleeding disorders per 1,00,000 population [4].

Bleeding diathesis are broadly categorized on the basis of platelet function defects which includes Bernard Soulier, Glanzmann's Thrombasthenia and Coagulation factor deficiencies which includes hemophilia A & B. VWD is the most frequently inherited bleeding disorder. Partial quantitative deficiency of von Willebrand factor (VWF) leads to Type1 VWD while qualitative defect in the VWF molecule leads to type 2 VWD and type 3 VWD

(recessive transmission) is characterized by almost complete deficiency of VWF in homozygous patients [5]. The genetic transmission is generally co-dominant or dominant. Deficiency of blood coagulation factors, F VIII and F IX results in hemophilia A and hemophilia B respectively, which are serious bleeding disorders [6]. These disorder reportedly affect 1 in 1,000 men and women globally [5]. The most prevalent types of bleeding disorders are Hemophilia A and B and VWD. The incidence of hemophilia in India is 15-20 males per 10,000 in year 2017 with more number of newly diagnosed cases each year [7]. But this could be just the tip of iceberg as many undiagnosed and unregistered cases exists the society.

Practically, problems with these inherited disorders today is the delay in identification and ignorance about the inheritance pattern. In India, most of the hemophiliac families have more than one affected male child and female child as carriers. Consequently, new cases will be added to the population through birth of progeny of known

hemophiliac male with carrier females, besides occurrence of novel mutations in 30% of the cases [8]. An assessment of patients with abnormal bleeding disorder requires an objective clinical assessment of their bleeding history, their family history and, if required, their physical examination followed by laboratory investigations.

To prevent bleeding disorders, one way is to either establish specialized laboratories at grass root level for diagnosis and prenatal screening which requires much of expenditure on infrastructure. Another way can be, devising a screening tool which is economical and effective. The latter can be achieved by using a set of questions given by International Society of Bleeding and Thrombosis-Bleeding assessment tool (ISTH-BAT) 2010, based on which, a score for bleeding symptoms can be calculated to categorize high risk patients, which require further advanced work up and genetic counseling [9].

To suspect the bleeding disorder, a history of mucocutaneous bleeding is an important component. In this study we used ISTH-BAT score and analyzed the 14 specific bleeding symptoms and scored each symptom on a scale of 0 to 4. By adding all the scores, we calculated the total score of each of subject. Normal range of total score according to previous studies was 0-3 for adult males, 0-5 for adult females and 0-2 in children for both males and females and the cut-off for a positive or abnormal BS is ≥ 4 in adult males, ≥ 6 in adult females and ≥ 3 in children was established by them [10]. Presently Uttarakhand possesses some 180 families with bleeding diathesis with the number rising every day. The aim of our study was to use ISTH- BAT to calculate the bleeding score in the voluntary donors of our population (Uttarakhand) and to derive the cutoff to identify inherited bleeding disorder patients in our population. The objective of the study is to prove BAT score to be as efficient as basic coagulation screening test done to identify inherited bleeding disorders.

MATERIAL AND METHODS

The design of our study was cross sectional observational study. Bleeding Assessment Tool (BAT) Score was analyzed in normal individuals above the age of 18 yrs. All subjects were basically belonged to the state of Uttarakhand (technologists, voluntary blood donors, students and faculty). The inclusion criterias of

our study were individuals with no history of any identified or formerly diagnosed bleeding disorders and individuals with no known crisis with bleeding or bruising. These normal subjects were investigated for Bleeding Time, Prothrombin Time (PT) & Activated Partial Thromboplastin Time (APTT). The normal reference range in our laboratory for bleeding time was 2-6 minutes and reference range for PT and APTT was 11.25-14.13 and 25.52-31.92 seconds respectively. Bleeding time was done using Modified Ivy's method. Coagulation studies were done on STAGO STA Compact. End point detection of clot was done using electromechanical method. The Prothrombin Time and activated Partial Thromboplastin Time was measured using neoplastin and CK-PREST with Kaolin respectively. The quality control for the instrument (STAGO) used for coagulation study were taken care as per the NABL guidelines. Data was collected and entered in M.S. Excel 2010. The different statistical analysis was performed using SPSS software version 22. The one sample Kolmogorov-Smirnov test were employed to determine whether the data sets were normally distributed or not. Normally distributed data was analysed using parametric test and non normally distributed data was analysed using non parametric test. Descriptive statistics was calculated for quantitative variables. Frequency along with percentages were calculated for qualitative and categorical variables. Graphical representation of the variables are shown to understand the results clearly. To determine the normal range, middle 95th percentile was used after removing the outliers. Informed consent were taken from all the volunteers and the details of the donors were kept confidential before analysis of data.

RESULTS

The median age of the adult population was 27 year. Among these, 43% were adult females and 57% were adult males. The bleeding score of our study was ranged from (0-6) in adult females and (0-4) in adults males. The majority of cases were scores 0 both in male and female. The distribution of data was not normal. We excluded the outliers (BS >3 in adult males, BS >5 in adult females). Using the methodology outlined above, the normal BS range was found to be 0-3 in adult males, 0-5 in adult females. The median BS was 0 in adult males and 1 in adult females.

Table-1: Mean value for Prothrombin Time, activated Partial Thromboplastin Time and bleeding time in adult males and females

	Male	Female
Bleeding Time	3.5 \pm 1.32 min	3.4 \pm 1.4 min
Prothrombin Time	12.54 \pm 1.24 sec	12.6 \pm 1.24 sec
Activated Partial Thromboplastin Time	28.2 \pm 4 sec	28.7 \pm 3.92 sec

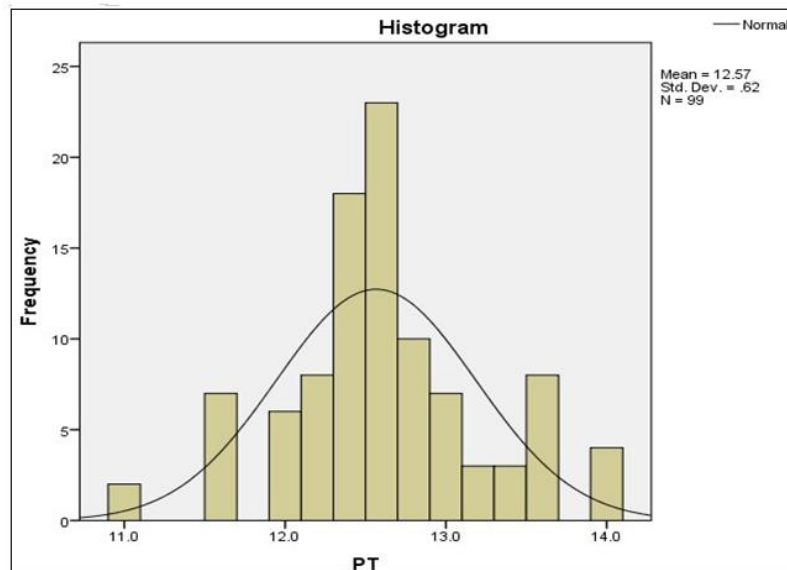


Fig-1: PT ranged from 11.0 to 14.0 with maximum frequency of 12.5 seconds

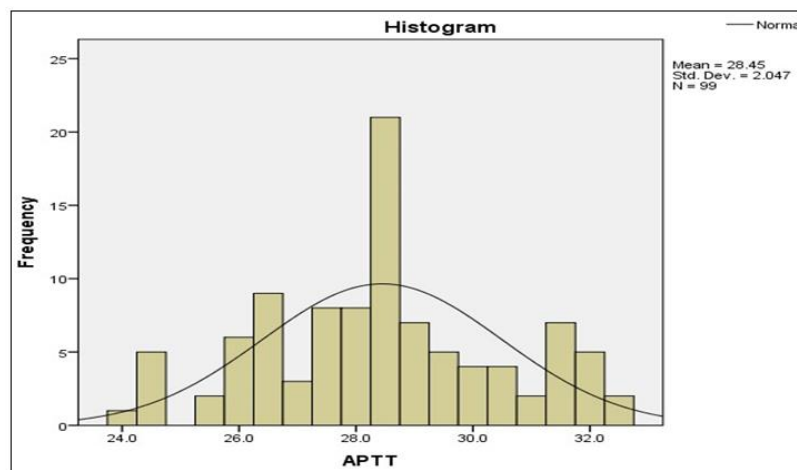


Fig-2: APTT ranged from 24 to 32.5 with maximum frequency of 28.5 seconds

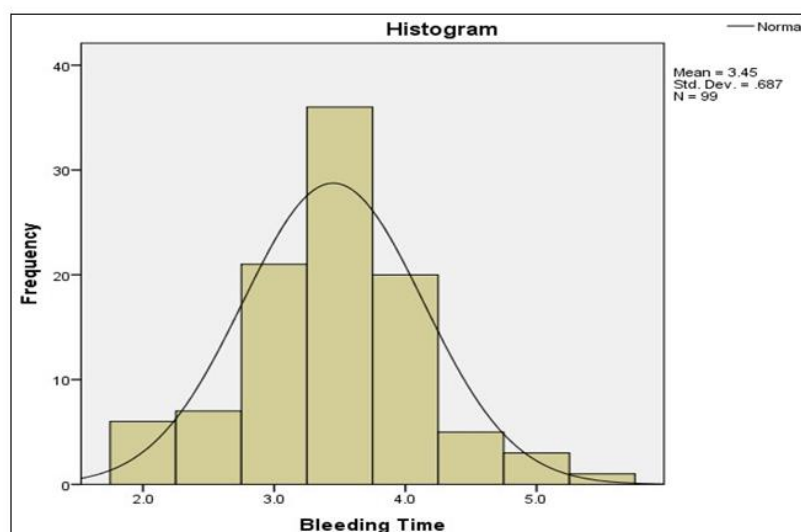


Fig-3: Bleeding Time ranged from 2 to 5.5 with maximum frequency of 3.5 minutes

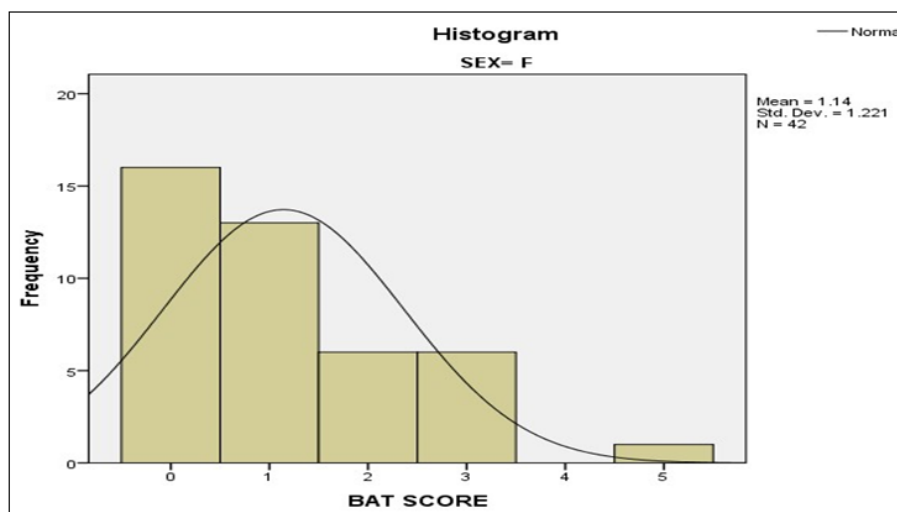


Fig-4: BAT score in Females ranged from 0 to 6 (without excluding the outliers).

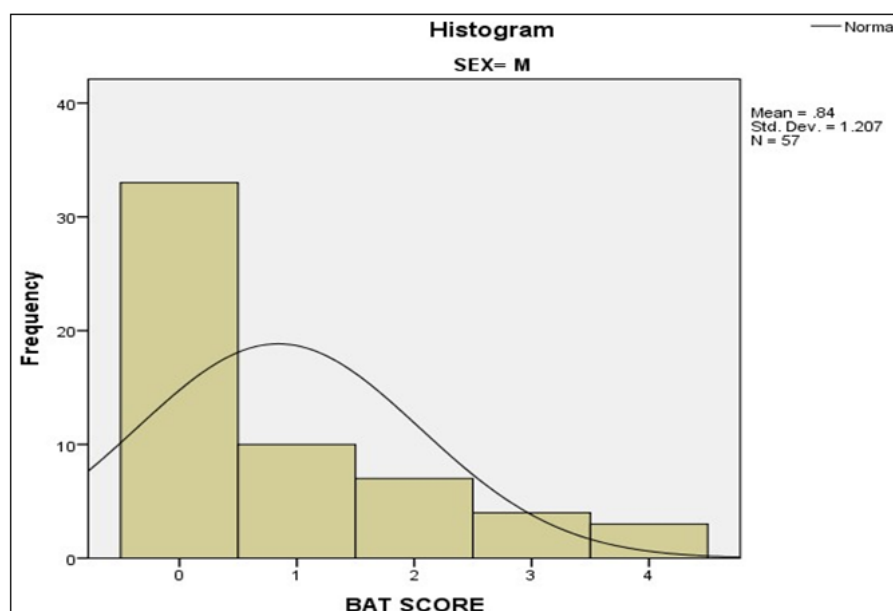


Fig-5: BAT score in Males ranged from 0 to 4 (without excluding the outliers).

DISCUSSION

Clinical assessment of the severity of bleeding symptoms is the most important step in evaluating a patient with possible bleeding disorder because of the complicatedness in reporting subjective bleeding symptoms in a reproducible manner. Many attempts have been made to harmonize the collection and reproducibility of the bleeding history. This leads to the development of BATs that can transform the range of severities of bleeding symptoms into a concluding and summative BS. Many investigators attempted to standardize the bleeding history. The International Society on Thrombosis and Hemostasis (ISTH) Scientific and Standardization Committee (SSC) in year 2005 on VWF established a set of provisional criteria for the diagnosis of VWD type 1 [11]. Rodeghiero *et al.*, developed and validated a BAT for the diagnosis of Type 1 VWD in a primarily adult population [9]. This

scoring system was revised and the score were given from -1 to 4 (higher scores to symptoms requiring medical attention and intervention) and this revised score was used by European Molecular and Clinical Markers for the Diagnosis and Management of type 1 VWD (MCMDM-1 VWD) [12]. To conquer the mentioned boundaries and to promote the equivalence of the available BATs [13-18], a working group was established within the framework of the ISTH/SSC Subcommittees on VWF and on Perinatal/Pediatric Hemostasis (ISTH/SSC-BAT) during the 53rd SSC Annual Meeting held in Geneva in 2007. The ISTH/SSC-BAT together agreed on this structured questionnaire and its clinical use. We used this questionnaire to analyse our data.

The median age in most of the studies done previously ranged from 39 to 49 years [5, 10, 12, 19], however in our study the mean and median age was 29

and 27 years respectively. The cutoff for an abnormal bleeding symptoms in adult males and adult females using the ISTH-BAT score was 0-3 and 0-5 in respectively in a study done by M. Elbatarny *et al.*, [10]. Our study also showed the same results where we found the same cutoff for both males and females. Our ranges were also consistent with the results derived from the original Vicenza BQ and normal range of bleeding scores for the ISTH-BAT [5]. Like most of the studies [5, 10], large majority of scores were 0 in our study. The median BS in our study was 0 in adult males and 1 in adult females this was similar to the study done by M. Elbatarny *et al.*, and Rodeghiero F *et al.*, [5, 10].

We included 99 donors in our study which was less in comparison to the study done by M. Elbatarny *et al.*, who analyzed data from 1040 normal adults. However Rodeghiero F *et al.*, analysed some 215 donors to derive the cutoff. Also most of the studies did elaborate coagulation studies including factor assays and von willibrand assays to define their control population, however we did basic coagulation studies like PT, APTT and bleeding time, which could have increased the likelihood of patients with mild factor deficiencies and mild von willibrand disease to be included in normal controls. The study emphasizes on the importance of bleeding histories and ISTH-BAT and by defining its normal range for the state of Uttarakhand to make it easy in interpretation, so that it becomes easy for any clinician to decide whether the patients needs further investigation or not, even without doing the basic laboratory work up.

CONCLUSION

The recent established cutoffs for abnormal BS, for adult males ≥ 4 and ≥ 5 for adult females, can be used to evaluate the status of affected individuals using ISTH-BAT in a standard manner. In addition, the collection of these data is an essential initiative for the standardization of bleeding phenotype data. In doing this, main objective of our study is to improve data accessibility in the long term by making these data available to investigators by using the web-based ISTH-BAT system. Finally, the main focus of our study is to expedite the relationship between bleeding phenotypes and their genetic, molecular, and environmental data in order to improve their diagnostic accuracy and provide understanding into the factors that determine an individual's liability to bleed. By making the ISTH-BAT and its normal data available to investigators to conduct and analyze studies, we hope to expedite the development of new knowledge in the field.

REFERENCES

1. KAR, A. (2011). Preventing birth defects in India. *Economic and Political Weekly*, 46(48), 21-22.
2. Christianson, A., Howson, C. P., & Modell, B. (2005). *March of Dimes: global report on birth defects, the hidden toll of dying and disabled children.*
3. Parks Textbook of Preventive & social medicine (2017 edition).
4. World Federation of Hemophilia (WFH) Canada: WFH. (2016). Report on the Annual Global Survey 2011. Available from: <http://www1.wfh.org/publications/files/pdf-1488>.
5. Rodeghiero, F., Castaman, G., Tosetto, A., Batlle, J., Baudo, F., Cappelletti, A., ... & Lethagen, S. (2005). The discriminant power of bleeding history for the diagnosis of type 1 von Willebrand disease: an international, multicenter study. *Journal of thrombosis and haemostasis*, 3(12), 2619-2626.
6. Storb, R., Marchioro, T. L., Graham, T. C., Willemin, M., Hougie, C., & Thomas, E. D. (1972). Canine hemophilia and hemopoietic grafting. *Blood*, 40(2), 234-238.
7. UNICEF India statistics. (2017). Available from: <http://www.unicef.org/infobycountry/indiastatistics.html>.
8. Haldane, J. B. (1935). The rate of spontaneous mutation of a human gene. *Journal of genetics*, 31(3), 317-326.
9. Rodeghiero, F., Tosetto, A., Abshire, T., Arnold, D. M., Collier, B., James, P., ... & ISTH/SSC joint VWF and Perinatal/Pediatric Hemostasis Subcommittees Working Group. (2010). ISTH/SSC bleeding assessment tool: a standardized questionnaire and a proposal for a new bleeding score for inherited bleeding disorders. *Journal of Thrombosis and Haemostasis*, 8(9), 2063-2065.
10. Elbatarny, M., Mollah, S., Grabbell, J., Bae, S., Deforest, M., Tuttle, A., ... & Riddell, J. (2014). Normal range of bleeding scores for the ISTH-BAT: adult and pediatric data from the merging project. *Haemophilia*, 20(6), 831-835.
11. Sadler, J. E., & Rodeghiero, F. (2005). Provisional criteria for the diagnosis of VWD type 1. *Journal of thrombosis and haemostasis: JTH*, 3(4), 775-777.
12. Tosetto, A., Rodeghiero, F., Castaman, G., Goodeve, A., Federici, A. B., Batlle, J., ... & Eikenboom, J. (2006). A quantitative analysis of bleeding symptoms in type 1 von Willebrand disease: results from a multicenter European study (MCMDM-1 VWD). *Journal of Thrombosis and Haemostasis*, 4(4), 766-773.
13. Rees, M. (1987). Menorrhagia. *British medical journal*, 294: 759-762.
14. Kadir, R. A., Economides, D. L., Sabin, C. A., Owens, D., & Lee, C. A. (1998). Frequency of inherited bleeding disorders in women with menorrhagia. *The Lancet*, 351(9101), 485-489.
15. Mauer, A. C., Barbour, E. M., Khazanov, N. A., Levenkova, N., Mollah, S. A., & Collier, B. S. (2009). Creating an ontology-based human

phenotyping system: the Rockefeller University bleeding history experience. *Clinical and translational science*, 2(5), 382-385.

16. Philipp, C. S., Dilley, A., Miller, C. H., Evatt, B., Baranwal, A., Schwartz, R., ... & Saidi, P. (2003). Platelet functional defects in women with unexplained menorrhagia. *Journal of thrombosis and haemostasis*, 1(3), 477-484.
17. Katsanis, E., Luke, K. H., Hsu, E., Li, M., & Lillicrap, D. (1988). Prevalence and significance of mild bleeding disorders in children with recurrent epistaxis. *The Journal of pediatrics*, 113(1), 73-76.
18. Bowman, M., Riddel, J., Rand, M. L., Tosetto, A., Silva, M., & James, P. D. (2009). Evaluation of the diagnostic utility for von Willebrand disease of a pediatric bleeding questionnaire. *Journal of thrombosis and haemostasis*, 7(8), 1418-1421.
19. Bowman, M., Mundell, G., Grabell, J., Hopman, W. M., Rapson, D., Lillicrap, D., & James, P. (2008). Generation and validation of the Condensed MCMDM-1VWD Bleeding Questionnaire for von Willebrand disease. *Journal of thrombosis and haemostasis*, 6(12), 2062-2066.