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Translation, validation and usability of the International Society on Thrombosis and Haemostasis Bleeding Assessment Tool (Self-ISTH-BAT)

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PLAIN LANGUAGE SUMMARY

What is the new aspect of your work?

Large comparison study of patient-administered bleeding questionnaire (self-ISTH-BAT) and health care practitioner-administered (expert-ISTH-BAT) on unselected individuals attending hospital.

What is the central finding of your work?

The self-ISTH-BAT had 82% true positive rate and 89% true negative rate compared to accepted cut-off scores. Three (3%) had normal self-ISTH-BAT with abnormal expert-BAT. We found high exact agreement between expert-ISTH-BAT and self-ISTH-BAT, and high interobserver agreement.

What is (or could be) the specific clinical relevance of your work?

Our findings indicate that self-ISTH-BAT can replace expert-ISTH-BAT as a screening tool in the general population. The self-ISTH-BAT can potentially improve patient safety by systematically evaluate detailed bleeding history before procedures with bleeding risk and thus identifying patients with bleeding tendency.

ABSTRACT

Background: Bleeding questionnaires are effective and recommended screening tools for potential bleeding disorder, but health care practitioner-administered bleeding assessment tools (expert-ISTH-BAT) is time consuming. A patient-administered ISTH-BAT (self-ISTH-BAT) has been developed and validated. We translated, validated and evaluated the usability of self-ISTH-BAT.

Methods: We conducted a forward-backward translation of self-ISTH-BAT from English to Danish. Expert-ISTH-BAT and Danish self-ISTH-BAT was administered to 106 random individuals aged ≥18 years attending Odense University Hospital between August and November 2020 for elective blood sampling. Results comprise a score of bleeding symptoms.

Results: Mean age of included individuals were 49 years (range: 18-83), and 59% were female. Median self-ISTH-BAT score was 2 (range: 0-18) and 1 (range: 0-22) for expert-ISTH-

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BAT (p=0.09). All organ systems had ≥90% exact score agreement between expert-ISTH-BAT and self-ISTH-BAT, except gastrointestinal-bleeding (77%) and other bleedings (72%). We found an acceptable correlation (r^2=0.80) between expert-ISTH-BAT and self-ISTH-BAT. The self-ISTH-BAT had 82% sensitivity and 89% specificity at the recommended cut-off for expert-BAT (Female:<6; Male:<4). At this cut-off, 10 had abnormal self-ISTH-BAT scores with normal expert-ISTH-BAT. Three (3%) had normal self-ISTH-BAT with abnormal expert-ISTH-BAT.

Conclusion: Self-ISTH-BAT can replace expert-ISTH-BAT as a screening tool for bleeding disorders in Danish individuals as only 3% were not identified with the self-ISTH-BAT tool.

Key words: Bleeding Assessment Tool, Screening, Danish

INTRODUCTION

The World Federation of Haemophilia estimates that one per 880 individuals worldwide suffers from a bleeding disorder (1), but only around 4% are diagnosed (1, 2). Undiagnosed bleeding disorder possesses a health risk, and critical or lethal bleeding may occur if experiencing a trauma or major surgery, along with a potential reduction in quality of life (2-4). In the work-up of bleeding disorders a detailed bleeding history is crucial to identify candidates for biochemical testing (5-8) and establish a diagnosis (8). The International Society on Thrombosis and Haemostasis (ISTH) Scientific and Standardization Committee (SSC) has developed and validated a bleeding questionnaire, ISTH Bleeding Assessment Tool (ISTH-BAT) (9), for identifying individuals suffering from von Willebrand disease (VWD) (9), haemophilia (10) and some platelet disorders (11). However, the ISTH-BAT is expert-administered (expert-ISTH-BAT) and should be filled out by health care practitioners with knowledge of bleeding disorders, which limits its use as a general screening tool. A patient-administered version of the expert-ISTH-BAT (self-ISTH-BAT) is developed (12), and has been validated on individuals suffering from VWD (12), haemophilia (13), congenital platelet defect (CPD) (14) along with the general population (15). The self-ISTH-BAT is in English, and therefore not applicable in non-English speaking countries. A Dutch version of the self-ISTH-BAT has been reported and compared with expert-ISTH-BAT in individuals with suspected CPD (14). However, to the best of our knowledge, no study has investigated if self-ISTH-BAT can be used as a general screening tool in individuals attending hospital, by comparing self-ISTH-BAT and expert-ISTH-BAT in unselected individuals attending hospital. The purpose of

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this study was to translate the self-ISTH-BAT to Danish, validate the Danish self-ISTH-BAT, and evaluate its usability in clinical practice.

MATERIALS AND METHODS

We performed a translation, validation and efficacy study of the self-ISTH-BAT questionnaire in a Danish setting. The study was conducted in agreement with the tenets of the Declaration of Helsinki and the principles of good clinical practice. The Danish Data Protection Agency approved the study. Since it was a questionnaire study, local ethics committee permission was not required according to Danish law. The authors of the original English self-ISTH-BAT study (12) approved this project.

Translation

The original self-ISTH-BAT (in English) was extracted from the supplementary material of the original publication (12). We conducted a forward-backward translation from English to Danish using the guidelines for cross-cultural adaption of self-reported measures (16-18).

Stage 1 (Translation): A translation from English to Danish was conducted by two individuals; An independent professional certified English translator with Danish as mother tongue who was not a healthcare professional and a medical doctor (RSH) with ISTH-BAT experience, bleeding disorder knowledge, Danish as mother tongue and expert level English.

Stage 2 (Synthesis): A written report about challenges and solutions with the translation was done, and the two Danish translations were merged based on agreement between the two translators.

Stage 3 (Back translation): An independent bilingual professional certified translator with English as mother tongue and Danish as second language, who was also a trained medical doctor, then translated the Danish version of the self-ISTH-BAT back to English. A report about challenges and solutions of the translation was performed.

Stage 4 (Expert committee review): An expert committee (RSH and PJV) discussed the translations and any disagreement was solved with discussion, leading to unanimous approval the Danish self-ISTH-BAT.

Stage 5 (Pretesting): The Danish self-ISTH-BAT was administered to 22 random anonymous healthy individuals attending the blood bank at Odense University Hospital (OUH) on May 2020 for blood donation. Each individual completed the Danish self-ISTH-BAT without

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assistance, and commented in writing on their experience with focus on the understanding and meaning of the statements and responses.

Validation:

To evaluate the patient's ability to understand the questionnaire, the question "mother tongue language" was added to self-ISTH-BAT. The Danish self-ISTH-BAT and the original English expert-ISTH-BAT were imported to Research Electronic Data Capture (REDCap) (Vanderbilt University, Nashville, Tennessee, United States). Study data were collected and managed using REDCap electronic data capture tools hosted at OUH (19). REDCap is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources (19). By using an electronic questionnaire, branching logic features enable participants to potentially complete the questionnaire faster and minimize errors, since only relevant questions will appear according to answers provided by the individuals.

The Danish self-ISTH-BAT was administered to random individual's aged ≥18 years attending the outpatient clinic at the Department of Clinical Biochemistry and Pharmacology (CBP) at OUH between August 28th and November 27th 2020 for blood sampling. The outpatient clinic serves individuals referred for blood testing from medical doctors on the island of Funen, with a population of approximately 500,000 inhabitants, which is considered a representative sample of the Danish population (20). All included individuals gave oral and written consent. Each individual completed the Danish self-ISTH-BAT without assistance. Upon completion of self-ISTH-BAT, a medical doctor administered the expert-ISTH-BAT (9). The medical doctor was blinded for the self-ISTH-BAT answers. Three medical doctors (RSH, MC, KFR) performed the validation study. After inclusion of eight patients, the question "Har du haft problemer med kraftig menstruation [Ja / Nej]" (English: "Have you had problems with heavy menstrual bleeding [Yes / No]") was added, since females without menorrhagia did not have the opportunity to skip menorrhagia questions in the original self-ISTH-BAT. We render that the added question had no impact on the scoring of self-ISTH-BAT or the comparison with expert-ISTH-BAT, since the question "Have you ever had very heavy menstrual bleeding" is part of expert-ISTH-BAT.

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To evaluate interobserver variation, three medical doctors (RSH, MC, KFR) scored all self-ISTH-BAT and then all expert-ISTH-BAT, blinded for the self-BAT score. The same scoring scheme published with the original ISTH-BAT (9) was used for both self-ISTH-BAT and expert-ISTH-BAT, and normal scores were defined as: female: <6 and male: <4 (9, 12). Clinical significant bleeding symptoms were scores ≥1 (9). The score of RSH is reported.

Clinical characteristics

Besides bleeding symptoms, the ISTH-BAT includes questions regarding age, sex, ethnicity, co-morbidities, medication and dispositions to bleeding disorders.

Statistics

Since data was not normally distributed, a two-tailed Wilcoxon Signed-Rank Test was performed when comparing scores between groups. For comparison of 2x2 contingency tables, a two-tailed Fisher's exact test was performed. Sensitivity (true positive rate), specificity (true negative rate), positive and negative predictive values (PPV and NPV) were calculated for all thresholds for abnormal score, using the same formulas as previously defined (21). To evaluate interobserver variation, Cohen´s Kappa value was calculated. A P-value <0.05 was considered statistical significant. Data analysis was performed using Stata (StataCorp, College Station, Texas, USA) and Excel (Microsoft®, Redmond, Washington, USA).

RESULTS

Translation

The expert committee discussed the translations and comments from the translation process, leading only to grammatical changes and final approval of the Danish self-ISTH-BAT (**Supplementary material 1**).

Cohort characteristics

The Danish self-ISTH-BAT was administered to 106 individuals, of which 59% were females. The mean age was 49 years (range: 18-83). Overall, 30% (n=32) had no co-morbidities and we deemed that 8% (n=8) had one or more co-morbidity associated with increased bleeding risk (inflammatory bowel disease (n=4), gastrointestinal (GI) cancer (n=2), large T cell leukaemia (n=1), liver transplantation (n=1)). There was 3% (n=3) reporting to receive acetylsalicylic acid. Two reported to have family members with an unspecified bleeding

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disorder. Among the 106 included individuals, seven were referred to CBP for evaluation of potential bleeding disorder.

Performance

For self-ISTH-BAT the median score was 2 (range: 0-18) and 1 (range: 0-22) for expert-ISTH-BAT (p=0.07). When stratifying for gender, the same median self-ISTH-BAT and expert-ISTH-BAT score was found (females = 3 and males = 1). In total, 19% (n=12) females and 12% (n=5) males had abnormal expert-ISTH-BAT scores, while 29% (n=18) females and 14% (n=6) males had abnormal self-ISTH-BAT (**Figure 1**). On average it took mean 9.7 minutes (range 3 – 25) to complete self-ISTH-BAT.

The most common symptom in expert-ISTH-BAT was menorrhagia (n=21) and GI-bleeding (n=21), where for self-ISTH-BAT it was other bleedings (n=32) and menorrhagia (n=18) (**Table 1**). We found that all organ systems had 90% or above exact score agreement between expert-ISTH-BAT and self-ISTH-BAT, except GI-bleeding (77%) and other bleedings (72%) (**Table 1**).

The expert-ISTH-BAT and self-ISTH-BAT correlated acceptably (r^2 = 0.80) (**Figure 2**). Ten (9%) individuals had normal expert-ISTH-BAT, but abnormal self-ISTH-BAT, while three (3%) individuals had abnormal expert-ISTH-BAT but normal self-ISTH-BAT.

From the 17 individuals with abnormal expert-ISTH-BAT and the 89 individuals with normal expert-ISTH-BAT, we found that self-ISTH-BAT had 82% sensitivity, 89% specificity, 96% NPV and 58% PPV (**Table 2**). Explorations of performance for other thresholds are provided in **Table 2**.

There was a 93% (n=99) and 92% (n=98) classification (normal / abnormal) agreement between the three medical doctors regarding self-ISTH-BAT and expert-ISTH-BAT. Interobserver agreement in self-ISTH-BAT was ≥0.74 (Cohen´s Kappa value) for all symptoms, except post-partum haemorrhage (0.54), hematuria (0.61) and GI-bleeding (0.48). For expert-ISTH-BAT Cohen´s Kappa values was ≥0.76 for all symptoms, except cutaneous bleeding (0.67), hematuria (0.44), GI-bleeding (0.44) and oral cavity bleeding (0.42).

DISCUSSION

The translation and validation process of the Danish self-ISTH-BAT followed international recognized guidelines and the original self-ISTH-BAT validation study (12, 16-18). From 106

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individuals, we found an acceptable correlation (r^2=0.8) between self-ISTH-BAT and expert-ISTH-BAT. To the best of our knowledge, this is the largest comparison study of self-ISTH-BAT and expert-ISTH-BAT on unselected individuals attending hospital.

Validation and performance

Exploration of other thresholds supported the commonly accepted cut-off for abnormal score, as sensitivity decreased markedly if the threshold was increased, while specificity decreased disproportionate with lower thresholds (**Table 2**). We found a high specificity and NPV indicating that self-ISTH-BAT is useful as a screening tool, because it will be equally safe to rule out bleeding disorder based on patient self-reporting compared to expert assessment. Disagreement in classification according to the accepted cut-off for abnormal bleeding scores was seen in 13 individuals (12%). Ten (9%) individuals had normal expert-ISTH-BAT, but abnormal self-ISTH-BAT. The consequence in clinical praxis would be that these patients would undergo thorough examination and we suggest that an interview with a health care practitioner would be first step. Three (3%) individuals had abnormal expert-ISTH-BAT score but normal self-ISTH-BAT score, and potential bleeding disorders could thus be missed in these individuals. Of the three, one reported extensive cutaneous bleeding in expert-ISTH-BAT (total score = 4), but no symptoms in the self-ISTH-BAT (total score=0). One reported ovulation bleeding leading to surgery (total expert-ISTH-BAT score = 6), which was not reported in the self-ISTH-BAT (total score = 3), since ovulation bleeding is not part of self-ISTH-BAT. The third individual, reported unexplained GI bleeding leading to medical attention and abnormal bleeding in 1 out 1 surgical intervention (total expert-ISTH-BAT score = 7), which was not reported in self-ISTH-BAT (total score = 3). We found no systematic cause of the three misclassifications, but it may be due to error in the reporting of either the patient or the observer. Another explanation could be that the tools are not identical and therefore differences in question and scoring can lead to discrepancies. Nevertheless, a 3% misclassification is comparable to previous findings (14) and we expect that the expert-ISTH-BAT can also be erroneous in few cases.

Between the three observers, the classification agreement was high for both questionnaires. The exact score agreement among observers for any bleeding symptom was high (all >80%). We render our findings is within the expected range of disagreement, but it indicates that a bleeding questionnaire cannot stand alone and should always be interpreted in relation to

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other findings. In clinical praxis, this indicates that self-ISTH-BAT can be used by general practitioners and therefore be used as a screening tool in the general population.

Comparison with other studies

The original self-ISTH-BAT study, found the range of both self-ISTH-BAT and expert-ISTH-BAT score to be 0-4 (mean 1.2 and 1.5) in 38 healthy adult control subjects (12). We found comparable median self-ISTH-BAT on 2 and expert-ISTH-BAT on 1, but significantly higher maximum (up to 22). We included patients attending an outpatient clinic that serves all clinical departments at the hospital, and was therefore not healthy, but representative for individuals who would undergo a self-ISTH-BAT test and in accordance high scores was found. Punt et al. investigated reliability and feasibility of self-ISTH-BAT in 156 patients referred for suspected CPD who had previously undergone expert-ISTH-BAT (14). Like Punt et al. (14), we also found an 88% correct normal/abnormal outcome classification between self-ISTH-BAT and expert-ISTH-BAT. Moreover, we found similar reliability, although lower sensitivity (82% versus 97%) and PPV (58% versus 90%), but counterbalanced by a higher specificity (89% versus 48%) and NPV (96% versus 77%) (14). Compared to Punt et al (14), we found a higher exact agreement and agreement ± 1 for all bleeding symptoms, except GI-bleeding (77% versus 88%) (**Table 1**). The lowest exact agreement was found in other bleedings (72%), probably due to the fact that self-ISTH-BAT includes questions regarding subconjunctival bleeding and bleeding after sexual intercourse, which expert-ISTH-BAT does not. We suggest that any future revision of the original expert-ISTH-BAT should seek to reduce the discrepancy regarding “Other bleedings” between expert-ISTH-BAT and self-ISTH-BAT, perhaps by including more examples of “other bleedings” in expert-ISTH-BAT. All in all, our study supports previous findings (12, 14), indicating that the correlation between self-ISTH-BAT and expert-ISTH-BAT is acceptable.

Self-ISTH-BAT

The self-ISTH-BAT has previously proven easy to use (14), and we found it on average took 9.7 minutes to perform. We used an electronic version of self-ISTH-BAT and included individuals representative for those who would undergo a self-ISTH-BAT test with none reporting problems with the electronic questionnaire. The self-ISTH-BAT can be filled out before attending the hospital, potentially improving patient safety as it will be feasible to systematically evaluate detailed bleeding history before procedures with bleeding risk and thus

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identifying patients with bleeding tendency. Further, we recommend using self-ISTH-BAT before referral for diagnostic work-up of bleeding disorder to spare patients without bleeding tendency. Also, it may reduce the time consumption for health care practitioners, as the expert-ISTH-BAT can be substituted with a focused interview based on positive symptoms in the self-ISTH-BAT.

Translation

The translation procedure followed international guidelines, and no major challenges were encountered in the translation process or for the users of the questionnaire. This study proves that self-ISTH-BAT can be translated to non-English languages, which widens the usability of self-ISTH-BAT markedly.

Limitations

Firstly, a limitation could be that the self-ISTH-BAT preceded the expert-ISTH-BAT. However, if limited by this, we would expect that the recollection of symptoms during the expert-ISTH-BAT would lead to more symptoms reported, causing higher scores in the expert-ISTH-BAT. In contrary, we found a higher median self-ISTH-BAT than expert-ISTH-BAT score, which also was found by Punt et al (14). The reason could be that self-ISTH-BAT is a more extensive questionnaire that includes questions which is not a part of the expert-ISTH-BAT, e.g. regarding abortions, subconjunctival bleeding and bleeding after sexual intercourse. In clinical praxis, it implies that self-ISTH-BAT is suitable as a screening tool to identify patients with suspected bleeding tendency that need further evaluation by experts.

Secondly, the self-ISTH-BAT score was not compared to laboratory values for bleeding disorder, and therefore not validated for any specific bleeding disorder.

Despite these limitations, we found that the Danish self-ISTH-BAT is a suitable supplement in the workup of potential bleeding disorder in Danish individuals and can replace the expert-ISTH-BAT as a screening tool. Abnormal self-ISTH-BAT should lead to diagnostic work-up for bleeding disorder including focused expert-ISTH-BAT and laboratory diagnostics. Moreover, further studies are needed to validate the Danish self-ISTH-BAT on individuals with verified bleeding disorder and classify the optimal cut-off for abnormal score in a Danish cohort.

TABLES

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Table 1. Number of individuals with clinical significant bleeding (score ≥1) according to expert and patient bleeding assessment tool (expert-ISTH-BAT and self-ISTH-BAT), along with percentage of agreement between the two questionnaires. For both expert-ISTH-BAT and self-ISTH-BAT, the median score was 0 for all individually symptoms. Agreement is classified as the exact same score in both questionnaires. Other bleedings were excessive umbilical stump bleeding (n=0), cephalhematoma (n=0), bleeding at circumcision (n=1), venipuncture bleeding (n=17), suction bleeding (n=1), subconjunctival bleeding (n=15) and bleeding after sexual intercourse or ovulation bleeding (n=23). Above reported other bleedings are for expert-ISTH-BAT and self-ISTH-BAT combined and 14 individuals reported more than one other bleeding symptom. GI = Gastrointestinal; CNS = central nervous system.

Bleeding symptoms (score ≥1)	**Expert-ISTH-BAT** (n)	**Self-ISTH-BAT** (n)	**P-value**	**Agreement** (%)	**Agreement ± 1** (%)
- Menorrhagia	21	18	0.70	93%	98%
- GI bleeding	21	15	0.36	77%	93%
- Cutaneous	15	11	0.53	92%	95%
- Epistaxis	14	17	0.70	92%	98%
- Other bleedings	12	32	<0.01	72%	94%
- Surgery	11	10	1.00	92%	93%
- Muscle hematomas	11	16	0.41	94%	99%
- Hematuria	10	10	1.00	96%	100%
- Tooth extraction	9	7	0.80	91%	94%
- Oral cavity	7	10	0.61	90%	91%
- Post-partum haemorrhage	7	6	1.00	90%	95%
- Minor wounds	5	14	0.05	91%	100%
- Hemarthrosis	2	3	1.00	99%	99%
- CNS bleeding	1	1	1.00	100%	100%

Table 2. Specificity and sensitivity presented for different patient self-reported bleeding assessment tool (self-ISTH-BAT) scores. Expert bleeding assessment tool (Expert-ISTH-BAT)

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is evaluated as golden standard, and the cohort is defined using the commonly accepted threshold for normal bleeding score (Female: <6 and Male: <4) (9).

Female	**≥1**	**≥2**	**≥3**	**≥4**	**≥5**	**≥6**	**≥7**	**≥8**
Sensitivity	100%	100%	100%	83%	83%	83%	75%	67%
Specificity	35%	45%	55%	69%	78%	84%	94%	98%
Male	**≥1**	**≥2**	**≥3**	**≥4**	**≥5**	**≥6**		
Sensitivity	80%	80%	80%	80%	60%	40%		
Specificity	50%	66%	84%	95%	95%	95%		
Both (F;M)	**≥4; ≥3**	**≥5; ≥3**	**≥5; ≥4**	**≥6; ≥4**	**≥6; ≥5**	**≥7; ≥5**		
Sensitivity	82%	82%	82%	82%	76%	71%		
Specificity	75%	81%	85%	89%	89%	94%		

FIGURES

Figure 1. Distribution of expert and patient bleeding assessment tool (expert-ISTH-BAT and self-ISTH-BAT) total scores from 106 individuals (63 females and 43 males).

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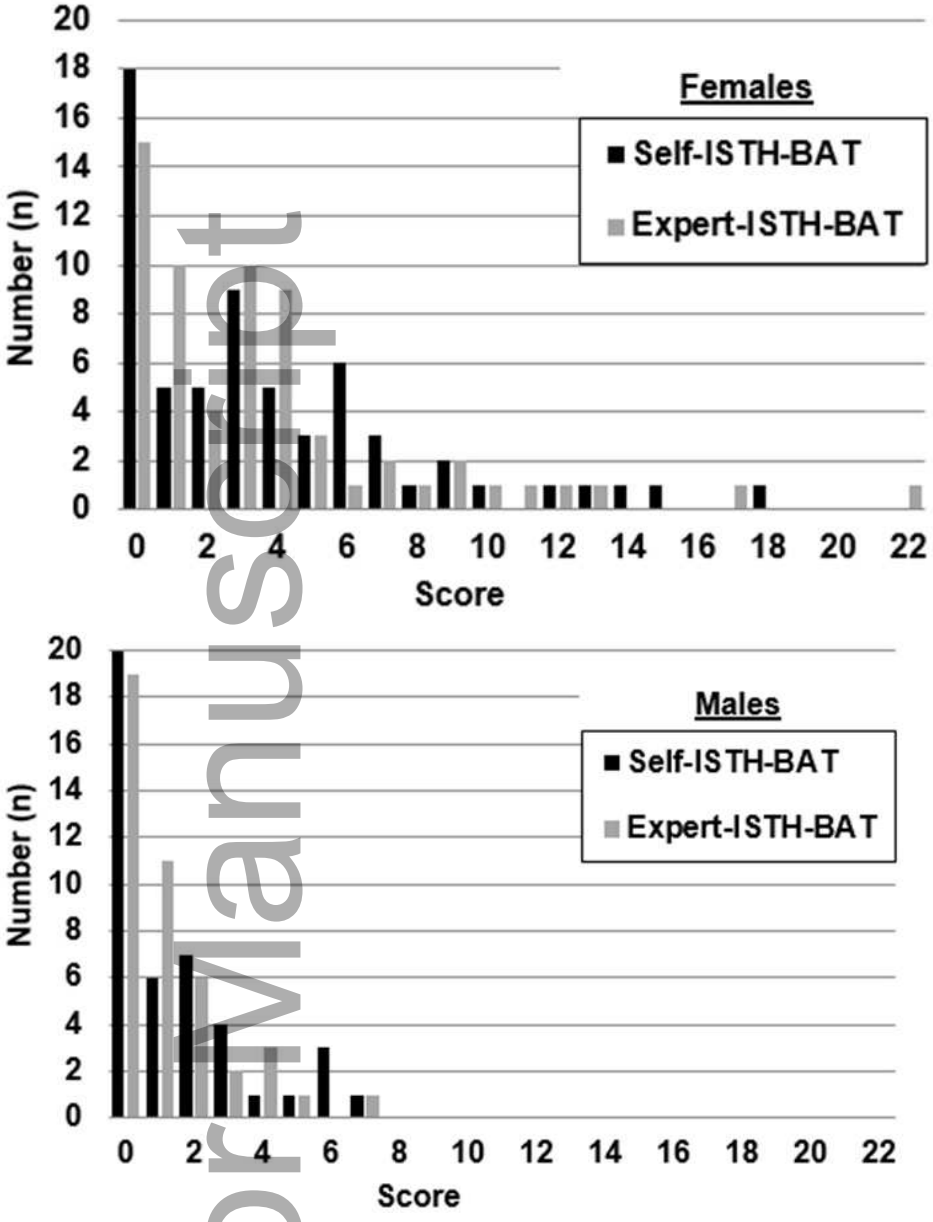

Figure 2. Correlation between expert and patient bleeding assessment tool (expert-ISTH-BAT and self-ISTH-BAT) for 106 individuals. Regression analysis found r^2=0.80 and expert-ISTH-BAT = 0.907 * self-ISTH-BAT + 0.025. The table presents the count of different score combinations. Score combinations with only one count (n=26) is not represented in the table.

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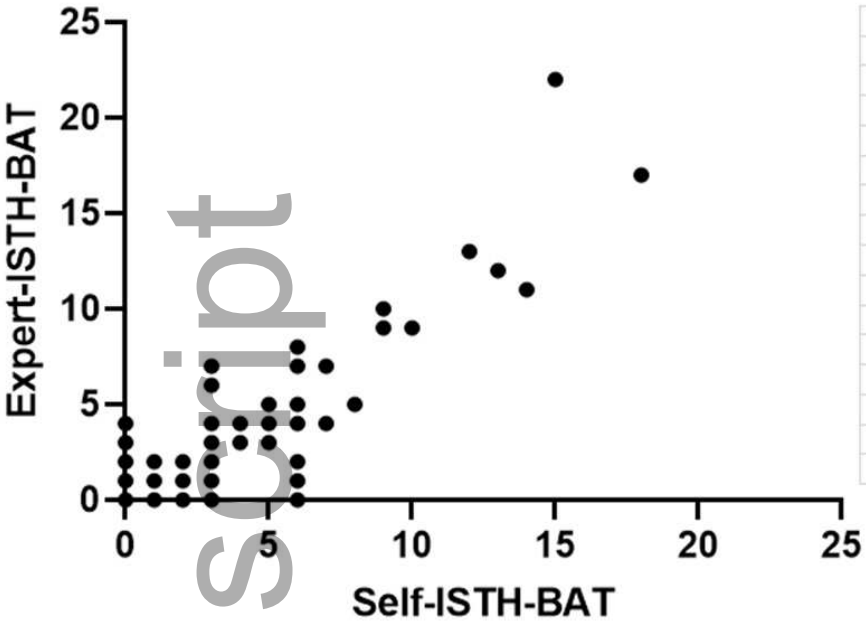

Self	Expert	Count
0	0	25
1	0	5
2	0	3
0	1	10
1	1	2
2	1	6
1	2	4
2	2	3
3	3	7
4	3	2
5	3	2
4	4	4
6	4	2
7	4	3
6	5	2

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SUPPLEMENTARY MATERIAL

Supplementary material 1: Danish version of the patient administrated International Society on Thrombosis and Haemostasis Bleeding Assessment Tool (Self-ISTH-BAT).

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Conflict of Interest

Dr. Hansen has nothing to disclose.
Dr. Carlsen has nothing to disclose.
Dr. Rasmussen has nothing to disclose.
Dr. Vinholt has nothing to disclose.

Data Availability Statement

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The data that support the findings of this study are available in anonymized form on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions

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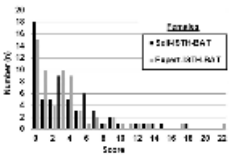

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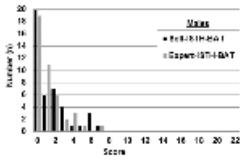

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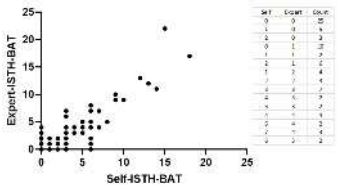

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