Clin. Lab. 2021;67:XXX-XXX

ORIGINAL ARTICLE

Medical Staff Training - Quality Initiative to Reduce Errors in the Pre-Preanalytical Phase

Carmen Delianu [1, 2], Loredana L. Hurjui [1, 2], Claudia C. Tărniceriu [1, 2], Mihaela Blaj [1, 2], Camelia Tamaș [1, 2], Vasilica Toma [1], Oana-Viola Bădulescu [1, 2], Liliana Foia [1, 2]

All authors contributed equally to this work
[1] *Grigore T. Popa University of Medicine and Pharmacy, Iasi, Romania*
[2] *Emergency County Hospital "Sf. Spiridon", Iași, Romania*

SUMMARY

Background: **Numerous studies indicate that most error sources in hemostasis laboratories occur during the pre pre-analytical phase through biological product sampling.**
Objectives: **The purpose of this study was documentation, monitoring, and reduction of preanalytical errors through operator training.**
Methods: **For a period of 4 months in the "St. Spiridon" Hospital from Iași, 978 specimens were identified with non-conformities, due to the following causes: insufficiently-collected, hemolyzed- and coagulated samples. Data collection was conducted in two stages: before and after training of medical staff in clinical departments, upon improving the coagulation specimen sampling practices.**
Results: **The study pointed out that subsequent to training, a reduction of the coagulated samples has been registered as follows: in medical departments from 33.33% to 16.78%, in surgery from 27.20% to 17.02%, ICU (intensive care units) from 10.63% to 8.74%, and slightly in EU (emergency) from 10.63% to 8.74%. Moreover, we noticed that the incidence of hemolyzed samples increased in clinical sections, as follows: EU from 4.50% to 14.89%, medical departments from 3.42% to 9.21%, surgery from 1.44% to 6.38%, and 4.50% to 14.89% for ICU. The insufficiently sampled volume persisted during the study in almost all sections: surgery from 1.80% to 4.96%, medical from 2.52% to 4.96%, EU from 1.80% to 3.78% with a slight decrease in ICU from 1.26% to 1.18%.**
Conclusions: **Nurses traditionally represent the core of quality medical services. Peer education is effective and implementation and compliance of sample collection procedure rules ultimately providing patient safety.**
(Clin. Lab. 2021;67:xx-xx. DOI: 10.7754/Clin.Lab.2020.200346)

Correspondence:
Loredana Liliana Hurjui, MD, PhD
Grigore T. Popa University of Medicine and Pharmacy
Morpho-Functional Science Department II
Universității str. 16
Iași
România
Email: loredana.hurjui@umfiasi.ro

Manuscript accepted May 25, 2020

KEY WORDS

training, insufficiently sampled, hemolyzed, coagulated

LIST OF ABBREVIATIONS

PT - prothrombin time
APTT - activated partial thromboplastin time
CBC - complete blood counting
ESR - erythrocyte sedimentation
EU - Emergency Unit
ICU - Intensive Care Unit
ADP - adenosine diphosphate
AT - anti-thrombin
TT - thrombin time

INR - international normalized ratio
OAMGMAMR - Order of General Medical Assistants, Midwives and Nurses in Romania

INTRODUCTION

An important role in modern medicine is played by the laboratory through the quality of the released results, which are essential for clinicians to establish or exclude a pathology, to obtain an integrated clinical picture of the patient, and, last but not least, to initiate an adequate treatment plan [1]. Concerning the hemostasis assays, the reduction of analytical errors is guaranteed through measures ensuring the quality as a result of the use of modern laboratory analyzers [2]. As in the sampling of the biological product, which is considered to be the most vulnerable to errors [3,4], there are also other factors in the pre-analytical phase that may impact laboratory determinations, starting with: medical staff training, assay requests, patient preparation, and transport conditions [3-6]. These pre-analytical actions are the basis for reporting inappropriate or incorrect results, although they are not under the control of laboratories, but with a potential critical consequence for the patients on one hand due to interference with the determinations, as well as for the health care system in general, on the other hand [2,7,8]. Pre-analytical and especially pre-pre-analytical nonconformities, which are considered major sources of error for the results of clotting tests, will not accurately reflect the clinical condition of the patient, but the correctness of the collected sample [9-11].

Taking into account the fact that specialized hemostasis tests are often considered "diagnostic" and laboratory tests generally account for 80% of the diagnosis procedures, the standardization of the biological product sampling strategy could have a direct influence on the quality of the results, hence reducing the secondary effects of the influencing factors [6,12,13]. Procedures like sampling, storage, and transport of biological products are managed in the pre-pre-analytical phase by the Clinical Laboratory; furthermore, centrifugation and preparation of samples to be inserted into automatic analyzers represent the “conventional” pre-analytical phase [13-16]. The analytical stage contains well-defined specifications and indicators for a large number of biological products, which are also accepted at the international level [16,17]. Due to the involvement of various professionals such as nurses, clinicians as well as specialists in laboratory medicine, the extra-analytical processes are the most difficult to manage, being considered the most critical operations [16,18-20].

One of the conditions which is necessary for the collected biological product to accurately reflect the real pathophysiology of the patients is to develop a broader training program for nurses in the clinical departments, as well as the full implementation of the global quality control standards to reduce errors in the laboratories [11,21]. Empowering medical staff is therefore an important step in providing medical services that have to meet requirements to offer confidence and to be effective, so that patient safety can be guaranteed. Through these skills, the laboratory provides rigorous tools to the clinicians in order to obtain a solid clinical picture of the patient and to subsequently settle on an optimal therapeutic plan. It is desirable for all medical staff to honestly realize what negative impact the inadequate results might have, before becoming fatal to the patient. The main purpose of our retrospective study is to evaluate the frequency of the pre-pre-analytical errors in order to quantify the post-analytical performance in the testing process, while relying ourselves on the information and training program for the medical nurses in our hospital clinical departments with the aim to reduce their incidence.

MATERIALS AND METHODS

Our observational study was carried out over a period of 4 months (June - September) in the Department of Hematology of the "St. Spiridon" Hospital of Iasi. Ethical approval was not necessary, as our research did not aim any interaction with the patient. The objective was to identify nonconforming samples and to create a laboratory policy in order to reduce the error sources in the pre-pre-analytical phase, which otherwise interferes with the detection of hemostasis tests, based on the clinical department’s medical staff training. Pre-pre-analytical variables that were recorded as reference data included criteria such as:

- insufficiently collected volume (less than 90% of the required volume)
- hemolyzed plasma
- pre-analytically identified coagulated samples and post-analytically identified specimens with clot in the sediment (Figure 1)

We payed particular attention to the identification of the clot in the collected samples for determining both, the CBC (complete blood counting), ESR (erythrocyte sedimentation rate), and the coagulation tests. Check-up of clot samples was performed both pre-analytically by inversion, and post-analytically by transvasation - a procedure implemented in our laboratory starting with September 2014. Transvasation is achieved through the passing of the blood from the primary sample suspected of having a clot in the sediment, in an anticoagulant-free test tube, called "control" test tube [22,23]. The operation is carried out gently, in both directions, so that the clot in the sample can be easily identified (Figure 2). In view of the training, nurses permanently employed in the clinical departments of our hospital were included in the program. The training program was conducted through an informative and documentary oral presentation followed by two months (June - July) of registration and centralization of nonconformities. It focused on the following topics:

- patient preparation
- time and place of placing the tourniquet before sampling
- recommendations for hemolysis avoidance
- sampling specimen (blood) and required amount
- type of anticoagulant and vacutainer recommended for coagulation determinations
- correct blood-anticoagulant homogenization operations after sampling
- coagulation tests assayed from plasma
- stability of the analysis
- causes of sample rejections
- correct positioning of samples after sampling
- optimal time and appropriate transport

Following the presentation, in order to verify the acquired knowledge, the nurses from clinical departments received a multiple-choice test that included questions related to:

- the negative effects of prolonged tourniquet stasis
- in appropriate manipulation and prevalent areas with negative interference in determinations which appeared during the sampling
- the type of vacutainer recommended for the determination of coagulation tests
- the needles recommended for sampling
- the way to avoid hemolysis and in vitroclot formation

In order to verify and certify the effectiveness of training and the correct adjustment of sampling procedures through this program, the recording and monitoring of nonconformities continued in the following two months (August and September), allowing us to assess whether the quality of the collected biologic product improved, or if more errors were recorded in the clinical laboratory testing.

Statistical Evaluation

The use of this quantitative, experimental pilot study which is applicable to data analysis, was considered the best suited program to provide clear information on the incidence of nonconformities in the clinical departments, with potential of their future reduction or elimination, based on the educational programs, thus paying special attention to the collected biological product. Taking into account the variability measure and the observation rate, as well as the sampling variants and their transformation into comparable sizes, we used Student's *t*-test and the Fischer-Snedec or F-distribution test for the data analysis. The frequency of nonconformities is presented by using tables and graphs.

RESULTS

During the four months of study, out of the total of 24,670 samples taken for carrying out coagulation determinations, 978 (3.96%) nonconforming samples as described (Figure 3) were introduced into the study, while respecting the criteria for inclusion in the batch. These nonconforming specimens presented either insufficiently sampled volume (10.63%), hemolyzed plasma (20.75%) identified post-centrifugation, totally coagulated or partially coagulated samples (clot evidence) (68.62%).

Of the total of 671 coagulated samples graphically represented in Figure 4, 490 were identified before centrifugation by inversion, and in 181 samples, the clot displayed in the sediment was post-analytically identified by transvasation (Figure 2), namely in the cases where results obtained revealed a possible hemorrhagic risk for the patient or could not be interpreted by the analyzer as they were situated outside the maximum reference range.

During the first two months, out of the total of 12,460 coagulation samples collected, the nonconformities (555 samples) were sorted and described by error sources (Table 1) and clinical sections (Table 2) to have an over view regarding their incidence depending on medical specialties: Emergency Unit (EU), Intensive Care Unit (ICU), surgical and medical departments.

Based on the results of assessing the nonconformities in the first two months of the study, establishing a training program for nurses represented a necessity as they are responsible for ensuring the quality of the collected biological product in the pre-pre-analytical phase of laboratory determinations recommended by the clinician. After the training, during the period August - September; out of the total of 12,210 collected samples, 423 nonconforming samples as described in (Table 3) were identified and grouped by source of error and incidence in clinical sections in (Table 4).

Subsequent to training, there was an increase in the incidence of samples with insufficient volume and hemolyzed plasma in clinical sections, as well as a decrease in the incidence of coagulated specimens, depicted in Table 5.

DISCUSSION

Although the global estimate of laboratory errors is modest, in the case of the hemostasis testing process, the error sources from the pre-analytical phase negatively affect the quality of laboratory results, providing important premises for erroneous diagnosis, equally leading to adverse clinical events that could translate into actual patient illness if not properly identified prior to the report of the results [2,24,25]. Medical errors appearing due to the sampling process of the biological product, when nurses are not familiar with the best laboratory practice, can generate critical negative outcomes for the patient [1,8,12,13,26]. The increased fluctuation rate of staff in the medical institutions, the lack of understanding of the best laboratory practice, and inadequate training are all causes of errors in the laboratory results, through inadequate collection of specimens for testing [27,28]. Since training materials and quality control procedures do not include information on possible

Table 1. Incidence of nonconforming coagulation specimens in June - July, prior to training.

Nonconforming	Insufficiently collected	Hemolyzed	Totally coagulated
555 (100%)	41 (7.38%)	60 (10.81%)	454 (81.80%)

Table 2. Incidence of nonconforming coagulation specimens in preclinical departments during June - July.

EU	ICU	Surgical Departments	Medical Departments
16.93%	13.33%	30.45%	39.27%

Table 3. Incidence of nonconforming coagulation specimens during August - September, after the training program.

Nonconforming	Insufficiently collected	Hemolyzed	Total no. coagulated
423 100%	63 14.90%	143 33.80%	217 51.30%

Table 4. Incidence of nonconforming coagulation specimens in clinical departments during August - September, following the training of nurses from clinical departments.

EU	ICU	Surgical Departments	Medical Departments
27.42%	13.23%	28.36%	30.96%

Table 5. Description of nonconformities by clinical sections, prior to and post-training.

Non-conforming	EU		ICU		Surgical Departments		Medical Departments	
Period	Jun - Jul	Aug - Sept	Jun - Jul	Aug - Sept	Jun - Jul	Aug - Sept	Jun - Jul	Aug - Sept
Insufficiently collected	1.80%	3.78%	1.26%	1.18%	1.80%	4.96%	2.52%	4.96%
Hemolyzed	4.50%	14.89%	1.44%	3.30%	1.44%	6.38%	3.42%	9.21%
Total no. coagulated	10.63%	8.74%	10.63%	8.74%	27.20%	17.02%	33.33%	16.78%

sources of error, it is desirable that the newly hired or non-experienced medical staff coming from different educational environments and with poor background benefit from continuous monitoring and training in order to reduce nonconformities, thus maintaining quality outcomes [25,29]. Considering Al-Ghaithi and co-workers' initiatives, our educational activities were introduced as part of the quality control plan, relying ourselves on high-quality operational procedures. We aimed therefore to resolve these nonconformities by strengthening the best practices in collecting and processing the samples, targeting patients' satisfaction, eliminating the

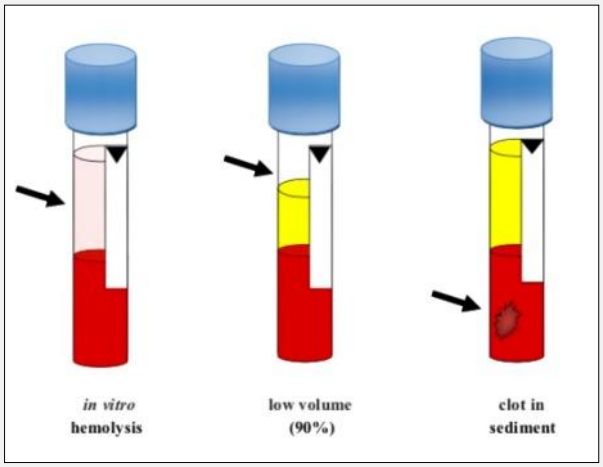

Figure 1. Description of possible sources of error that could interfere with the lab assays.

Figure 2. *In vitro* clot observed by transvasation (personal collection).

discomfort created by resampling [25]. In their study, Lima-Oliveira et al. reported that 80% of the total errors identified in the laboratory come out in the extra-analytical phase, the so-called "dark part of the moon" in laboratory medicine [20,30-32]. Referring to other studies, they stress that routine procedures for detecting errors also exist in this phase [29,33,34].

The analysis of our results during the 4 months of the study described in Figure 3 pointed toward a 3.96% frequency of error sources of the total of 24,670 clotting samples considered as non-conformities; furthermore, in all these cases we proceeded to a complementary statement associated with the results, this being consistent with the study performed by Marín et al. [16]. In order to draw attention to the possible interference with the determination of the coagulation tests, also mentioned in the international literature, we considered the following nonconformities: insufficiently collected volume

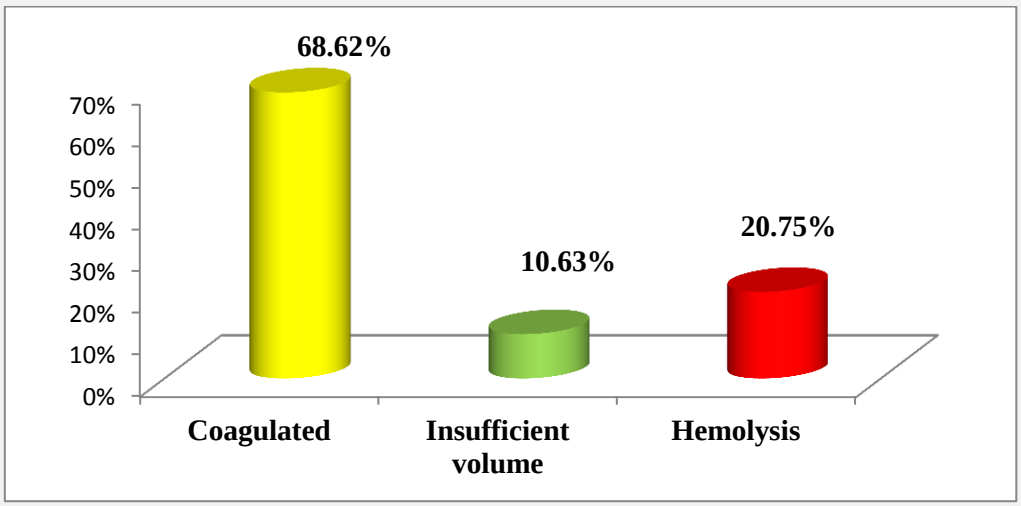

Figure 3. Incidence of nonconforming coagulation specimens.

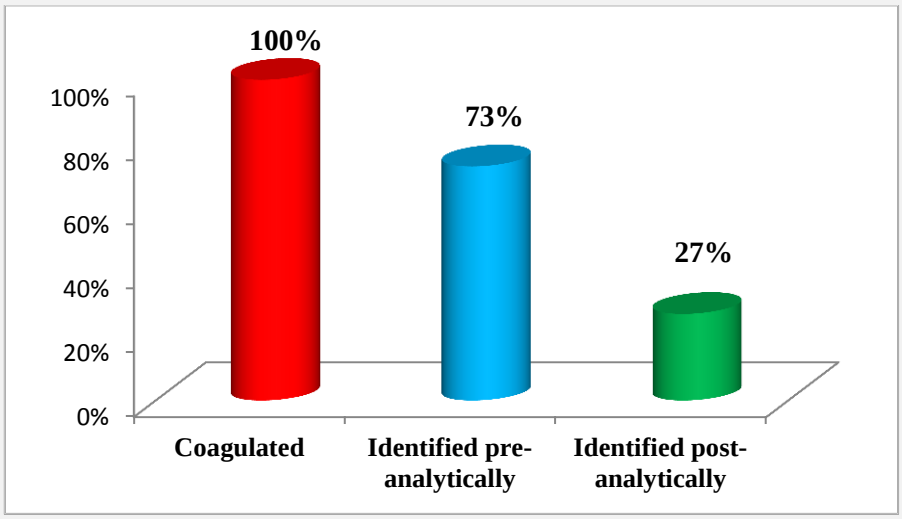

Figure 4. Frequency of coagulated samples identified before centrifugation and postanalytically.

identified in 10.63% of the samples, hemolyzed plasma highlighted post-centrifugation in 20.75% of samples, and 68.60% were coagulated, as described in Figure 3. Magnette and co-workers reported in their study that insufficiently collected blood volume, less than 80% of the recommended amount, interferes negatively with the coagulation assays: this is clinically very important for the APTT and fibrinogen assay, with a significance of 78% and of 67% for the anti-hemophilic factor A (FVIII), being in agreement with additional literature studies [35,36]. Also, the research conducted by Lippi et al. at the same time with the above-study revealed that determination of routine and specialized coagulation tests from samples containing less than 90% of the

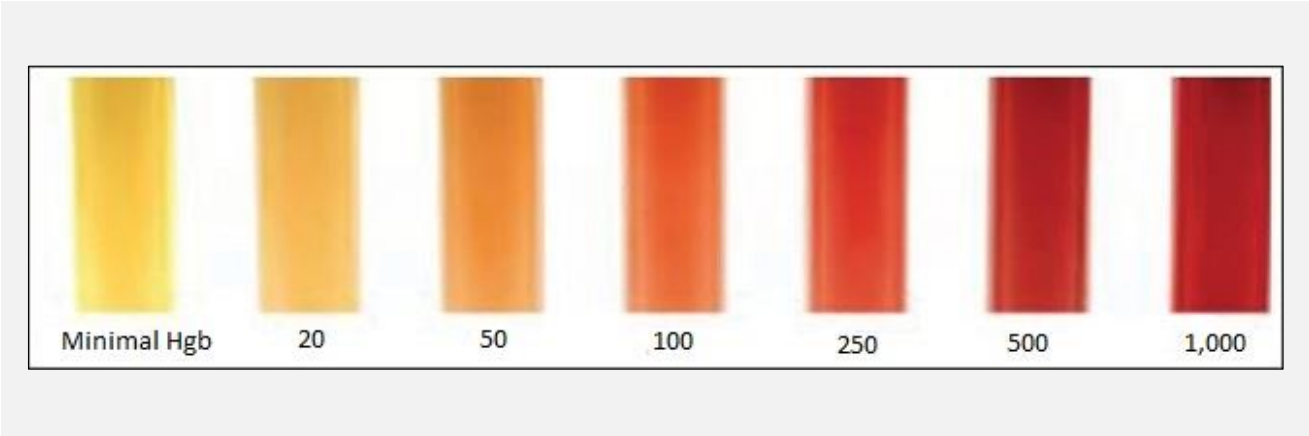

Figure 5. Color chart for the detection of *in vitro* hemolysis. The numbers indicate the degree of hemolysis expressed in (mg/dL) [41,49].

recommended volumes were seriously affected [36,37]. In our study, for the 10.63% of the samples with insufficiently collected volume as described in Figure 3, resampling was recommended while complementary explanatory text for the non-compliance have been issued as well. In situations when the sample volume was 90% of the recommended volume, we performed the clotting assessment and informed the clinician about the possible interference with the test determination, describing thus the nonconformity as follows: "Sample with insufficiently collected volume, missing 0.5 mL of blood, possible interference with the determination" [38]. Although the causes of *in vitro* hemolysis are well presented in the literature, this topic remains questionable as a result of the interference with the determinations of coagulation assays. In a paper on hemolyzed specimens, Carraro and colleagues addressed this issue starting from the recommendation to reject the sample [39]. Based on the obtained results, they have concluded that these samples are controversial and it is more appropriate to notify the clinician about the *in vitro* hemolysis, assisting thus in identification of otherwise unsuspected *in vivo* hemolysis situation, thereby improving the medical decisions [39]. Laga and colleagues mention in their article that the *in vitro* hemolysis can be evaluated with the naked eye [40], in agreement with studies performed by Carraro and Arora, and describes it as pink to red shade colored plasma identified post-centrifugation of the sample [39,41]. In this context, they advised at that time the revision of the rejection policy of such specimens. According to the obtained results, they concluded that there were no differences between the results of the PT and APTT assays determined from the samples with hemolyzed plasma compared to the non-hemolyzed samples [40]. Being in agreement with this author with regard to the definition and evaluation of hemolysis, as well as the lack of a noticeable difference between coagulation tests in hemolyzed and non-hemolyzed specimens, Arora and colleagues recommend to repeat the sampling and cautiously report the results obtained in the case of patients receiving anticoagulant therapy [41]. They also conclude that the tests' results for routine screening can be reported if they fall within the normal reference range [41]. Two years later, in their study, other researchers support the rejection of samples with hemolyzed plasma as a result of erroneous results from these specimens [42]. In 2017, Hernaningsih and Akualing returned to their study on the recommendation to review the policy to reject the specimens which present post-centrifuge hemolysis, agreeing with Laga et al. [40], but recommending further research on larger batches in order to be able to highlight the effect of hemolysis on PT and APTT tests [43]. With damage to the red blood cells, hemoglobin that interferes with the photonic systems is released *in vitro*, and thromboplastic compounds can affect the determination of coagulation tests. By releasing ADP and intracellular enzymes as a result of destruction of the red blood cells' membranes, plasma parameters of coagulation are activated, thus altering both platelet and leukocyte activity [6]. *In vitro* hemolysis causes the shortening of fibrinogen and AT (anti-thrombin), curtailed or prolonged APTT, as well as elevated D-dimers and prolonged PT [2,6,41,44,45]. Favaloro recommend the rejection of specimens with a high level of hemolysis and the use of electromechanical or mechanical methods in order to highlight the *in vitro* clotting in mildly hemolyzed specimens from which hemostasis determinations can be performed [2]. Furthermore, the same team of authors advises that depending on the extent of hemolysis, the fibrinogen may be flat, causing a decrease in PT, while by fibrinogen consumption the APTT value may either increase or decrease [2]. In the literature, it is mentioned that centrifugation of coagulation specimens can be one of the causes of *in vitro* hemolysis [2,6,45-48]. According to the color diagram (Figure 5) present-

ed by Arora and colleagues [41,49], we performed the determination of coagulation tests from the samples with slightly hemolyzed plasma which, according to the literature studies correspond to a concentration of as little as < 50 mg/dL of hemoglobin in the supernatant [39,40]. Referring to the color and concentration scale proposed by other authors, Woolley and colleagues consider the plasma as being slightly hemolyzed at a concentration of 0.3 - 1.0 g/L supernatant hemoglobin [42]. As for the samples with extensively hemolyzed plasma, we recommend resampling, by explaining to the clinician the nonconformity through a text: "Sample with intensively hemolyzed plasma, repeat sampling."In our study, 20.75% specimens with slightly hemolyzed plasma post-centrifugation have been identified (Figure 3), the results being therefore issued with the explanation of the interference: "Specimen with slightly hemolyzed plasma, possible interference with the determination." All specimens with hemolyzed plasma are also reverified post-analytically by the trans vasation procedure described in (Figure 2), to exclude the accidental presence of a clot in the sample's sediment, which, depending on the activation or consumption of some coagulation factors, could generate false results upon the level of fibrinogen, PT or APTT [2]. Prior to centrifugation, the coagulation samples are checked for coagulation, as this could be a reason for specimen rejection and is in agreement with Favaloro and colleagues [2]. The determination of coagulation tests is achieved from the plasma obtained by centrifugation, and by the accidental presence of the *in vitro* clot, among the coagulation factors the following being consumed: fibrinogen, prothrombin, proaccelerin, anti-hemophilic A factor, as well as high molecular weight von Willebrand factor, thus resulting in serum, which leads to falsely prolonged results or results that cannot be properly interpreted by means of PT, APTT and TT (thrombin time) tests [2,50,51]. Depending on the activation or consumption of fibrinogen, conditions rather often difficult to identify, performing coagulation assays from partially coagulated samples defined by the presence of the *in vitro* clot, generates falsely curtailed or prolonged results [2]. In their study, Magnete and colleagues recommend the homogenization of blood with anticoagulant by 3 - 6 complete inversions, an important procedure in preventing *in vitro* clot formation [6,44,52,53,54]. In our study, out of the total of 671 coagulated samples (Figure 4), 490 (73.02%) were identified before centrifugation by inversion, while post-analytically by the transvasation procedure described in Figure 2, the presence of *in vitro* clot was highlighted in 181 (26.97%) samples [22].The post-analytical recheck by transvasation (Figure 2) is used in all cases where the sample produce results which present a state of hypercoagulability with hemorrhagic risk for the patient (INR = 6) or undetectable results due to serum testing [2], a situation where the analyzer cannot measure the end point of the coagulation, and the signaling code is "failed".

Favaloro and colleagues have effectively described how these interferences can have particularly critical consequences for hemostasis screening tests, hence generating anxiety for the investigated patients due to the repeated samplings, and last but not least, the unnecessary delay of therapeutic procedures [2]. According to their evidence, a "specific diagnosis" could be erroneously set up based on falsely prolonged results, while up on a false positive result, the subject could be placed at an unwarranted hemorrhagic risk in the case of biopsies, dental extractions or surgical interventions, and last but not least, the inappropriate treatment of hemophilia [2]. In the case of anticoagulant dosing, the patient may be exposed to a hemorrhagic or thrombotic risk based on falsely increased or decreased results depending on the consumption or *in vitro* activation of some coagulation factors [2]. The non-conformities recorded in the first two months (Table 1 and Table 2) have been used as a reference point for introducing the educational activity into clinical departments in order to strengthen the best practices for the collection and processing of the biological product. After initiating corrective measures and verifying the acquired knowledge, an appreciable decrease in the incidence of coagulated samples from 81.80% to 51.30%, as described in Table 1 and Table 3, has been noticed.

Subsequent to medical staff training, however, there were areas of concern with regard to hemolyzed plasma samples, with an elevation of the incidence: from 10.81% prior to training (Table 1) to 33.80% after the training (Table 3), considering that this could be justified by the fact that the focus was on the homogenization between blood and post-sampling anticoagulant in order to avoid the *in vitro* clot formation [6], the procedure was likely carried out in an aggressive manner. As for the samples with insufficiently collected volume, their incidence increased from 7.38% to 14.89% (Table 1 and Table 3), considering that this could be associated with the recommendation to avoid a prolonged stasis, namely more than 60 seconds [5,29], a period during which no special attention was paid to the filling of the specimen according to the volume of blood engraved on the vacutainer. Although there was no absolute reduction in non-conforming samples at baseline, the main contribution of this study allowed us to test whether training of healthcare staff in the workplace had an effect on the best sampling practice, which is still an important step towards the general reduction of these types of errors in the clinical departments. It would be unrealistic to consider that we can totally reduce the incidence of non-compliant specimens. However, based on continuing education activities we could improve their gradually reduction. In our case, as described in Table 5, we were able to obtain an appreciable decline in the incidence of coagulated specimens within the medical departments from 33.33% to 16.78%, as well on surgery from 27.20% to 17.02%. Unfortunately, the incidence of hemolysis plasma samples increased considerably in the medical departments from 3.42% to 9.21%, and

from 1.44% to 6.38% in the surgical sections (Table 5), very likely directly related to a more aggressive post-sampling blood homogenization of the anticoagulant, in an attempt to avoid sample coagulation.

Based on the results of this study, certified courses for general and laboratory nurses were organized in collaboration with the professional nurses' organization OAMGMAMR (Order of General Medical Assistants, Midwives and Nurses in Romania) in 2016, 2017, and 2018. Moreover, starting from 2015 and continuing in 2017 and 2019, informative articles in the organization's journal publication have been issued, so that the medical staff can actively and continuously learn about the error sources from the pre-pre-analytical phase and their negative implications within hemostasis test outcomes, for controlling the monitoring of anti-coagulant therapy, and last but not least for patients' health, thus enabling continuous improvement of medical practices, in agreement with other researchers in the field [16]. This pilot study was the basis for widening the information activities upon the negative effects of the errors in the pre-pre-analytical phase among clinicians and clinical laboratory specialists, by organizing postgraduate courses which were also offered through the continuous medical education system rolled out at the University of Medicine and Pharmacy of Iasi, starting in 2018 and continuing in 2019 and further. In agreement with Dennis J. Ernst of the Carydon Phlebotomy Training Centre in Indiana, informing clinicians about all advances in diagnostic technology helps reduce the risk of preanalytical errors prior to conducting coagulation tests, therefore enabling proper medical care. Since 1998, Ernst has emphasized the importance and necessity of training and assessing the healthcare staff at regular intervals as being essential in preventing errors, thus completing the well-designed and implemented training programs that positively influence the performance of nurses [1,55]. Although it is unrealistic to consider that all critical errors are recorded, learning from mistakes based on reports of nonconformities is also essential [16]. Despite the fact that all studies that analyze pre-pre-analytical aspects are methodologically different, managing and measuring non-conformities remains a major challenge for clinical laboratories [16,56-58], requiring preventive and corrective measures based on the analysis of the cause or the potential of harm for the patient, and result in a systematic and efficient design, as well [16].

CONCLUSION

The hemostasis tests in the hematology laboratory constitute an integral part of the decision-making process, and the false results of laboratory analyses often affect the diagnostic and medical or surgical therapy. The pre-pre-analytical monitoring difficulties beyond the control or direct supervision of laboratory staff thus require effective educational and preventive policies, directed primarily at the medical staff in clinical departments. These findings highlight the need to improve the standardization of sampling techniques, along with the dissemination of operational guides, continuous education, and certification and training of health professionals with responsibilities in the collection and management of biological fluids. This would allow an increase in the chance of obtaining high quality accurate specimens and consistent financial savings for the budget of hospitals, the health system and, last but not least, the patient's safety.

Acknowledgment:
We thank the nurses from the clinical sections of the "St. Spiridon" Hospital, Iași, România, for collaboration and assistance in carrying out the training activities during the study.

Source of Funding:
No funding was received for this study.

Declaration of Interest:
There are no potential conflicts of interest for each named author relevant to the contents of the article.

References:

1. Crous L, Armstrong SJ. The bloody truth: Investigating nurse phlebotomy competencies at a private laboratory in Johannesburg, South Africa. Health SA Gesondheid 21 2016;339-347. https://doi.org/10.1016/j.hsag.2016.06.002

2. Favaloro EJ, Funk DM, Lippi G. Pre-analytical Variables in Coagulation Testing Associated with Diagnostic Errors in Hemostasis. Laboratory Medicine 2012;43:1-10. https://doi.org/10.1309/LM749BQETKYPYPVM

3. Lippi G, Salvagno GL, Montagnana M, Franchini M, Guidi GC. Phlebotomy issues and quality improvement in results of laboratory testing. Clin Lab 2006;52:217-30 (PMID: 16812947).

4. ISO/WD TS 22367:2008. Medical laboratories-Reduction of error through risk management and continual improvement. https://www.iso.org/standard/40918.html

5. Ellouze R, Guermazi S. [Importance of preanalytical step in hemostasis]. Ann Biol Clin (Paris) 2013;71(4):401-7 (PMID: 23906 567).

6. Magnette A, Chatelain M, Chatelain B, Ten Cate T, Mullier F. Pre-analytical issues in the haemostasis laboratory: guidance for the clinical laboratories. Thromb J 2016;14:49 (PMID: 279994 75).

7. Plebani M. Errors in clinical laboratories or errors in laboratory medicine? Clin Chem Lab Med 2006;44:750-9 (PMID: 167298 64).

8. Green SF. The cost of poor blood specimen quality and errors in preanalytical processes. Clin Biochem 2013 Sep;46(13-14):1175-9 (PMID: 23769816).

9. Simundic AM, Nikolac N, Vukasovic I, Vrkic N. The prevalence of preanalytical errors in Croatian ISO 15,189 accredited laboratory. Clin Chem Lab Med. 2010;48:1009-14 (PMID: 20441481).

10. Lippi G, Becan-McBride K, Behúlová D et al. Preanalytical quality improvement: in quality we trust. Clin Chem Lab Med 2013;51:229-41 (PMID: 23072858).

11. Nikolac N, Supak-Smolcic V, Simundic AM, Celap I, Croatian Society of Medical Biochemistry and Laboratory Medicine. Croatian Society of Medical Biochemistry and Laboratory Medicine: national recommendations for venous blood sampling. Biochem Med (Zagreb) 2013 Oct; 23(3):242-54 (PMID: 24266294).

12. Agarwal R, Chaturvedi S, Chhillar N, Goyal R, Pant I, Tripathi CB. Role of Intervention on Laboratory Performance: Evaluation of Quality Indicators in a Tertiary Care Hospital. Indian J Clin Biochem 2012;27:61-8 (PMID: 23277714).

13. Englezopoulou A, Kechagia M, Chatzikiriakou R, Kanellopoulou M, Valenti M, Masedu F. Pre Analytical Errors as Quality Indicators in Clinical Laboratory. Austin J Public Health Epidemiol. 2016;3(5):1048. https://austinpublishinggroup.com/public-health-epidemiology/fulltext/ajphe-v3-id1048.php

14. Saurav P, Brijesh M, Ashok KD. Pre Analytical Errors in the Clinical Laboratory and how to minimize them. International Journal of Bioassays 2013;2:551-3. DOI:10.21746/ijbio.2013.03.0017

15. Ambruster DA, Overcash DR, Reyes J. Clinical Chemistry Laboratory Automation in the 21st Century - Amat Victoria curam (Victory loves careful preparation). Clin Biochem Rev 2014;35: 143-53 (PMID: 25336760).

16. Giménez-Marín A, Rivas-Ruiz F, Pérez-Hidalgo Mdel M, Molina-Mendoza P. Pre-analytical errors management in the clinical laboratory: a five-year study. Biochem Med (Zagreb) 2014 Jun; 24(2):248-57 (PMID: 24969918).

17. Kenny D, Fraser CG, Petersen PH, Kallner A. Consensus agreement. Scand J Clin Lab Invest 1999;59:585. https://doi.org/10.1080/00365519950185409

18. Plebani M, Carraro P. Mistakes in a stat laboratory: types and frequency. Clin Chem 1997;43:1348-51 (PMID: 9267312).

19. Wiwanitkit V. Types and frequency of preanalytical mistakes in the first Thai ISO 9002:1994 certified clinical laboratory, a 6-month monitoring. BMC Clin Pathol. 2001;1:5 (PMID: 11696253).

20. Carraro P, Plebani M. Errors in a Stat Laboratory: Types and Frequencies 10 Years Later. Clin Chem 2007;53:1338-42 (PMID: 17525103).

21. Clinical Laboratory Standards Institute. Procedures for the Collection of Diagnostic Blood Specimens by. Venipuncture; Approved Standard-Sixth Edition. CLSI document H3 - A6. Clinical Laboratory Standards Institute, Wayne, Pennsylvania, USA, 2007. https://clsi.org/media/1371/gp42a6_sample.pdf

22. Delianu C, Tuchilus C, Filip F, Foia L. Post-analytic clot detection *in vitro* by transvazation. Rev Rom Med Lab 2018:S92. http://www.rrml.ro/articole/2018/2018_2_supliment.pdf

23. Delianu C, Foia L, Hurjui LL et al. Blood Clot Identification Procedures in Clinical Laboratory Sampling. Clin Lab 2019 Nov 1;65(11). https://www.researchgate.net/publication/337235460_Blood_Clot_Identification_Procedures_in_Clinical_Laboratory_Sampling

24. Plebani M, Lippi G. To err is human. To mis diagnose might be deadly. Clin Biochem 2010;43:1-3 (PMID: 19607820).

25. Al-Ghaithi H, Pathare A, Al-Mamari S, Villacrucis R, Fawaz N, Alkindi S. Impact of Educational Activities in Reducing Pre-Analytical Laboratory Errors. A quality initiative. Sultan Qaboos Univ Med J 2017 Aug;17(3): e309-e313 (PMID: 29062553).

26. Brennan TA, Gawande A, Thomas E, Studdert D. Accidental deaths, saved lives and improved quality. N Engl J Med 2005; 353:1405-9 (PMID: 16192489).

27. Lee EJ, Kim M, Kim HS, Park MJ, Lee YK, Kang HJ. Development of a novel quality improvement indicator based on the hemolysis index. Ann Lab Med 2016;36(6):599-602 (PMID: 27578515).

28. Shaikh MS, Moiz B. Analytical performance evaluation of a high-volume hematology laboratory utilizing sigma metrics as standard of excellence. Int J Lab Hematol 2016;38(2):193-7 (PMID: 26847366).

29. Lima-Oliveira G, Guidi GC, Salvagno GL et al. Is Phlebotomy Part of the Dark Side in the Clinical Laboratory Struggle for Quality? Laboratory Medicine 2012;43:172-6. https://doi.org/10.1309/LMZ7YARD6ZSDIID

30. Lippi G, Guidi GC, Mattiuzzi C, Plebani M. Preanalytical variability: The dark side of the moon in laboratory testing. Clin Chem Lab Med 2006;44(4):358-65 (PMID: 16599826).

31. Lippi G. Governance of preanalytical variability: Travelling the right path to the bright side of the moon? Clin Chim Acta 2009; 404:32-6 (PMID: 19302993).

32. Wallin O, Söderberg J, Van Guelpen B, Stenlund H, Grankvist K, Brulin C. Preanalytical venous blood sampling practices demand improvement-A survey of test-request management, test-tube labelling and information search procedures. Clin Chim Acta 2008 May;391(1-2):91-7 (PMID: 18342012).

33. Lippi G, Guidi GC. Risk management in the preanalytical phase of laboratory testing. Clin Chem Lab Med 2007;45:720-7 (PMID: 17579523).

34. Lippi G, Fostini R, Guidi GC. Quality improvement in laboratory medicine: Extra-analytical issues. Clin Lab Med 2008;28:285-94 (PMID: 18436071).

35. Adcock DM, Kressin DC, Marlar RA. Minimum specimen volume requirements for routine coagulation testing: dependence on citrate concentration. Am J Clin Pathol 1998;109:595-9 (PMID: 9576579).

36. Lippi G, Salvagno GL, Montagnana M, Lima-Oliveira G, Guidi GC, Favaloro EJ. Quality standards for sample collection in coagulation testing. Semin Thromb Hemost. 2012;38:565-75 (PMID: 22669757).

37. Lippi G, Simundic AM, Rodriguez-Manas L, Bossuyt P, Banfi G. Standardizing *in vitro* diagnostics tasks in clinical trials: a call for action. Ann Transl Med 2016 May; 4(9):181 (PMID: 27275494).

38. Delianu C, Tuchilus C, Filip F, Foia L. *In vitro* false hypercoagulability-possible source of error from the pre-analytical phase. Rev Rom Med Lab 2018:S91. http://www.rrml.ro/articole/2018/2018_2_supliment.pdf

39. Carraro P, Servidio G, Plebani M. Hemolyzed specimens: a reason for rejection or a clinical challenge? Clin Chem 2000 Feb; 46(2):306-7 (PMID:10657399).

40. Laga AC, Cheves TA, Sweeney JD. The effect of specimen hemolysis on coagulation test results. Am J Clin Pathol 2006 Nov; 126(5):748-55 (PMID: 17050072).

41. Arora S, Kolte S, Dhupia J. Hemolyzed samples should be processed for coagulation studies: the study of hemolysis effects on coagulation parameters. Ann Med Health Sci Res 2014;4:233-7 (PMID: 24761244).

42. Woolley A, Golmard JL, Kitchen S. Effects of haemolysis, icterus and lipaemia on coagulation tests as performed on Stago STA-Compact-Max analyser. Int J Lab Hematol 2016 Aug;38(4):375-88 (PMID: 27306848).

43. Hernaningsih Y, Akualing JS. The effects of hemolysis on plasma prothrombin time and activated partial thromboplastin time tests using photo-optical method. Medicine (Baltimore) 2017 Sep; 96(38):e7976 (PMID: 28930835).

44. Mackie I, Cooper P, Lawrie A, Kitchen S, Gray E, Laffan M, British Committee for Standards in Haematology. Guidelines on the laboratory aspects of assays used in haemostasis and thrombosis. Int J Lab Hematol 2013;35:1-13 (PMID: 22978493).

45. Kitchen S, Olson JD, Preston FE. Quality in Laboratory Hemostasis and Thrombosis. Bognor Regis: Wiley-Blackwell, 2nd Edition 2013;22-44.
https://www.wiley.com/en-us/Quality+in+Laboratory+Hemostasis+and+Thrombosis%2C+2nd+Edition-p-9780470671191

46. Ricos C, Garcia-Victoria M, de la Fuente B. Quality indicators and specifications for the extra analytical phases in clinical laboratory management. Clin Chem Lab Med 2004;42:578-82 (PMID: 15259371).

47. Chawla R, Goswami B, Singh B, Chawla A, Gupta VK, Mallika V. Evaluating laboratory performance with quality indicators. Lab Med 2010;41:297-300.
https://doi.org/10.1309/LMS2CBXBA6Y0OWMG

48. Guder WG, Narayanan S. Pre-Examination Procedures in Laboratory Diagnostics: Preanalytical. Aspects and Their Impact on the Quality of Medical Laboratory Results. De Gruyter 2015.
https://doi.org/10.1515/9783110334043

49. Plumhoff EA, Masoner D, Dale JD. Preanalytic laboratory errors: Identification and prevention. Mayo Medical Laboratories 2008; 33(12):4.
http://preq.in/images/Mayo.pdf

50. Favaloro EJ, Bonar R, Duncan E et al. Identification of factor inhibitors by diagnostic haemostasis laboratories: A large multicentre evaluation. Thromb Haemost 2006;96:73-8 (PMID: 16807 654).

51. Favaloro EJ, Bonar R, Duncan E et al. Mis-identification of factor inhibitors by diagnostic haemostasis laboratories: Recognition of pitfalls and elucidation of strategies. A follow up to a large multicentre evaluation. Pathology 2007 Oct;39(5):504-11 (PMID: 178 86101).

52. CLSI GP41-A6 (replaces H03-A6). Procedures for the Collection of Diagnostic Blood Specimens by Venipuncture; Approved Standard-Sixth Edition. Vol. 27 No. 26.
https://clsi.org/media/1372/gp41ed7_sample.pdf

53. CLSI H21-A5: Collection, Transport, and Processing of Blood Specimens for Testing Plasma-Based Coagulation Assays and Molecular Hemostasis Assays; Approved Guideline-Fifth Edition. Vol. 28 No. 5.
https://clsi.org/media/1399/h21a5_sample.pdf

54. Harrison P, Mackie I, Mumford A, et al. British committee for standards in Haematology. Guidelines for the laboratory investigation of heritable disorders of platelet function. Br J Haematol 2011;155:30-44 (PMID: 21790527).

55. Ernst DJ. Four indefensible phlebotomy errors and how to prevent them. J Healthc Risk Manag 1998;18(2):41-6 (PMID: 10185 077).

56. Plebani M, Ceriotti F, Messeri G, Ottomano C, Pansini N, Bonini P. Laboratory network of excellence: Enhancing patient safety and service effectiveness. Clin Chem LabMed 2006;44:150-60 (PMID: 16475899).

57. Boone DJ. How can we make laboratory testing safer? Clin Chem Lab Med 2007;45:708-11 (PMID: 17579521).

58. Nichols JH. Laboratory quality control based on risk management. Ann Saudi Med 2011;31:223-8 (PMID: 21623049).