Opinion Paper

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Blood sample quality

Abstract: Several lines of evidence now confirm that the vast majority of errors in laboratory medicine occur in the extra-analytical phases of the total testing processing, especially in the preanalytical phase. Most importantly, the collection of unsuitable specimens for testing (either due to inappropriate volume or quality) is by far the most frequent source of all laboratory errors, thus calling for urgent strategies for improving blood sample quality and managing data potentially generated measuring unsuitable specimens. A comprehensive overview of scientific literature leads us to conclude that hemolyzed samples are the most frequent cause of specimen nonconformity in clinical laboratories (40–70%), followed by insufficient or inappropriate sample volume (10–20%), biological samples collected in the wrong container (5–15%) and undue clotting (5–10%). Less frequent causes of impaired sample quality include contamination by infusion fluids (i.e. most often saline or glucose solutions), cross-contamination of blood tubes additives, inappropriate sample storage conditions or repeated freezing-thawing cycles. Therefore, this article is aimed to summarize the current evidence about the most frequent types of unsuitable blood samples, along with tentative recommendations on how to prevent or manage these preanalytical non-conformities.

Keywords: blood samples; errors; hemolysis; laboratory medicine; quality.

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Introduction

The total testing process is conventionally defined as a complex and multifaceted enterprise aimed at generating results of in vitro diagnostic testing and hence encompassing a vast array of activities comprises between ordering diagnostic tests and reporting data generated from analytical measurements [1]. In a broader perspective, the total testing process can thus be seen as a "loop", beginning from the physician's brain with the test prescription best fitting the patients symptoms, patient preparation for testing, collection, handling, transportation, storage and preparation of biological samples (i.e. the so-called preanalytical phase), sample analysis (i.e. the so-called analytical phase), followed by test validation, interpretation and reporting, as well as by the clinical decisions driven by test results (i.e. the so-called postanalytical phase) [1].

As with many other human activities, the total testing process is also vulnerable to errors [2]. Reliable scientific evidence, garnered throughout the past decades, attests that the overall frequency of errors in laboratory medicine is approximately 0.3%, thus much lower than that of other medical diagnostic disciplines such as echography (i.e. ~0.8%), radiology (i.e. ~4.0%) and pathology (i.e. ~5.0%) [3]. Albeit these figures would lead us to conclude that laboratory medicine is much safer than other diagnostic disciplines, continuous improvement will be needed to make it an even safer enterprise [4].
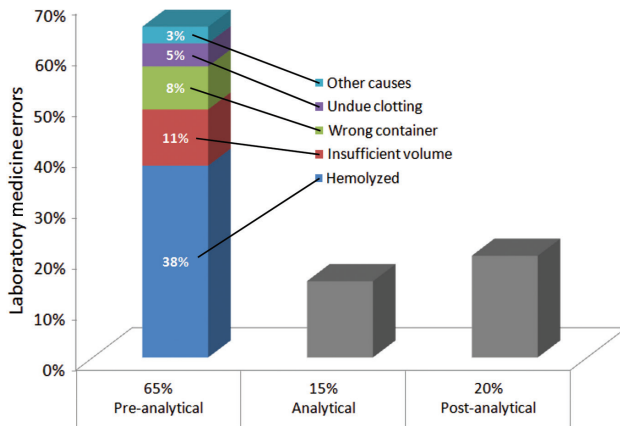
Reliable statistics unquestionably attests that the vast majority of errors in laboratory medicine occur in the extra-analytical phases of the total testing processing, especially in the preanalytical phase [5]. Overall, the frequency of preanalytical errors comprises between 60 and 70% of all laboratory errors, thus approximately four-fold and three-fold higher than errors occurring in the analytical (i.e. ~15% of all errors) and post-analytical phases (i.e. ~20% of all errors), respectively (Figure 1) [6, 7]. As was defined earlier, the pre-analytical phase encompasses a series of still manually-intensive activities which are performed mostly outside of the laboratory environment. Albeit this evidence would lead us to conclude that preanalytical errors are out of responsibility and control of laboratory professionals, the clinical laboratory plays a major role in lessening the vulnerability of the preanalytical phase, by

Figure 1: Types and frequency of laboratory errors.

systematic monitoring of errors, developing preanalytical phase quality indicators and by educating the healthcare staff to the best practice(s) in the preanalytical phase [8].

Blood sample quality

Reliable evidence suggests that the vast majority of preanalytical errors is attributable to inappropriate procedures used for the collection and management of biological samples. Overall, the collection of unsuitable specimens for testing (either due to inappropriate sample volume or quality) is by far the most frequent source (i.e. approximately 80–90%) of all laboratory errors [9–11]. More specifically, a comprehensive overview of the scientific literature concluded that hemolyzed samples are the most frequent cause of specimen non-conformity in clinical laboratories (40–70%), followed by insufficient or inappropriate sample volume (10–20%), biological samples collected in the wrong container (5–15%) and undue clotting (5–10%) (Figure 1) [9]. Less frequent causes of impaired sample quality (i.e. approximately 3% overall) include contamination by infusion fluids (i.e. most often saline or glucose solutions) [12], cross-contamination of blood tubes additives [13], inappropriate sample storage conditions or repeated freezing-thawing cycles [14].

Therefore, the following sections of this article will be focused on summarizing the current evidence about the different types of unsuitable blood samples, along with tentative recommendations (when available) on how to prevent or manage the most frequent preanalytical non-conformities. Although additional interfering substances, especially high concentrations of bilirubin and lipids, are known to potentially impair sample quality, the presence of these compounds is frequently attributable to biological causes (i.e. icterus, dyslipidemia) rather than to preanalytical errors

(except for high serum or plasma turbidity due to noncompliance with minimum requirements for fasting status) [15], so that their discussion is beyond the scope of this article.
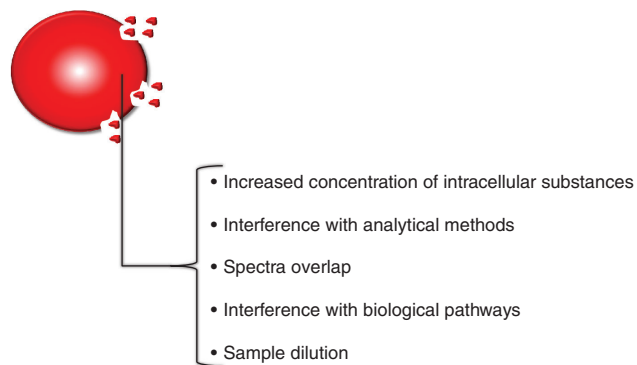
Sample hemolysis

Hemolysis is conventionally defined as a generalized process of injury to blood cells, which is usually reflected by the presence of increased concentrations of cell-free hemoglobin in serum or plasma [16]. Hemolysis can be attributable to either biological conditions leading to red blood cells (RBCs) breakdown in vitro (i.e. intravascular hemolysis) [17], or to non-biological causes occurring during sample collection and handling (i.e. spurious hemolysis), the most frequent of which include traumatic venipunctures, sample collection with inappropriate devices (i.e. indwelling catheters or very small needles), inappropriate sample management (i.e. vigorous mixing or shaking of blood samples after collection), inadequate storage conditions (sample freezing, long distance transportation under inappropriate conditions), sample re-spun after centrifugation, etc. [16].

Beside the fact that spurious hemolysis alone represents ~40% of all potential problems encountered throughout the total testing process (Figure 1), the presence of increased concentrations of cell-free hemoglobin in serum or plasma causes a number of biological or analytical issues, which would make diagnostic testing potentially unreliable. Briefly, the "normal" concentration of cell-free hemoglobin is usually comprised between 0.22 and 0.25 g/L in serum and between 0.10 and 0.13 g/L in plasma, respectively [18]. Although cell-free hemoglobin values >0.3 g/L will henceforth reflect a minor extent of intravascular or spurious hemolysis, the threshold of clinically or analytical significant hemolysis for most assays has usually been set (by consensus) at 0.5 g/L [19]. When this value is exceeded in diagnostic samples, a number of biological or analytical issues may then jeopardize diagnostic testing. The most frequent sources of interference encompass (i) release of cell components into the sample, which may then lead to a spurious increase of some analytes less abundant in blood than within the cells (e.g. potassium, lactate dehydrogenase), (ii) chemical interference by release of intracellular compounds which interfere with some analytical techniques (e.g. adenylate cyclase with creatine kinase assessment), (iii) spectrophotometric interference, especially at 415, 540 and 570 nm wavelengths; (iv) biologically active substances which may then activate or inhibit biological pathways (e.g. phospholipids and

other prothrombotic compounds which interfere with primary and secondary hemostasis), (v) dilution of some analytes, which are more abundant in blood than into the cells (Figure 2) [16, 20, 21].

These many and multifaceted mechanisms of interference urgently call for reliable strategies for the prevention and management of hemolyzed samples. Recently, the Working Group on the Preanalytical Phase (WG-PRE) of the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) released practical consensus recommendations for managing test results generated in hemolyzed samples. These recommendations basically entail the use of a standardized approach for identifying hemolyzed samples and rating the hemolysis degree by means of the so-called hemolysis index (H-index), along with a practical strategy for dealing with test results, which hence encompasses the release of test results with an accompanying comment when the bias is lower than the reference change value (RCV) or suppression of all data generated on hemolyzed specimens when the predictable bias will exceed the RCV [19]. Finally, the use of formulas aimed to adjust test results of hemolysis-sensitive tests is not currently recommended, as these equations are basically inaccurate and highly instrument- and method-dependent [22].

As discussed earlier, the use of the H-index is a mainstay for the appropriate management of hemolyzed samples. This measure, despite being still poorly standardized [23], is based on a rapid, virtually inexpensive and reliable photometric assessment of serum or plasma at specific wavelengths, aimed to estimate (by means of specific equations) the potential concentration of cell-free hemoglobin [24, 25]. The widespread use of the H-index, along with the adoption of standardized strategies for managing test results, would henceforth enable achieving a higher degree of quality, safety and reproducibility throughout the total testing process.

- Increased concentration of intracellular substances
- Interference with analytical methods
- Spectra overlap
- Interference with biological pathways
- Sample dilution

Figure 2: Hemolysis interference in laboratory testing.

Insufficient or inappropriate sample volume

Albeit that blood loss due to laboratory testing (i.e. iatrogenic blood loss) is unlikely to be a serious threat to a patient's health [26], blood volume conservation in subjects undergoing frequent blood draws is a frequent matter of concern in clinical practice, especially for anemic subjects and newborns [27]. Moreover, blood collection in patients with poor venous access or small veins may also lead to collection of an insufficient volume of blood into the collection tube [28, 29]. The issue of insufficient blood volume for testing can be typically divided in two categories, wherein the missing amount of blood can be absolute or relative.

In the former case, encompassing also the paradigmatic example of receiving empty blood tubes, the laboratory cannot perform any or all the tests requested because the amount of available samples is insufficient. Although the modern laboratory instrumentation uses very little amounts of blood, serum or plasma (i.e. typically between 2 and 20 μL per test), yet a minimum volume is required for processing samples automatically. Rather understandably, when the laboratory staff receives a small amount of blood, there is not much that can be done but to contact the clinicians and ask which are the most important tests that should be performed on the available volume and/or to ask for another sample [30, 31].

In the latter case, encompassing all those circumstances when the blood tube is partially underfilled but the overall amount of blood is still adequate for performing all the diagnostic tests requested, the problem is usually more complicated and clinically challenging. Although it seems reasonable to conclude that up to 75% underfilling in serum blood tubes or in those containing additives such as lithium-heparin, ethylenediaminetetraacetic acid (EDTA) and procoagulant compounds (i.e. thrombin), may very rarely generate a clinically significant bias and only for a very limited number of analytes [32, 33], the minimum specimen volume has been clearly defined for coagulation testing, as the concentration of anticoagulant (i.e. 0.105–0.109 mol/L buffered sodium citrate) and the volume of blood need to fulfill strict requirements [34]. Hence, recent experimental studies have demonstrated that a clinically significant bias can be observed in test results of hemostasis tests when blood tubes are drawn at less than 90% of their nominal volume. The requirement to reject underfilled blood tubes (i.e. with >10% underfilling) is more stringent for some hemostasis tests (i.e. activated partial thromboplastin time [APTT] and clotting factors assay), whilst prothrombin time (PT) and the fibrinogen (Clauss) assay seem overall to be less biased, up to 30% underfilling [35].
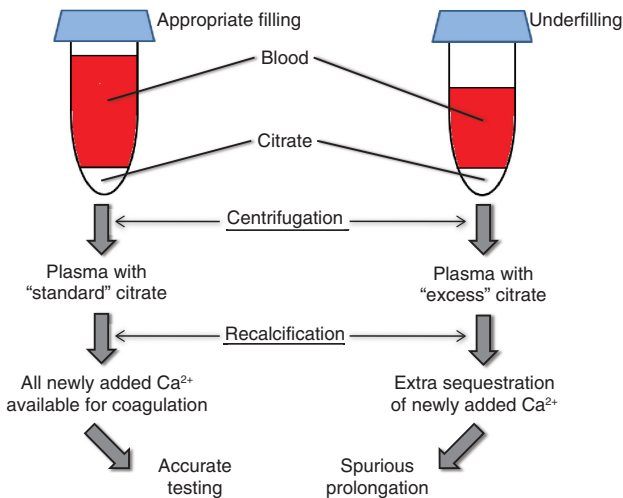
Figure 3: Underfilling of citrate blood tubes.

The impact of blood tube underfilling on clotting assays is basically due to the fact that a fixed ratio (i.e. 1:9) has been set between blood and sodium citrate within evacuated collection tubes. The predefined final concentration of sodium citrate in the tube is hence supposed to sequestrate all the available amount of ionized calcium (Ca^{2+}) present in venous blood, thus making blood temporarily incoagulable until restoration of a physiological Ca^{2+} concentration will be needed for purposes of hemostasis testing (i.e. a process known as plasma "recalcification") [36]. Whenever an imbalance between citrate and Ca^{2+} occurs, and this is most frequently attributable to underfilling of blood tubes, this last condition will lead to a citrate-mediated over-sequestration of Ca^{2+} upon plasma recalcification, so that test results of hemostasis testing may be impaired (i.e. spuriously prolonged), as schematically outlined in Figure 3. Therefore, whenever the laboratory cannot easily identify the types of hemostasis tests requested, coagulation blood tubes filled at less than 90% of their nominal volume should be rejected and otherwise test results should be suppressed. Notably, citrate concentration should be adjusted in samples with high hematocrit values (i.e. typically over 55%) for obtaining accurate hemostasis test results [37].

Wrong container (blood tube)

Laboratory testing encompasses the analysis of specific biological matrices, which are often different according to the different type of testing. For example, hematological testing requires samples irreversibly anticoagulated with EDTA, hemostasis testing needs to be performed in samples reversibly anticoagulated with sodium citrate, whilst clinical chemistry and immunochemistry can only be performed in serum or in samples anticoagulated with lithium-heparin. A summary of the different types of biological matrices and related laboratory testing is shown in Table 1 [38]. Although blood collection tubes may differ among different manufacturers [13], the collection of an appropriate sample for testing is conventionally facilitated by the adoption of different colors for blood tubes caps, which are aimed to ease the visual recognition of the different blood tubes by the phlebotomists (Table 1).

Blood drawn in the correct tube will hence be necessary for accurate results of laboratory testing. Understandably, hemostasis testing will not be possible in EDTA anticoagulated samples (blood coagulation will be irreversible inhibited) or in serum (the sample is irreversibly clotted), whilst hematological testing will not be possible in serum (all blood cells will be entrapped in the clot) and highly discouraged lithium-heparin anticoagulated samples (heparin interferes with blood smear staining and the heparin-mediated inhibition of blood coagulation is not as efficient as using EDTA) [39]. As quality testing will henceforth entail receiving a correct biological sample matrix, rejection of blood samples drawn in wrong tubes is a relatively frequent occurrence in routine laboratory practice (i.e. ~8% of all non-conformities), which often led to sample rejection, tests suppression and to the need

Table 1: Blood tubes, color cap (according to the International Standard ISO 6710), additive and related laboratory testing.

Color cap	Additive	Sample matrix	Tests
(Light) Blue	Sodium citrate	Plasma, whole blood[a]	Hemostasis, platelets[a]
Red	None/clot activators	Serum	Clinical chemistry, immunochemistry
(Light) green	Lithium-heparin	Plasma	Clinical chemistry, immunochemistry
(Dark) green	Sodium-heparin	Plasma	Ions, metals
Lavender	EDTA	Whole blood, plasma[b]	Hematology, immunochemistry[b]
Gray	Glycolysis inhibitors	Plasma	Glucose
Yellow	ACD	Whole blood	Blood group typing

ACD, Acid citrate dextrose; EDTA, ethylenediaminetetraacetic acid. [a]Suggested in the presence of platelets aggregates; [b]For certain fragile molecules.

Table 2: List of concise recommendations for managing unsuitable samples.

Hemolyzed specimens
  – Systematic monitoring of sample quality by means of the hemolysis index (or visual inspection, when the hemolysis index is unavailable)
  – Indentify the cause of hemolysis (i.e. distinguish between intravascular and spurious hemolysis)
  – Release test results with an accompanying comment when the bias is lower than the reference change value (RCV) or suppress data when the bias exceeds the RCV
Insufficient or inappropriate sample volume
  – Ask to recollect the blood sample when the volume is insufficient for performing essential laboratory tests
  – Reject all coagulation blood tubes filled at less than 90% of their nominal volume and suppress test results when the types of tests requested cannot be identified
  – In exceptional circumstances (i.e. urgent conditions), prothrombin time and fibrinogen assay may be analyzed in blood coagulation tubes filled up to 70% of their nominal volume
Wrong container
  – Samples received in the wrong container should be rejected and test suppressed
  – Serum and lithium-heparin plasma may be interchangeable, provided that the assays are validated for use on either biological matrix and the decisional thresholds overlap
Undue clotting
  – Reject all blood samples referred for hematological or hemostasis testing when fibrin strands or clots can be identified
  – Remove fibrin strands or clots from serum or plasma samples before use for automated analyses

of recollecting blood. In general, as also clearly discussed in the ensuing paragraph, samples received in the wrong container should be rejected. The only exception is interchanging serum and lithium-heparin plasma (provided that the assays are validated for use on either biological matrix), and considering that the values of some analytes may be slightly different in these two matrices (e.g. potassium is slightly higher in serum than in plasma) [40].

Undue clotting

Blood clotting is conventionally defined as a process leading to the activation of primary and secondary hemostasis, culminating in the generation of a stable blood clot comprising blood cells and clotting factors [41]. As discussed earlier, the different types of laboratory tests typically entail the use of different biological matrices. Blood clotting in the collection tube is hence a normal process in serum tubes, which can also be amplified by using specific clot activators [42, 43].

In other circumstances, however, partial or complete coagulation within the blood collection tube is highly unadvisable, as the presence of even small clots will interfere with laboratory testing, thus making test performance unfeasible or results inaccurate. This is especially important for hematological and coagulation testing, as blood cell counts will be unreliable when corpuscular elements (especially platelets) are entrapped within the clot and the clotting factors have been consumed during the coagulation process [41]. Analyzer malfunctions are other possible side effects of partial or complete clotting of samples,

as fibrin strands or organized clots may be aspirated by the laboratory analyzers, thus obstructing the probes and leading to instrument failures [44]. Therefore, whenever fibrin strands or clots can be identified in samples conveyed to the laboratory for hematological or hemostasis testing (either visually by the laboratory staff, or with generation of flags by the laboratory analyzers), the samples should be immediately rejected or test results suppressed. Provided that clot aspiration by the analyzer can be prevented, partial clotting of lithium-heparin samples is acceptable, as it does not substantially impair test results, except when measuring fibrinogen [45].

Conclusions

Blood sample quality remains a mainstay for the quality of the total testing process [46], as the receipt of unsuitable samples may be associated with diagnostic delay, missed or wrong diagnoses, and also poses a considerable economic burden on the hospital and laboratory budgets [47]. According to the predictable evolution of laboratory diagnostics, increasingly committed to the generation of large networks of facilities (i.e. the "hub-and-spoke" paradigm) [48], strengthening efforts to monitor the quality of diagnostic blood samples will become ever more important. We also believe that the adoption of a set of standardized and universally agreed policies for managing unsuitable samples and related quality indicators [49] will become increasingly compelling for reinforcing the total quality in laboratory diagnostics (Table 2).

References

1. Plebani M, Lippi G. Closing the brain-to-brain loop in laboratory testing. Clin Chem Lab Med 2011;49:1131–3.
2. Lippi G, Plebani M, Graber ML. Building a bridge to safe diagnosis in health care. The role of the clinical laboratory. Clin Chem Lab Med 2016;54:1–3.
3. Lippi G, Plebani M. A Six-Sigma approach for comparing diagnostic errors in healthcare – where does laboratory medicine stand? Ann Transl Med 2018. doi: 10.21037/atm.2018.04.02.
4. Aita A, Sciacovelli L, Plebani M. Laboratory-related errors: you cannot manage what you don't measure. You manage what you know and measure. Diagnosis (Berl) 2017;4:193–5.
5. Simundic AM, Lippi G. Preanalytical phase–a continuous challenge for laboratory professionals. Biochem Med (Zagreb) 2012;22:145–9.
6. Plebani M. Diagnostic errors and laboratory medicine – causes and strategies. EJIFCC 2015;26:7–14.
7. Lippi G, Mattiuzzi C, Bovo C. Are we getting better at the preanalytical phase or just better at measuring it? J Lab Precis Med 2018;3:11.
8. Lippi G, Simundic AM. The EFLM strategy for harmonization of the preanalytical phase. Clin Chem Lab Med 2017 Jun 3. doi: 10.1515/cclm-2017-0277. [Epub ahead of print].
9. Lippi G, Guidi GC. Risk management in the preanalytical phase of laboratory testing. Clin Chem Lab Med 2007;45:720–7.
10. Hammerling JA. A Review of medical errors in laboratory diagnostics and where we are today. Lab Med 2012;43:41–4.
11. Lippi G, Becan-McBride K, Behúlová D, Bowen RA, Church S, Delanghe J, et al. Preanalytical quality improvement: in quality we trust. Clin Chem Lab Med 2013;51:229–41.
12. Lippi G, Avanzini R, Sandei F, Aloe R, Cervellin G. Blood sample contamination by glucose-containing solutions: effects and identification. Br J Biomed Sci 2013;70:180–3.
13. Cornes M, van Dongen-Lases E, Grankvist K, Ibarz M, Kristensen G, Lippi G, et al. Order of blood draw: Opinion Paper by the European Federation for Clinical Chemistry and Laboratory Medicine (EFLM) Working Group for the Preanalytical Phase (WG-PRE). Clin Chem Lab Med 2017;55:27–31.
14. 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;4:181.
15. Simundic AM, Cornes M, Grankvist K, Lippi G, Nybo M. Standardization of collection requirements for fasting samples: for the Working Group on Preanalytical Phase (WG-PA) of the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM). Clin Chim Acta 2014;432:33–7.
16. Lippi G, Plebani M, Di Somma S, Cervellin G. Hemolyzed specimens: a major challenge for emergency departments and clinical laboratories. Crit Rev Clin Lab Sci 2011;48:143–53.
17. Lippi G, Favaloro EJ, Franchini M. Hemolysis index for the screening of intravascular hemolysis: a novel diagnostic opportunity? Blood Transfus, in press. DOI: 10.2450/2018.0045-18.
18. Lippi G, Giavarina D, Gelati M, Salvagno GL. Reference range of hemolysis index in serum and lithium-heparin plasma measured with two analytical platforms in a population of unselected outpatients. Clin Chim Acta 2014;429:143–6.
19. Lippi G, Cadamuro J, von Meyer A, Simundic AM. Practical recommendations for managing hemolyzed samples in clinical chemistry testing. Clin Chem Lab Med 2018;56:718–27.
20. Simundic AM, Topic E, Nikolac N, Lippi G. Hemolysis detection and management of hemolysed specimens. Biochem Med (Zagreb) 2010;20:154–9.
21. Simundic AM, Nikolac N, Guder WG. Preanalytical variation and preexamination processes. In: Rifai N, Horvath R, Wittwer C, editors. Tietz textbook of clinical chemistry and molecular diagnostics. 6th ed. New York, USA: Elsevier, 2018:81–120.
22. Lippi G, Avanzini P, Pavesi F, Bardi M, Ippolito L, Aloe R, et al. Studies on in vitro hemolysis and utility of corrective formulas for reporting results on hemolyzed specimens. Biochem Med (Zagreb) 2011;21:297–305.
23. von Meyer A, Cadamuro J, Lippi G, Simundic AM. Call for more transparency in manufacturers declarations on serum indices: On behalf of the Working Group for Preanalytical Phase (WG-PRE), European Federation of Clinical Chemistry and Laboratory Medicine (EFLM). Clin Chim Acta 2018 Apr 2. doi: 10.1016/j.cca.2018.03.043.
24. Goyal T, Schmotzer CL. Validation of hemolysis index thresholds optimizes detection of clinically significant hemolysis. Am J Clin Pathol 2015;143:579–83.
25. Nikolac Gabaj N, Miler M, Vrtarić A, Hemar M, Filipi P, Kocijančić M, et al. Precision, accuracy, cross reactivity and comparability of serum indices measurement on Abbott Architect c8000, Beckman Coulter AU5800 and Roche Cobas 6000 c501 clinical chemistry analyzers. Clin Chem Lab Med 2018;56:776–88.
26. Wisser D, van Ackern K, Knoll E, Wisser H, Bertsch T. Blood loss from laboratory tests. Clin Chem 2003;49:1651–5.
27. McPherson RA. Blood sample volumes: emerging trends in clinical practice and laboratory medicine. Clin Leadersh Manag Rev 2001;15:3–10.
28. 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.
29. Nikolac N, Supak-Smolčić V, Simundić AM, Celap I. Croatian Society of Medical Biochemistry and Laboratory Medicine: national recommendations for venous blood sampling. Biochem Med (Zagreb) 2013;23:242–54.
30. Wisser D. Blood loss from laboratory tests. Clin Chem 2003;49:1651–5.
31. Lippi G, Banfi G, Buttarello M, Ceriotti F, Daves M, Dolci A, et al. Recommendations for detection and management of unsuitable samples in clinical laboratories. Clin Chem Lab Med 2007;45:728–36.
32. Lippi G, Avanzini P, Cosmai M, Aloe R, Ernst D. Incomplete filling of lithium heparin tubes affects the activity of creatine

kinase and gamma-glutamyltransferase. Br J Biomed Sci 2012;69:67–70.

33. Xu M, Robbe VA, Jack RM, Rutledge JC. Under-filled blood collection tubes containing K2EDTA as anticoagulant are acceptable for automated complete blood counts, white blood cell differential, and reticulocyte count. Int J Lab Hematol 2010;32:491–7.

34. 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.

35. 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.

36. Lippi G, Salvagno GL, Brocco G, Gelati M, Danese E, Favaloro EJ. Impact of experimental hypercalcemia on routine haemostasis testing. PLoS One 2017;12:e0175094.

37. Marlar RA, Potts RM, Marlar AA. Effect on routine and special coagulation testing values of citrate anticoagulant adjustment in patients with high hematocrit values. Am J Clin Pathol 2006;126:400–5.

38. Simundic AM, Cornes MP, Grankvist K, Lippi G, Nybo M, Ceriotti F, et al. Colour coding for blood collection tube closures – a call for harmonisation. Clin Chem Lab Med 2015;53:371–6.

39. Banfi G, Salvagno GL, Lippi G. The role of ethylenediamine tetraacetic acid (EDTA) as in vitro anticoagulant for diagnostic purposes. Clin Chem Lab Med 2007;45:565–76.

40. Asirvatham JR, Moses V, Bjornson L. Errors in potassium measurement: a laboratory perspective for the clinician. N Am J Med Sci 2013;5:255–9.

41. Lippi G, Favaloro EJ. Laboratory hemostasis: from biology to the bench. Clin Chem Lab Med 2018 Feb 19. doi: 10.1515/cclm-2017-1205. [Epub ahead of print].

42. Dimeski G, Johnston J, Masci PP, Zhao KN, Brown N. Evaluation of the Greiner Bio-One serum separator BCA Fast Clot tube. Clin Chem Lab Med 2017;55:1135–41.

43. Cadamuro J, Mrazek C, Leichtle AB, Kipman U, Felder TK, Wiedemann H, et al. Influence of centrifugation conditions on the results of 77 routine clinical chemistry analytes using standard vacuum blood collection tubes and the new BD-Barricor tubes. Biochem Med (Zagreb) 2018;28:010704.

44. Cervellin G, Aloe R, Lippi G. A case of factitious hyponatremia and hypokalemia due to the presence of fibrin gel in serum. Diagnosis (Berl) 2015;2:73–4.

45. Bowen RA, Remaley AT. Interferences from blood collection tube components on clinical chemistry assays. Biochem Med (Zagreb) 2014;24:31–44.

46. Seemann TL, Nybo M. Continuous quality control of the blood sampling procedure using a structured observation scheme. Biochem Med (Zagreb) 2016;26:337–45.

47. Erdal EP, Mitra D, Khangulov VS, Church S, Plokhoy E. The economic impact of poor sample quality in clinical chemistry laboratories: results from a global survey. Ann Clin Biochem 2017;54:230–9.

48. Lippi G, Simundic AM. Laboratory networking and sample quality: a still relevant issue for patient safety. Clin Chem Lab Med 2012;50:1703–5.

49. Sciacovelli L, Panteghini M, Lippi G, Sumarac Z, Cadamuro J, Galoro CA, et al. Defining a roadmap for harmonizing quality indicators in Laboratory Medicine: a consensus statement on behalf of the IFCC Working Group "Laboratory Error and Patient Safety" and EFLM Task and Finish Group "Performance specifications for the extra-analytical phases". Clin Chem Lab Med 2017;55:1478–88.