Opinion Paper

Mario Plebani*, Giuseppe Banfi, Sergio Bernardini, Francesco Bondanini, Laura Conti, Romolo Dorizzi, Fulvio Enrico Ferrara, Rita Mancini and Tommaso Trenti

Serum or plasma? An old question looking for new answers

https://doi.org/10.1515/cclm-2019-0719
Received July 15, 2019; accepted August 22, 2019; previously published online September 17, 2019

Abstract: Serum or plasma? An old question looking for new answers. There is a continual debate on what type of sample a clinical laboratory should use. While serum is still considered the gold standard and remains the required sample for some assays, laboratories must consider turn-around time, which is an important metric for laboratory performance and, more importantly, plays a critical role in patient care. In addition, a body of evidence emphasise the choice of plasma in order to prevent modifications of some analytes due to the coagulation process and related interferences. Advantages and disadvantages of serum and plasma are discussed on the basis of current literature and evidence. In addition, data are provided on the current utilisation of the samples (serum or plasma) in Italy and in other countries. Finally, a rationale for a possible switch from serum to plasma is provided.

***Corresponding author: Prof. Mario Plebani,** Dipartimento Strutturale Medicina di Laboratorio, Azienda Ospedale Università di Padova, Via Giustiniani, 2, 35128 Padova, Italy,
Phone: 0498212792, E-mail: mario.plebani@unipd.it.
https://orcid.org/0000-0002-0270-1711
Giuseppe Banfi: Direttore Scientifico, IRCCS Istituto Ortopedico Galeazzi, Università Vita e Salute San Raffaele, Milan, Italy
Sergio Bernardini: Dipartimento di Medicina Sperimentale, Università degli Studi di Tor Vergata, Rome, Italy
Francesco Bondanini: Unità Operativa Complessa Patologia Clinica Presidio, Ospedaliero Sant'Eugenio/CTO ASL Roma 2, Rome, Italy
Laura Conti: Patologia Clinica, IRCCS Istituto Nazionale Tumori Regina Elena Roma, Rome, Italy
Romolo Dorizzi: Unità Operativa Patologia Clinica, AUSL della Romagna, Cesena, Italy
Fulvio Enrico Ferrara: Direttore Servizio Integrato di Medicina di Laboratorio e Anatomia Patologica, Centro Diagnostico Italiano Spa, Milan, Italy
Rita Mancini: Laboratorio Unico Metropolitano, AUSL Bologna, Bologna, Italy
Tommaso Trenti: Dipartimento di Medicina di Laboratorio e Anatomia Patologica Azienda Ospedaliera Universitaria e USL di Modena, Modena, Italy

Keywords: anticoagulants; clinical laboratory; plasma; sample of choice; serum; whole blood.

Introduction

The majority of tests in clinical laboratory are performed to identify the concentration of various hematic constituents (analytes) present in the liquid blood portion. If not stabilised with appropriate anticoagulants, whole blood *ex vivo* tends to coagulate naturally, due to the rapid transformation of fibrinogen into fibrin (the latter is a protein that harnesses cells in blood, helping to form the clot). Through specimen centrifugation, it is possible to separate the corpuscular elements harnessed by the fibrin from the liquid portion (i.e. serum) with a variable yield from 40% to 50% v/v. Except for fibrinogen and coagulation factors, all the metabolites produced in the body remain in serum and in particular, proteins, hormones, injury markers and circulating nucleic acids.

The choice of appropriate anticoagulants (substances that are able to block the coagulation process) allows to obtain after centrifugation the liquid portion of blood (i.e. plasma) which contains both fibrinogen and other coagulation factors in their original state. It goes without saying that, except for the anticoagulant (which could interfere with analysis, in selected tests), plasma obtained using this method is nearly identical to the circulating one: from the analytic and diagnostic point of view, this allows the maximum representativeness of the *in-vitro* specimen compared to the *in-vivo* state of the patient.

The most widely used anticoagulants in laboratory practice are salts of ethylenediaminetetraacetic acid ($EDTAK_3$, $EDTAK_2$), buffered sodium citrate and lithium heparin. Other anticoagulants (such as potassium oxalate) are used to a lesser extent to essentially preserve some metabolites and to maintain sample quality until testing (preanalytical stabilisation). EDTA salts are chelating agents on calcium and can bind irreversibly to many other components and/or interfere in the chemical reactions needed to test some analytes.

Sodium citrate is able to revert the bond with calcium and it is widely used for blood coagulation tests, where it is crucial to hold the coagulation process in plasma and later reactivate it.

Conversely, heparin is a non-competitive anticoagulant not acting on calcium ion; it blocks coagulation by forming a heparin-antithrombin III compound with a severe inhibition on the coagulation factors X and II. Leave out the presence of antithrombin in the sample (practically always the case) and the possible interference by the ion with which heparin forms the salt used as anticoagulant (usually lithium), heparin interferes to a far lesser extent than other anticoagulants in the vast majority of laboratory tests. So the plasma obtained is suitable for a number of analytic methods and to test almost all analytes.

Serum or plasma?

As serum was historically used before plasma and it is pretty easy to obtain, it has become the standard sample for clinical chemistry tests. Contrarily, plasma samples were used in the past only when it was necessary to avoid *in-vitro* activation of the coagulation cascade or special techniques were necessary to preserve and/or store the specimens.

For the aforementioned reasons, mainly related to tradition, serum continues to be the sample of choice for many laboratories. On the other hand, plasma offers many advantages compared to serum and since many years, the possible use of plasma in routine laboratory tests has received increasing attention. Starting from the 1970s, literature shows the interchangeability of the results obtained from serum and plasma samples [1, 2]. In the following years, plasma use has slightly increased and evidences of its possible routine use were further confirmed [3–6]. In 1999, the World Health Organization (WHO) noticed a change made by some laboratories, which indicated plasma as sample of choice for the analysis of blood extracellular constituents as, compared to serum, it was more representative of the *in-vivo* status of the patient. However, despite the number of proofs and evidences regarding the possibility to use plasma for many tests (and despite the clear benefits associated with this choice), the use of this biological matrix in Europe and worldwide still has not exceeded 20% of the total volume of samples in clinical chemistry (although with some noticeable and important exception).

For sure, the simultaneous and promiscuous use of the two matrixes (serum and plasma) is methodologically doubtful and should be carefully avoided. As numerous analytes show different concentrations in plasma and in serum, results obtained from the two different samples cannot be interpreted or compared without the risk of significant evaluation errors. This evidence leads to the need for harmonisation in the use of biological matrixes for the same analyte: nowadays this need is more urgent than in the past, due to the new organisational system of laboratory networks. To deal with the increasing complexity of sample and information flows, laboratories require a careful, in-depth reappraisal of the standardisation levels for methods and procedures. The matter, though purely technical, leads to consequences beyond the laboratory boundaries and which, rebounding through the whole diagnostic-therapeutic course, also affects treatment success, process efficiency and patient safety as well.

Advantages of plasma

For analytes detectable in both plasma and serum, the use of plasma samples offers significant advantages:

- *Time saving*. Plasma samples can be centrifuged immediately after collection. Contrarily, serum requires at least 30 min to complete coagulation before centrifuging the specimen. Earlier centrifugation of specimens with extended clotting times (for example, due to patients' anticoagulant treatments) could show unconsolidated fibrin in the supernatant serum and require remedy to remove the clot and further centrifugations, thus prolonging time. In some tests and in many clinical situations, time is a decisive factor for diagnostic quality. Short turn-around time (TAT) is essential to provide appropriate therapeutic treatment to the patient, to improve clinical outcomes, to reduce the time spent in the emergency department and the hospital stay and globally to improve the effectiveness and efficiency of the entire healthcare system, not only in emergency but also for elective treatments [7, 8].
- *Higher yield*. When an anticoagulated sample is centrifuged, it provides approximately 15%–20% more volume compared to serum. This important fact allows the use of low-draw tubes, which have the advantage to prevent anaemia due to repeated blood collections (not a rare event in hospitals, especially for children and patients with reduced circulating blood volume), as well as reducing the costs related to special waste disposal.
- *Prevention of coagulation interferences*. Fibrin strands in serum (associated with partial clotting) could clog the analysers' probes, impacting on the reliability/validity of the results and on the efficiency of the

testing process (instrument *breakdown*). Regarding this issue, it is worth remembering that literature shows that micro-clots can lead to sporadic errors in immunoassays [9, 10]. Due to its nature, plasma does not contain fibrin strands.

- *Prevention of coagulation-induced influences*. Clotting changes the concentration of numerous blood constituents. Compared to plasma, the concentration of some constituents in serum increases, such as potassium, magnesium, aspartate aminotransferase, lactate dehydrogenase, neuron-specific enolase (NSE) and zinc. Likewise, reductions in the concentrations of other constituents are reported (e.g. glucose, total proteins, platelets), caused by cellular metabolism during clotting. Due to the variability of this process, it is not possible to simply remedy these errors by introducing a correction factor but the test repetition is required to confirm results. It is not uncommon that preanalytical hyperkalaemia can lead to the patient's hospitalisation.
- *Less haemolysis*. Haemolysis in different matrixes continues to be controversial and, in particular, it is still being debated whether the plasma reduces the percentage of haemolysed specimens compared to serum. In fact, the concentration of free haemoglobin measured in a random outpatient population is higher in serum than in plasma [11]. On the other hand, pneumatic tube transport induces less haemolysis in serum specimens compared to plasma [12]. Further studies are required to confirm this evidence.
- *Biobanking*. Despite a number of studies, the ideal conditions for storing serum and plasma specimen in human biobanks are still to be definitively described. Plasma is recommended for metabolites in general, for circulating DNA and RNA associated with tumours in cell-free samples and for mitochondrial RNA, while serum remains the preferred sample for proteomics and lipidology [13, 14].

Advantages of serum

For analytes detectable in both plasma and serum, the use of the serum samples offers the following advantages:

- *Less cell contamination*. After centrifugation, serum is virtually free from cellular components, while a significant number of leucocytes, erythrocytes, platelets and non-specific cell debris may still be found in plasma [15]. In fact, cells may not be completely removed from plasma if the centrifugation is not sufficiently high and prolonged. Furthermore, after centrifugation, blood cells can be easily resuspended in the supernatant. The permanence of cells in plasma may lead to a reduction of some analytes due to cellular metabolism. Additionally, freezing samples could break the cells' walls, thus increasing the sample concentration of free haemoglobin, cytokines, receptors, etc. The freezing/thawing process may also enhance the risk of triggering the activation of the coagulation factors by warming/cooling in the anticoagulated plasma, causing the formation of fibrin gel in the separated sample. Separator gels can reduce, but not eliminate, the cells' presence in plasma as, during the centrifugation, leucocytes and platelets (buffy coat) sit over the gel and only the erythrocytes, which stay below it, are effectively separated and isolated from the above plasma. A recent study showed a promising new separation technology (non-gel mechanical separator) that allows a significant reduction of cell contamination in plasma samples obtained after different centrifugation conditions [16].
- *Better stability for some measurands*. A better glucose stability in serum than in plasma samples stored at room temperature has been recently reported [17, 18]. In addition, available evidence highlights the risk of pseudohyperkalaemia and pseudohyponatraemia in samples of patients with mild to elevated leucocytosis conveyed by a pneumatic transport system [19].
- *Absence of anticoagulants*. Serum does not require any type of anticoagulant to be produced, thus preventing every possible interference caused by these substances. For example, the effects of both EDTA and heparin as anticoagulants on immunoassays are well known and reported in the literature [20]. More recently, in exceptional circumstances, the use of citrate plasma for clinical chemistry and immunochemistry testing as a replacement for lithium-heparin plasma has been advocated, thus emphasising the need for further research in this field [21].
- *Possibility to use the sample for serum protein electrophoresis*. The lack of fibrinogen in serum allows to perform serum protein electrophoresis without any disturbance caused by the presence of this protein in the electrophoretic run (additional peak among β and γ components).

Lastly, a broader and more consolidated use of serum has led to greater availability of methods validated for this matrix (resulting in a higher metrological traceability). This situation, more determined by habits than by proven technical and methodological limits, is rapidly evolving and nowadays, the vast majority of analytes can be measured using both serum and plasma.

Table 1: Pros and cons in the use of plasma and serum.

Variable	Preference	Plasma	Serum
Time	Plasma	Centrifugable immediately after collection	Even with clot activators, it is necessary to wait at least 30 min before centrifugation, in order to form a stable clot
Volumes	Plasma	With equal haematocrit, the plasma yield is 15%–20% greater compared to serum	
Interference on analysers	Plasma		Fibrin strands could clog the probe
Interference due to clotting	Plasma	Coagulation may be activated during freezing/thawing process causing the formation of fibrin and reduction of factors. Uncommon with lithium-heparin and EDTA	Increased concentration of many analytes: potassium, magnesium, AST, LDH, NSE, zinc. Reduced concentration of some other: glucose, total proteins, platelets, due to cellular metabolism during clotting
Haemolysis	Plasma		Sporadic fibrin interference has been described for some immunoassays [10, 11]. There is a higher risk in samples collected from patients undergoing anticoagulation treatment
Analyte stability in the primary tube	Serum	Cellular metabolism is more active in plasma (e.g. gradual higher glucose consumption). New plasma separation technologies (non-gel separator) significantly reduce the concentration of cellular components in the supernatant [16]	
	Plasma	Plasma is more stable and, if frozen, can be stored indefinitely	
Stability of frozen specimen (biobanks)	Serum/ plasma	Increased haemolysis	
Transport stability of whole sample	Serum/ plasma	Leucocytes and platelets sit above the gel after centrifugation. Specimen movements can resuspend these elements. New plasma separation technologies (non-gel separator) significantly reduce the concentration of cellular components in the supernatant [16]	
Transport stability of centrifuged sample			
Interference with separator gel	Plasma	Lower risk of wrong separator gel positioning (or other material) [22, 23]	

AST, aspartate aminotransferase; LDH, lactate dehydrogenase; NSE, neuron-specific enolase.

The respective advantages and disadvantages of plasma and serum are listed in Table 1.

Situation in Italian and European clinical laboratories regarding plasma and serum use for clinical chemistry tests

Widespread use of plasma as the sample of choice in clinical chemistry within the European Union varies significantly between countries https://www.marketsandmarkets.com/Market-Reports/bloodcollection-market-39733117.html (accessed last time 18 August 2019). Data show that the percentage of plasma tubes compared to the total number of clinical chemistry tubes used in Europe in 2016 is 26%. Countries in Northern Europe (Finland, Sweden and the Netherlands) show an incidence over 50%, while only three other countries show plasma use above the European average (Switzerland, Denmark and France). Italy is in the ninth place with 18% and 17 other countries have a lower percentage (close to zero for Greece, Hungary and Slovakia) (Figure 1).

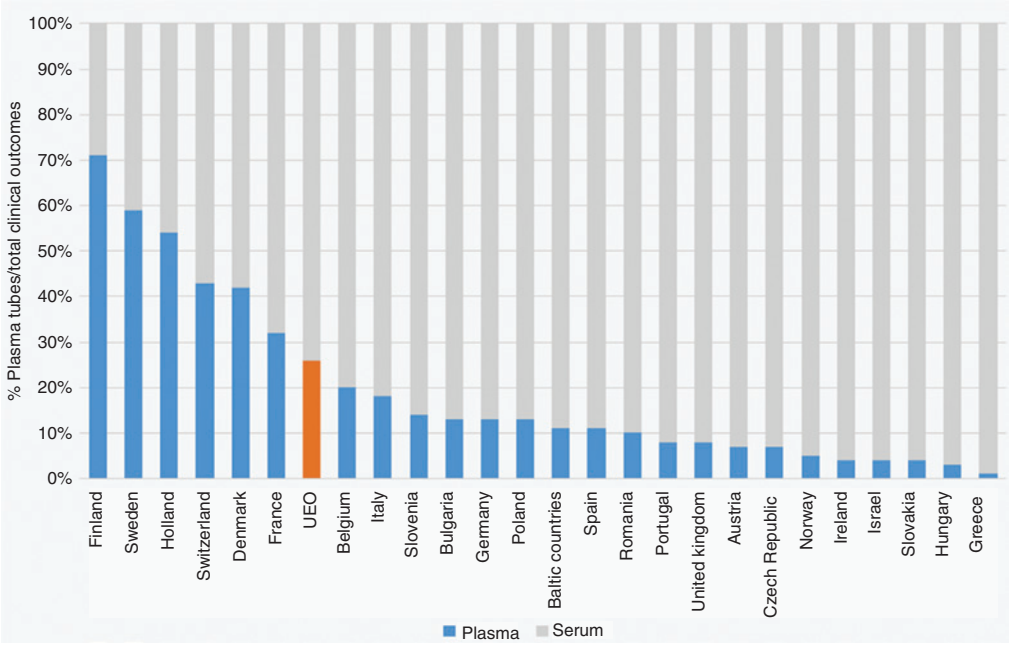

Figure 1: Distribution of plasma tubes in Western European countries in 2016.

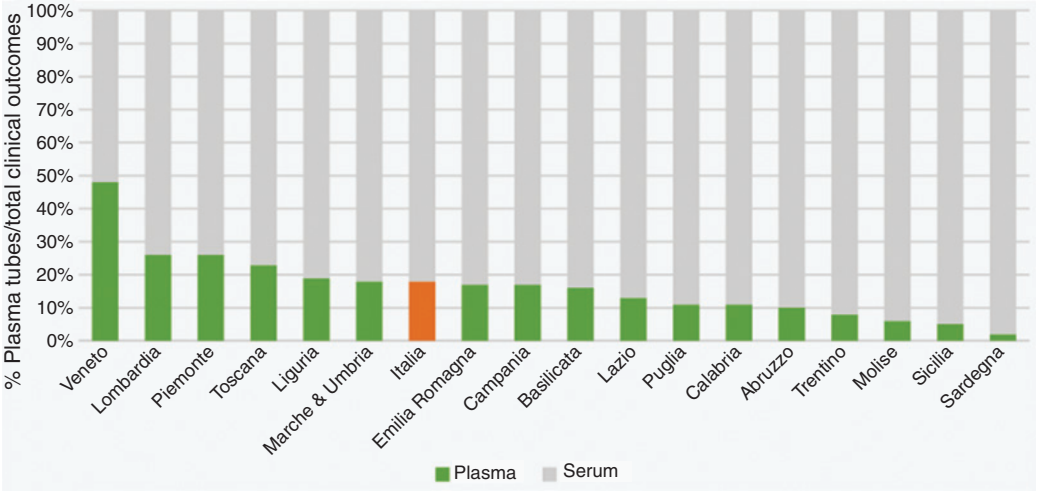

Figure 2: Distribution of plasma tubes in Italy in 2016.

Distribution in Italy is quite homogeneous and does not vary much between regions, reaching an average value of 18% [24]. The Veneto region represents a virtuous exception, with 48% of plasma tubes, while less than 10% of plasma tubes are used in Trentino, Molise, Sicily and Sardinia (Figure 2).

A survey carried out by the Study Group on Extra Analytical Variability of the Italian Association of Clinical Laboratory Professionals (SIBioC) showed interesting data regarding the use of plasma as well as the propensity to reconsider the most appropriate matrix in a harmonisation process [25]. The interviewed population, consisting of 229 professionals (the questionnaire was sent to almost 3000 members working in approximately 900 laboratories), was mostly employed in public laboratories (65%); 46% stated that they carried out more than 500,000 tests per year; 32% from 100,000 to 500,000; 5% between 100,000 and 10,000; the remaining 17% under 10,000. Although there are some limits to the population representativeness, due to the voluntary nature of participation in the survey, the laboratory professionals interviewed confirmed that over 76% consider serum as ideal matrix. Where there is no test urgency,

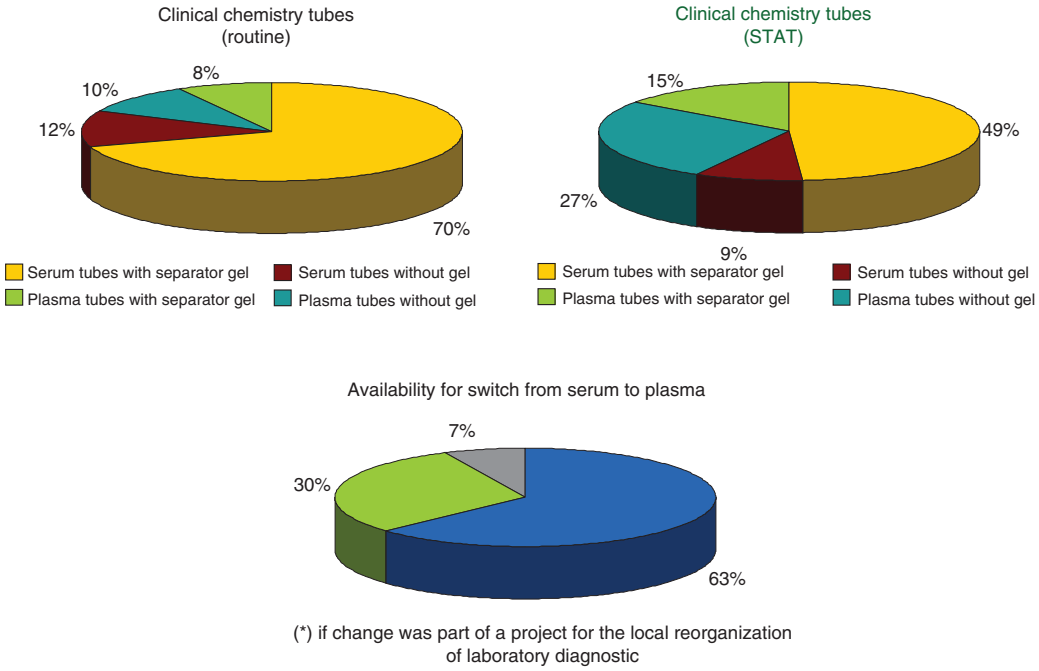

Figure 3: Outcomes of the survey on the use of serum and plasma tubes.

the serum use is almost exclusive, mainly with separator gel tubes. When tests are urgent, the percentage is much reduced (58% serum vs. 42% plasma) and with less use of separator gel tubes. The use of different samples (serum and plasma) for the same tests, according to whether they are in routine or STAT, is controversial and rises some concern, especially in the longitudinal evaluation of results from the same patient. The open-mindedness to change is noticeable. Around 30% of those interviewed thought it was possible to change matrix in the following 3 years and more than 90% said they were willing to consider a switch, if needed as part of the harmonisation project among networked laboratories (same region/geographical area) (Figure 3). Although serum is still considered the best matrix, this evidence shows that among physicians, biologists and laboratory technicians, there are widespread and well-founded reasons to reconsider this deep-rooted conviction.

Rationale for switch from serum to plasma and summary of the state-of-the-art about the use of plasma in different analytic settings

Scientific literature offers a wealth of evidences showing the importance of the correct matrix choice for the appropriate identification of analytes in laboratory medicine and, even more, discussing the pros and cons of using plasma samples as an alternative to serum.

However, no recent recommendations or guidelines exist on the matter which, as already highlighted, is critical to correctly perform not only traditional laboratory tests, but also the innovative ones (for example, "-omics").

Nowadays, the reasons for a definitive answer to the "serum or plasma?" question are essentially the following:

- Within the harmonisation for laboratory procedures and with the objective to improve the results' reliability (or even better, the laboratory information), the matrix choice represents a fundamental moment if not the *primum movens*, as it determines and influences all of the following phases, analytical and post-analytical. It is obvious that the reliability of laboratory information is not only based on methodologic standardisation, but it must also take into account pre-analytical variables (hence also the matrix) and post-analytical ones. Sample harmonisation, with a definitive clarification of whether or not plasma represents the better choice, is an actual theme that evokes great interest.
- Also in the reorganisation processes of laboratory activities promoted by regions and/or other institutions, it is imperative to reaffirm the relevance of a correct pre-analytical phase and therefore the

importance of the choice and the standardisation of the biological matrix within it.
- Considering the consolidation of urgent and routine test in clinical laboratories, sample harmonisation seems to be essential and mandatory. Current practice includes the use of plasma for STAT (from the Latin word *statim*, which means "urgent"), while serum is still the sample of choice for routine. The progressive inclusion of STAT into routine implies the need to homogenise the type of sample and therefore, the biological matrix to be recommended and used.
- As well as literature shows an amount of evidences about serum as the blood matrix for clinical diagnostics, the possibility to use plasma is reaching increasing consensus. The advantages related to time saving, lower risk of fibrin clog (especially in automation), greater yield and lower haemolysis seem to outweigh the few disadvantages related to plasma use. In many tests, the same manufacturers state that it is possible to use plasma, while in other areas, evidence is being collected or the theme is under discussion. So it is worth remembering the following:
  - Methods, based on spectrophotometry and enzymatic reactions, to test human metabolites are already largely validated also for plasma.
  - Turbidimetric methods seem not to be influenced by plasma.
  - Many molecules can be analysed by immunometric methods, both in serum and in plasma [26, 27]. The stability of some analytes (and their possible interactions) appears more critical, not only with plasma, but also with the tube materials and in particular, with separator gels [26].
  - Liquid chromatography and mass spectrometry do not show particular issues regarding the use of one or the other matrix. However, use of different types of anticoagulants could affect the accuracy and reliability of results [28–31].
  - In the -omics analysis, much more work is needed to define the ideal matrix. Some studies show that both serum and EDTA plasma allow to test the emerging biomarkers, miRNA and peptidomics.
  - However, further research is needed to better evaluate the effects of different matrices as some data demonstrate that the use of gel for some omics analyses (proteomics and metabolomics) could also affect the measurement of some components [32].
  - Additionally, refrigerated sample storage prevents the expression of miRNAs (often altered, even in case of delay between sample collection and analysis). Conversely, lithium heparin plasma seems to be not suitable for miRNA isolation.

Tips for the correct management of matrix switch

Following Good Laboratory Practices and ISO 15189-2012 (Medical Laboratories – Particular requirements for quality and competence [33]), the transition from serum to plasma also requires the implementation of a series of simple, yet important precautions. In particular:
- Ensure that the containers for plasma collection/separation are suitable for different analytes, as stated by the manufacturer in the instructions for use and supporting documentation.
- Ensure that the methods are suitable to test the different analytes in plasma, as stated by the manufacturer of the analytical platforms (Instrumentation Company) in the instructions for use and supporting documents. To date, many methods have already been validated as above. Table 2 lists the percentage of clinical chemistry and immunochemistry analytes that can be identified in plasma out of the total number of analytes on board, for four important instrumentation companies.

In case, for some analytes of interest, plasma is not validated by manufacturers, or if there are no published data to prove the possibility to use serum or plasma indifferently, the interchangeability of the matrixes must be validated by the laboratory. The comparative study and the research of possible bias could be carried out, as for other method comparisons, according to the standard CLSI EP09-A3 [35]. Any bias found between the matrixes can be annulled applying appropriate correction factors, or changing the comparison system and/or the reference intervals:
- Especially if a significant bias is observed, avoid simultaneous use of serum and plasma matrix to test the same analytes. To this regard, the convergence on

Table 2: Percentage of analytes measurable in plasma out of the total analytes on board [34].

	Clinical chemistry	Immunochemistry
Abbott	92.5% (81/87)	92.5% (75/80)
Beckman Coulter	89.2% (63/74)	84.4% (54/64)
Roche	95.7% (89/93)	97.5% (79/81)
Siemens	90.0% (66/73)	98.5% (68/69)

plasma as the sample of choice promotes the standardisation of processes, both intra-laboratory (e.g. same matrix for routine and STAT) and inter-laboratory (e.g. samples transported to one laboratory from external institutes or collection points).
- Ensure that the specimen transport and storage methods/conditions do not impede the use of plasma (it is useful to assess analyte stability over time at 24 h and 48 h from blood collection).
- Evaluate and manage any occurrence of preanalytical issues (e.g. centrifugation methods and times, yield, haemolysis, etc.).

First operative proposal

Also considering the findings of the mentioned SIBioC survey, the authors feel the need to undertake a serious route of harmonisation towards the use of plasma as the sample of choice for clinical chemistry routine. A first operative strategy proposal (submitted to the opinion and considerations of the involved professionals) could include the following steps:
- circulation and discussion of the present document in different relevant scientific areas;
- identification of centres of excellence interested in serum to plasma switch which could act as forerunners, sharing their experience;
- creation of a dedicated portal for the easy sharing of information, documentation and experience, also including forums and webinars;
- at least one study publication to assess in depth the impact of serum to plasma switch on the clinical and economic outcomes of diagnostic processes in the laboratory (Health Economics and Outcomes Research, HEOR);
- active involvement of instrumental companies and manufacturers of diagnostic systems for specimen collection, analysis and storage in order to:
  - collect essential information regarding the correct switch from serum to plasma;
  - assess the different technologies in the market;
  - ensure the necessary technical and scientific support during the switch phase.

Summary and first conclusions

The definition and standardisation of the sample of choice to test the majority of analytes in laboratory medicine represents one of the paradigms that clearly shows the gap between theory and practice frequently affecting medicine. In the face of the amount of evidences shown in the literature about the advantages (many) and limits (few) regarding the use of plasma in clinical practice, there is yet an operative inertia that has inhibited this switch in most clinical laboratories.

Today, in the era of framework and process optimisation, the well-known question "serum or plasma?" returns with renewed strength thanks to a growing interest in critical topics like suitability, harmonisation and the laboratory need for samples and information reliability in a world with less and less geographical and time limits [36].

Not by chance, the standards (like ISO 15189) for the accreditation of clinical laboratories require, for the assessment of pre-analytical quality, the definition of the sample of choice and so the validation of tests in that biological matrix. In this sense, plasma is confirmed as the sample of choice (thanks also to the continuous improvement in separation techniques and analysis) and it is able to:
- ensure, to a great extent, the necessary compatibility with tests currently in use;
- better represent the *in-vitro* state of the patient;
- significantly reduce the response times (TAT);
- increase the productivity for the entire laboratory, both reducing processing times and improving the efficient use of instruments (no fibrin, lower haemolysis, higher yield);
- standardise in a unique matrix routine and urgent tests providing the maximum comparability of intra- and inter-laboratory results.

In conclusion, this document, far from being a finish line, has the aim to stimulate the launch and implementation of shared projects to support and realise a conscious switch from serum to plasma, also by the evaluation/validation of new technologies/solutions and by the firm involvement of professionals in real clinical settings. It will be necessary to identify objective indicators to assess the outcomes of these projects in terms of their impact on laboratory services quality and with a viewpoint focused on the users' needs [37]. Now, however, it is time to get good ideas working.

Acknowledgments: Thanks to EDRA SpA for the editorial support for the manuscript.
Author contributions: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.
Research funding: None declared.
Employment or leadership: None declared.
Honorarium: None declared.

Potential conflicts of interest: This document was produced with the non-conditional contribution of Becton Dickinson Italia SpA.
Competing interests: The funding organisation(s) played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

References

1. Lum G, Gambino SR. A comparison of serum versus heparinized plasma for routine chemistry tests. Am J Clin Pathol 1974;61:108–13.
2. Ladenson JH, Tsai LM, Michael JM, Kessler G, Joist JH. Serum versus heparinized plasma for eighteen common chemistry tests. Am J Clin Pathol 1974;62:545–52.
3. Doumas BT, Hause LL, Simuncak DM, Breitenfeld D. Differences between values for plasma and serum in tests performed in the Ektachem 700 XR Analyzer, and evaluation of "plasma separator tubes (PST)". Clin Chem 1989;35:151–3.
4. Ebert SC, Leroy M, Darcey B. Comparison of aminoglycoside concentrations measured in plasma versus serum. Ther Drug Monit 1989;11:44–6.
5. Racine JF, Caya S, Delvin EE. Suitability of lithium heparinate plasma for the measurement of selected analytes on Beckman Synchron CX analyzers. Clin Biochem 1996;29:493–5.
6. Donnelly JG, Soldin SJ, Nealon DA, Hicks JM. Is heparinized plasma suitable for use in routine biochemistry? Pediatr Pathol Lab Med 1995;15:555–9.
7. Soffiati G, Giavarina D. Stat laboratory testing: integration or autonomy? Clin Chem Lab Med 2010;48:927–30.
8. Dolci A, Giavarina D, Pasqualetti S, Panteghini M. Total laboratory automation: do stat tests still matter? Clin Biochem 2017;50:605–11.
9. Tate J, Ward G. Interferences in immunoassay. Clin Biochem Rev 2004;25:105–20.
10. Kazmierczak SC, Sekhon H, Richards C. False-positive troponin I measured with the Abbott AxSYM attributed to fibrin interference. Int J Cardiol 2005;101:27–31.
11. 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.
12. Pasqualetti S, Szőke D, Panteghini M. Heparinate but not serum tubes are susceptible to hemolysis by pneumatic tube transportation. Clin Chem Lab Med 2016;54:785–9.
13. Mohamadkhani A, Poustchi H. Repository of human blood derivative biospecimens in biobank: technical implications. Middle East J Dig Dis 2015;7:61–8.
14. Ishikawa M, Maekawa K, Saito K, Senoo Y, Urata M, Murayama M, et al. Plasma and serum lipidomics of healthy white adults shows characteristic profiles by subjects' gender and age. PLoS One 2014;9:e91806.
15. Lippi G, Salvagno GL, Danese E, Lima-Oliveira G, Brocco G, Guidi GC. Inversion of lithium heparin gel tubes after centrifugation is a significant source of bias in clinical chemistry testing. Clin Chim Acta 2014;436:183–7.
16. Padoan A, Zaninotto M, Piva E, Sciacovelli L, Aita A, Tasinato A, et al. Quality of plasma samples and BD Vacutainer Barricor tubes: effects of centrifugation. Clin Chim Acta 2018;483:271–4.
17. Grzych G, Pekar JD, Maboudou P. Better glucose stability in serum than in plasma samples after 12-h stay at room temperature. Diabetes Technol Ther 2019;21:413–4.
18. Balboni F, Burbui S, Lippi G. Glucose variation in centrifuged serum and lithium-heparin gel tubes stored for up to 96 hours at room temperature or 4 °C. Scand J Clin Lab Invest 2018;78:546–50.
19. Grzych G, Pekar JD, Maboudou P, Lippi G. Leucocytosis-induced plasma hyperkalaemia in samples conveyed by a pneumatic transport system: tips and tricks. Br J Haematol 2019;186:e71–3.
20. Bowen RA, Remaley AT. Interferences from blood collection tube components on clinical chemistry assays. Biochem Med (Zagreb) 2014;24:31–44.
21. Demonte D, Pucci M, Salvagno GL, Lippi G. Can citrate plasma be used in exceptional circumstances for some clinical chemistry and immunochemistry tests? Diagnosis (Berl) 2019 May 4. doi: 10.1515/dx-2019-0027 [Epub ahead of print].
22. Daves M, Lippi G, Cosio G, Raffagnini A, Peer E, Dangella A, et al. An unusual case of a primary blood collection tube with floating separator gel. J Clin Lab Anal 2012;26:246–7.
23. Cervellin G, Aloe R, Lippi G. A case of factitious hyponatremia and hypokalemia due to the presence of fibrin gel in serum. Diagnosis 2015;2:73–4.
24. Lippi G, Giavarina D, Montagnana M. National survey on the pre-analytical variability in a representative cohort of Italian laboratories. Clin Chem Lab Med. 2006;44:1491–4.
25. Lippi G, Giavarina D. Indagine conoscitiva su matrice biologica e gestione della fase preanalitica nei laboratoriclinici. Biochim Clin 2017;41:142–7.
26. Woltering EA, Hilton RS, Zolfoghary CM, Thomson J, Zietz S, Go VL, et al. Validation of serum versus plasma measurements of chromogranin A levels in patients with carcinoid tumours: lack of correlation between absolute chromogranin A levels and symptom frequency. Pancreas 2006;33:250–4.
27. Giavarina D, Fortunato A, Barzon E, Church S, Bérubé J, Green S, et al. Evaluation of BD Vacutainer PST II tubes for a wide range of immunoassays. Clin Chem Lab Med 2009;47:237–41.
28. Denery JR, Nunes AA, Dickerson TJ. Characterization of differences between blood sample matrices in untargeted metabolomics. Anal Chem 2011;83:1040–7.
29. Gonzalez-Covarrubias V, Dane A, Hankemeier T, Vreeken RJ. The influence of citrate, EDTA, and heparin anticoagulants to human plasma LC–MS lipidomic profiling. Metabolomics 2013;9:337–48.
30. Khadka M, Todor A, Maner-Smith KM, Colucci JK, Tran V, Gaul DA, et al. The effect of anticoagulants, temperature, and time on the human plasma metabolome and lipidome from healthy donors as determined by liquid chromatography-mass spectrometry. Biomolecules 2019;9. pii: E200.
31. Lee J-E, Kim SY, Shin S-Y. Effect of repeated freezing and thawing on biomarker stability in plasma and serum samples. Osong Public Health Res Perspect 2015;6:357–62.
32. Zhou Z, Chen Y, He J, Xu J, Zhang R, Mao Y, et al. Systematic evaluation of serum and plasma collection on the endogenous metabolome. Bioanalysis 2017;9:239–50.
33. ISO 15189:2012 Medical laboratories: particular requirements for quality and competence. Geneva: International Organisation for Standardisation, 2012.

34. Da Rin G. Technological solutions in favour or using plasma in routines. 47th National Congress SIBioC, Firenze, 2015.
35. Clinical Laboratory Standards Institute (CLSI). Measurement procedure comparison and bias estimates using patient samples, approved guideline, 3rd ed. CLSI guideline EP09c. Wayne, PA: CLSI, 2018.
36. Plebani M. Harmonization in laboratory medicine: more than clinical chemistry? Clin Chem Lab Med 2018;56:1579–86.
37. Plebani M, Sciacovelli L, Aita A. Quality indicators for the total testing process. Clin Lab Med 2017;37:187–205.

Article Note: This paper is a translation, slightly modified, of the paper published in Biochimica Clinica:

Plebani M, Banfi G, Bernardini S, Bondanini F, Conti L. Dorizzi R. et al. Siero o plasma? Un quesito non nuovo che attende risposte nuove. Biochim Clin 2019;43:178–86.