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The Journal of the International Federation of Clinical Chemistry and Laboratory Medicine

In this issue

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Foreword: Introducing the eJIFCC special issue on "POCT – making the point"

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FOREWORD

Point of care testing (POCT) represents an important step forward in the clinical management of patients. POC assays are easy to use and do not require skilled personnel, thus they are particularly useful in low resource settings (where diagnostics laboratories equipped with complex instruments and well trained technicians are not available), as well as in the Proximity Medicine networks working in synergy with central laboratories. Furthermore, results are delivered in real-time, accelerating the decisional process behind the clinical decision as in the Emergency setting (air and ground ambulances, intensive care units, acute settings), remote rural settings, disasters, military conflicts, camps supporting vulnerable population (migrants and refugees camps), and sanitary residencies for the Elderly. A prompt diagnosis is also crucial in the case of contagious diseases allowing a rapid isolation of the infected patient and treatment; thus, reducing the risk of transmission of the pathogen. In this context, the role of POCT has been highlighted during the Covid-19 pandemic in screening and tracing programs.

This special issue includes a series of papers reflecting the topics planned for the "POCT: making the point" conference to be held between September 6 and 7, 2021 in Rome, Italy.

The aim of this Conference is to bring together IFCC and EFLM experts and representatives from the IVD Companies, in order to discuss various POCT dimensions: Quality Assurance, Training, Technological Innovations, Applications, Market and Sustainability.

Although POCT devices offer many advantages, their application goes hand in hand with numerous challenges, namely, clinical governance, connectivity, role of the laboratory director and staff, quality control, education and risk management. Furthermore, responsibility also extends to the manufacturer in the design and validation of POCT devices. Simultaneously, National and even supranational regulations and accreditations would be desired, but such procedures, at a global level, are still patchy.

Direct to Consumer Tests (DTCT) can be considered an extreme version of POC where patients perform the test themselves. Even if DTCT driven by the application of disruptive technologies has the potential for self-empowerment of patients, it raised many concerns and no regulatory safeguards for consumers exist as yet.

Finally, articles included in this issue by some of the authors are focused on the application of POCT devices in pediatrics, low-income countries and in the context of refugee and migrant care.

Organizing this conference started in the middle of the pandemic, when all my colleagues were under tremendous pressure fighting with Covid-19! The conference has been postponed to a new date with the faith that it shall be held eventually later in September, 2021 in Rome, Italy.

The present special issue is, in some way, evidence of our resilience in this very engaging time where Laboratory Medicine has demonstrated again its great value in patient care.

In this issue: POCT – making the point

The Journal of the International Federation of Clinical Chemistry and Laboratory Medicine

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Controlling reliability, interoperability and security of mobile health solutions

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ABSTRACT

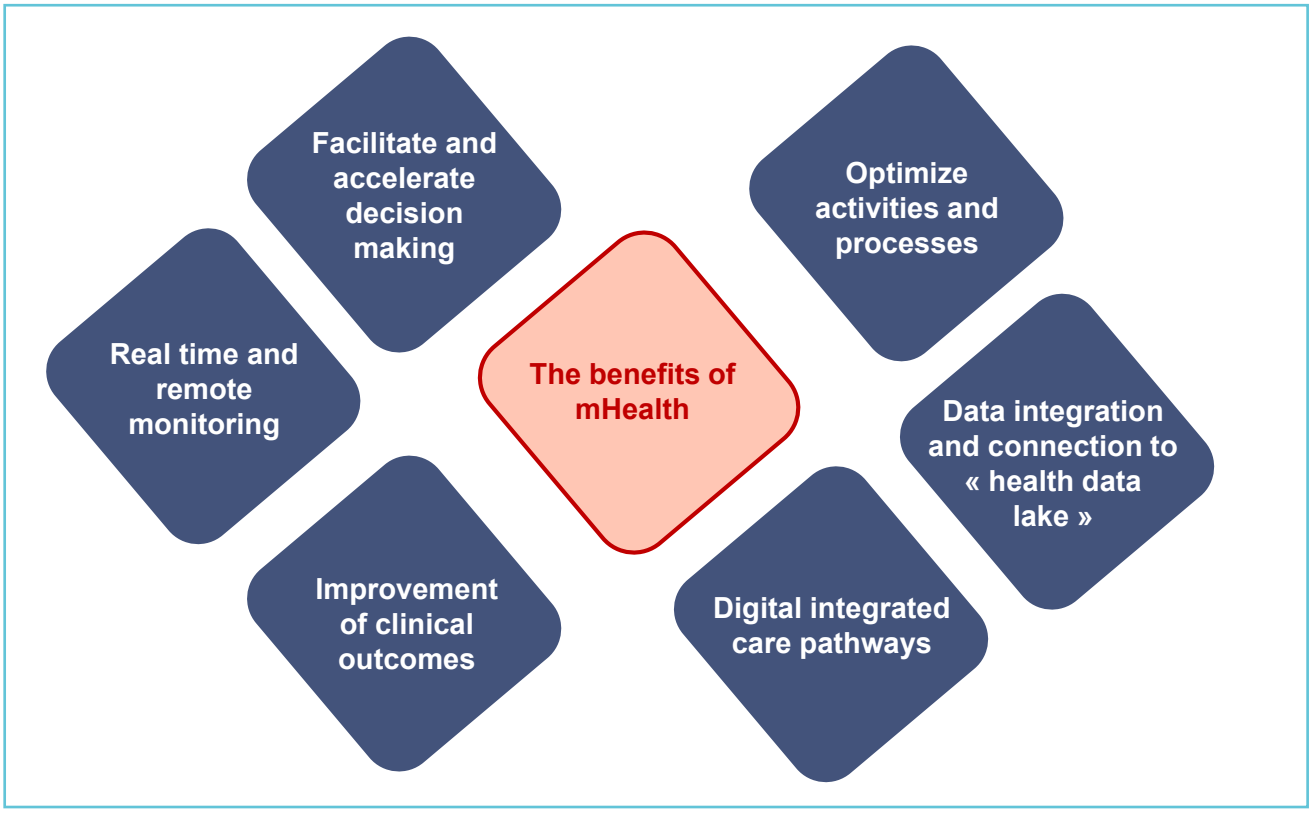
Mobile health (mHealth), including mobile devices and digital services, is a component of the transforming health ecosystem. The validation of the scientific validity, analytical performance, clinical performance and security of mHealth solutions is critical to guarantee patient care and safety. To this end, laboratory experts, scientific societies and notified bodies should define and recommend validation framework addressing multiple dimensions.

1. MOBILE HEALTH AS A PIECE OF A NEW HEALTH ECOSYSTEM

Mobile health (mHealth), including mobile devices and digital services, is a component of the transforming health ecosystem (1,2). The development of smart devices, sensors and digital applications is exponential since several years in our daily life and in health care (3,4). Through remote monitoring and digital services, mHealth also contribute to the accessibility to virtual health and new models of caring (5). The coronavirus disease 2019 (COVID-19) pandemic has generated a global public health crisis and rapid testing and contact tracing using smartphone technology are used to limit disease transmission (6,7). Covid19 pandemic has therefore clearly accelerated the transition to mHealth services (6,7). Covid19 also speeded up the use of telemedicine for safer consultations and diagnoses, and of artificial intelligence (AI) for epidemiologic modeling, prediction of severe forms or allocation of resources (6,7).

Mobile Health is offering new solutions and opportunities to healthcare professionals, to patients and citizen for monitoring health status and for improving health outcomes (5). Sensors, mobile devices and health applications allow also to collect and exchange a large amount of health data for offering a new class of advanced services characterized by being available anywhere, at any time and for multiple healthcare stakeholders (8). Through an interactive and structured data lake, interventions can therefore be conducted in real time (8). By allowing real time monitoring of clinical and biological variables as well as the integration of remote monitoring and telemedicine, the follow-up of outcomes is easier, which facilitates transition to value-based care (9). Figure 1 is summarizing some features related to mHealth.

Figure 1 The benefits of mHealth



It is clear that a new form of interconnection between the physical and digital worlds is accompanying mHealth (3). It is also clear that if mHealth is offering multiple advantages, several challenges such as safety and privacy of the solutions need to be overcome for a safe and valuable use and will be introduce in this article.

2. RELIABILITY AND SAFETY

The conformity assessment of the components of mHealth ecosystem is mandatory to ensure the quality of solutions or devices and to guarantee patient safety. In Europe, the new CE IVDR regulation is also reinforcing the control of the performances of device and post-market performance follow-up (10). With the new CE IVDR, as of May 2022 the level of clinical evidence needed to demonstrate the conformity of a device becomes progressively more stringent as the risk class increases.

The control of the mHealth solutions involving testing monitoring of laboratory data needs to involve specialist in laboratory medicine and scientific societies to ensure that multiple dimensions are evaluated according to recognized international standards. Experts in laboratory medicine have to validate the scientific validity, analytical performance and clinical performance of the mHealth solutions. Laboratory experts, scientific societies and notified bodies should define and recommend validation techniques and a standardized framework integrating of the mHealth solutions (11–13). Multiple dimensions should be considered in such validation framework and multiple players will be involved (13).

Manufacturers play a major role in setting internal diagnostics methods to improve the quality, control and maintenance of devices (11). This type of internal performance monitoring has to ensure a faulty data detection method consisting of the detection of faulty or incorrect values during the data acquisition and processing stages. Introduction of a data correction method consisting of the estimation of faulty or incorrect values obtained during the data acquisition and processing stages also has to be considered. In addition, a data context classification or uncertainty mechanism could be considered as possilble approaches for the correct validation of data (11).

Specialist in laboratory medicine will play a critical role for the education and training of the users, as well as in a dynamic control of the device supervised by clinical laboratories as illustrated by the initiative of the French society of laboratory informatics Control of glucose meter and INR device (14).

Another important point for the evaluation of mHealth solutions will be their level of data standardization and interoperability (15). Such interoperability allows mHealth solutions to communicate effectively without compromising the content of the transmitted data and to share patient health information among healthcare professionals and organizations (15). Interoperability and data exchange can be assess based on the recommendations of the European Interoperability Framework (16).

Table 1 summarizes some of the important dimensions to be considered for the assessment of mHealth solutions.

3. SECURITY AND PRIVACY

Ensuring the confidentiality of health data stored in mHealth solutions with rapidly advancing technology is a fundamental aspect for protecting personal information and privacy and mandatory at the time of Global Data Protection Regulation (GDPR) (3,17,18). A secured design of mHealth solutions will also allow more opportunities for scalability, usability and connectivity (3,17). (Table 2)

Table 1 Multidimensional score card to assess components of mHealth solutions

Dimension evaluated	Potential indicators
Clinical performances and clinical outcomes	Sensitivity, specificity, negative predictive value, positive predictive value, length of stay, mean time between readmission to hospital
Behavioral	Quality-adjusted life year, symptom clusters, patient satisfaction
Technical	Limit of quantification, limit of detection, range of measurement, fault detection systems, connectivity, interoperability, usability
Organizational	Turnaround time of analysis, impact on resources, integration in care pathways
Environmental	Waste and energy consumption, impact on test ordering
Economical	Price, total cost of ownership, time for training, resources needed for implementation and management of solution, cost of management

Table 2 Aspects related to security and privacy

Security	Guarantee of secure storage, secure communication and secure content
Identity management	Ensure authentication for users, devices, applications and associated services
Privacy	Maintain privacy
Scalability	Capacity of evolution to sustainable and scalable solutions
Reliability	Solutions should support identification of fault and self-repairing
Data integration	Real-time data collection, analytics, aggregation and transmission

Different possible threats and attacks have been identified and include communications, device/services, users, mobility and integration of resources (3). To face these risks, lessons can be learned from other communities such as cybersecurity or internet security which offer various techniques to reduce the potential risk of data breaches or tampering in mHealth (8). Different elements need to be considered:

- Include user-informed consent and privacy/policy information
- Carry out continouous user authentication, to guarantee only allowed device use while protecting authentication data

- Explore a combination of biometric features with privacy-preserving approaches
- Introduce risk assessments protocols and audits of the security system
- Combine multiple private blockchains to provide users with stronger location privacy protection without reducing the quality of service (19)

The evolution of legal frameworks allow also to gain better control of these issues and the recent European GDPR is a good example (20). According to their importance, these aspects could be considered in the criteria for funding. In Belgium, the National Institute for Health and Disability Insurance (INAMI) has introduced a structural framework for funding of digital solutions and including criteria such as the verification of the therapeutic relationship and informed consent, interoperability and data protection (21).

4. CONCLUDING REMARKS

The validation of the scientific validity, analytical performance, clinical performance and security of mHealth solutions is critical to guarantee patient care and safety. To this end, laboratory experts, scientific societies and notified bodies should define and recommend validation framework addressing multiple dimensions. To ensure an efficient and safe use of mHealth solutions, specialists in laboratory medicine and scientific societies must also provide guidance, education, and training to healthcare professionals, patients and helpers.

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In this issue: POCT – making the point

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Best laboratory practices regarding POCT in different settings (hospital and outside the hospital)

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POCT, quality; management, IQCP, EQA, root cause analysis

ABSTRACT

Point-of-care testing is proliferating at an alarming rate as technological improvements in miniaturization coupled with the need for rapid diagnostics drive the market globally. This review highlights best laboratory practices that must be communicated to the diverse group of people employing POC testing in their respective settings both inside and outside the hospital setting so that reliable results can be obtained.

INTRODUCTION

The COVID-19 pandemic highlighted the importance and versatility of point-of-care testing (POCT) in the triaging and management of disease [1]. This role, coupled with developments in miniaturization technology due to its appeal to the medical profession in monitoring of health has led to rapid proliferation of POCT. As such, POC testing has become an important component of healthcare maintenance across a wide spectrum of services from intensive care units, emergency rooms, skilled nursing facilities, outpatient clinics, physician offices, pharmacies, community wellness programs and direct-to-consumer testing. [2] The reliability of the test result is key in deciding the next step of a diagnostic, treatment or health maintenance plan, and hence requires best laboratory practices. As a result, responsibility extends from the manufacturer in the design and validation of the device, to the healthcare facility managing the service, to the ordering physician and/or personnel or consumer performing and acting on the test.

Best laboratory practices can be broken down into 4 areas of consideration [2]

A. Defining the roles and responsibilities of the personnel involved in the testing process

B. Ensuring the chosen POCT is appropriate for effective patient management. This comprises:

a. Economic aspects
b. Clinical aspects
c. Validation studies
d. Written procedures
e. Training and competency testing staff

C. Developing a process to identify and mitigate errors

D. Ensuring there is accurate documentation of all aspects of laboratory testing

A. Defining the roles and responsibilities of the personnel involved in the testing process

It is important to define the roles of the personnel involved in POC testing because it helps in managing the service. Who will train the personnel? Who will perform quality control (QC)? Who will perform and monitor quality assurance audits? Who will provide written procedures and available policies for staff? Who will investigate device data connectivity issues? These questions will help in the management as well as organizing root cause analysis and mediation of corrective actions. The POCT service should be supervised by a physician or doctoral-level scientist with training in laboratory medicine. They will be responsible for all aspects of the program, including giving or advising in the interpretation of test results. In a hospital setting, which is the most structured of settings, the laboratory director has to often delegate duties to others.

Here are some of the roles present in a hospital setting:

(i) Laboratory director – this can be a physician or doctoral level scientist that is responsible for delivering all aspects of the testing service.

(ii) Point-of-care coordinator – perform training, quality assurance audits, troubleshooting and is involved in daily communication with testing personnel.

(iii) Point-of-care testing manager – these can be site specific or system-wide and have been delegated by the laboratory director to oversee day-to-day testing. They also write-up procedures and policies, perform device verification/validation studies, provide assistance with troubleshooting, audits, and training when necessary.

(iv) Testing personnel – these are appropriately trained staff who will perform POC testing on patients.

B. Ensuring the chosen poct is appropriate for effective patient management

To ensure the chosen POCT for monitoring a clinical condition is appropriate, the laboratory director must ensure the device and method is suitable for use in the diagnostic and clinical care algorithm. This can be further subdivided as follows:

a. Economic aspects

POC testing needs to be economically sustainable otherwise it will not be able to bring lasting benefit to the community it serves. Some questions that need to be considered are: How much will this test cost to perform? What is the cost for quality control, proficiency testing cost, maintenance and supplies? How much will the reimbursement be? Will someone need to be hired? Connectivity costs? How much does the technical support cost from the manufacturer and is it timely?

b. Clinical aspects

A POC test needs to improve patient management. Some questions that need to be asked are: What will be the workflow? How reliable is this test? Will a confirmatory test be required? The package insert and any available scientific literature on the test can help answer this with respect to sensitivity, specificity, negative and positive predictive values. Scientific literature on POCT correlations with other POC tests or core laboratory instruments should also be reviewed to determine the suitability of the POC test.

c. Validation studies

It is important to determine whether a thorough validation of test has been performed by the manufacturer. This can be obtained from the package insert and any available scientific literature. The sensitivity, specificity, negative and positive predictable values need to be critically reviewed. A verification study should be performed to ensure the test performs as expected and the device has not been affected by the shipping process.

d. Written procedures

Procedures needs to be written for each test derived from information in the package insert as well as any other relevant information specific to the workflow at the facility. They must be available for the testing staff for reference. Therefore, the package insert needs to be critically inspected for methodology, specimen requirements, causes of interference, quality control and reagent storage requirements, procedures for trouble shooting when QC is incorrect/out of range, analytical measuring range of the instrument, interpretation and documentation of results. The package insert needs to be retained and be available as a reference. Periodic POCT updates by the manufacturer will be reflected in the package insert.

e. Training and competency testing of staff

Training of staff on the correct techniques is important and preferably by the same person or group so that there is standardization of how the test is performed. For example, if “3 drops of diluent” are required then adding 2 or 4 drops could lead to under saturation or over saturation effects that could give a false result. Likewise, where a reading after a defined period is required, reading the result before or after this period could lead to a false negative or a false positive. Staff should also be tested for color blindness as some tests are based on a color change. For example, urinalysis by dipstick employs reagent pads on the dipstick that produce a color change when they react with

a particular biomarker in the urine. The resulting color correlates with the concentration of the biomarker. Finally, training needs to be assessed periodically - at least annually to ensure skills are maintained and staff are kept abreast of manufacturer updates.

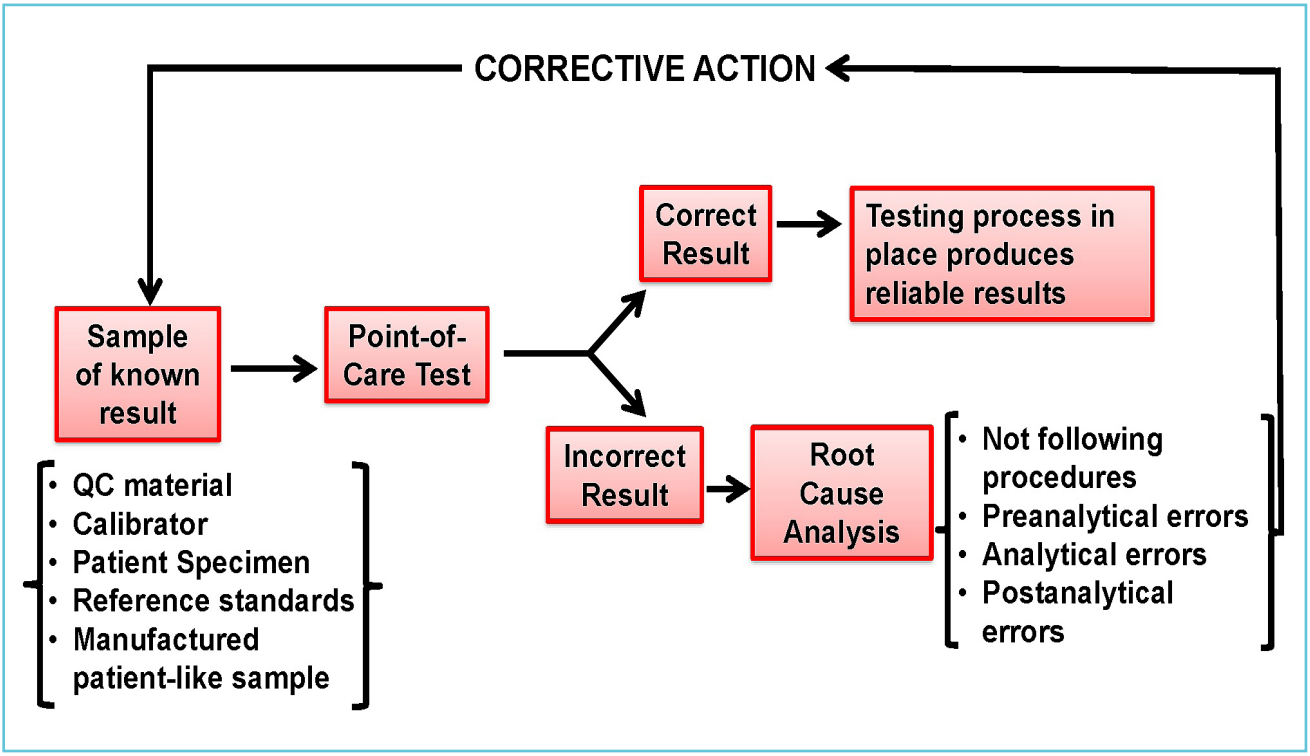
C. Developing a process to identify and mitigate errors

Errors in the pre-analytical, analytical and post-analytical stages of testing can affect the result and lead to misdiagnosis and incorrect management of the patient. Proficiency testing also known as external quality assessment (EQA) is an important tool to identify these errors because the test sample provided is treated like a patient specimen. Hence participation in an external EQA program is strongly recommended (Figure 1) and has shown to reduce errors.[3] In particular, EQA programs:

1. Identify if healthcare workers are adequately trained.
2. Identify if there are procedural deficiencies mentioned in the product insert but omitted in the final procedure.
3. Identify procedural deficiencies not mentioned in the product insert.

In Finland, Nissinen and co-workers[4] used an EQA program for evaluating group A streptococcal (GAS) antigen test in the hands of laboratory and nursing staff. Specimens were either GAS-negative, weakly positive or strongly positive.For GAS-negative samples, no significant difference in performance was observed between the laboratory and nursing staff (99.5% vs. 95.1% respectively). In contrast, laboratory staff performed statistically better for both strongly positive and weakly positive samples, with correct identifications being 98.9% vs. 95.1% and 79.3% vs. 65.3% respectively.[4]

Figure 1 Summary of the external quality assessment program showing how results can be used to identify errors in the testing process



The difference most likely was because laboratory technicians ensured they had a better understanding of the principle and showed exact compliance with test instructions (e.g. timing) and exposed to similar quality assurance processes as part of their routine work compared to nurses that work primarily with patient care issues. This experience enables them to make a better decisions when a test is weakly positive.[4]

Furthermore, this study showed that environment illumination could affect results and because this was not mentioned in the product insert, its importance was revealed through participation in the EQA and illustrated the usefulness of participation in EQA schemes. In another study, Skurtveit et al.,[5] evaluated physician office laboratories that used serological POC tests to identify infectious mononucleosis. Laboratories that were enrolled in an EQA scheme that had outdated test kits or kits close to their expiration date, did poorly in the assessment. This information helped them in establishing a quality assurance program that removed kits when they were close to their expiration date so that patient results were not misleading.

In situations where an EQA program is not available, an in-house scheme can be developed using split patient samples. Here, a patient specimen can be sent for testing with another instrument or using another operator to test the sample.[6] Acceptability criteria for sample correlation can be obtained from published guidelines[7] or using ± 2 or 3 standard deviations from the mean from quality control data for quantitative assays.[6]

In order to identify and mitigate errors an individual quality control plan (IQCP) can be developed. Traditional QC refers to daily running a sample that contains a normal or abnormal concentration of the analyte to be tested before patient testing. The frequency is tied to the stability of the analyzer's measuring system. However, with advances in technology, some measuring systems are stable for weeks or months.[8] The traditional quality control processes that were originally designed for large analyzers in centralized laboratories have become insufficient to address all the quality issues in POC testing. For instance, in certain point-of-care tests, the "analyzer" or measuring system, is often disposed-off soon after the test. As a result the Clinical Laboratory Standards Institute (CLSI) published the EP23-A, Laboratory Quality Control Based on Risk Management in October 2011.[9]

This guideline proposed that each test should have an IQCP and recommended a risk assessment approach to quality control, mapping out the testing process through the pre-analytical, analytical and post-analytical phases, to identify weak points in the process. Control mechanisms could then be placed at these points where there was a high probability of error to either prevent or monitor them and to take corrective action accordingly to maintain quality testing.[10]

This approach takes into consideration advances in technology by manufacturers for point-of-care instruments. In an attempt to continuously improve instrumentation several mechanisms have been put in place for POC tests by manufacturers to prevent reporting of unreliable results. Some examples of these quality assurance mechanism are:

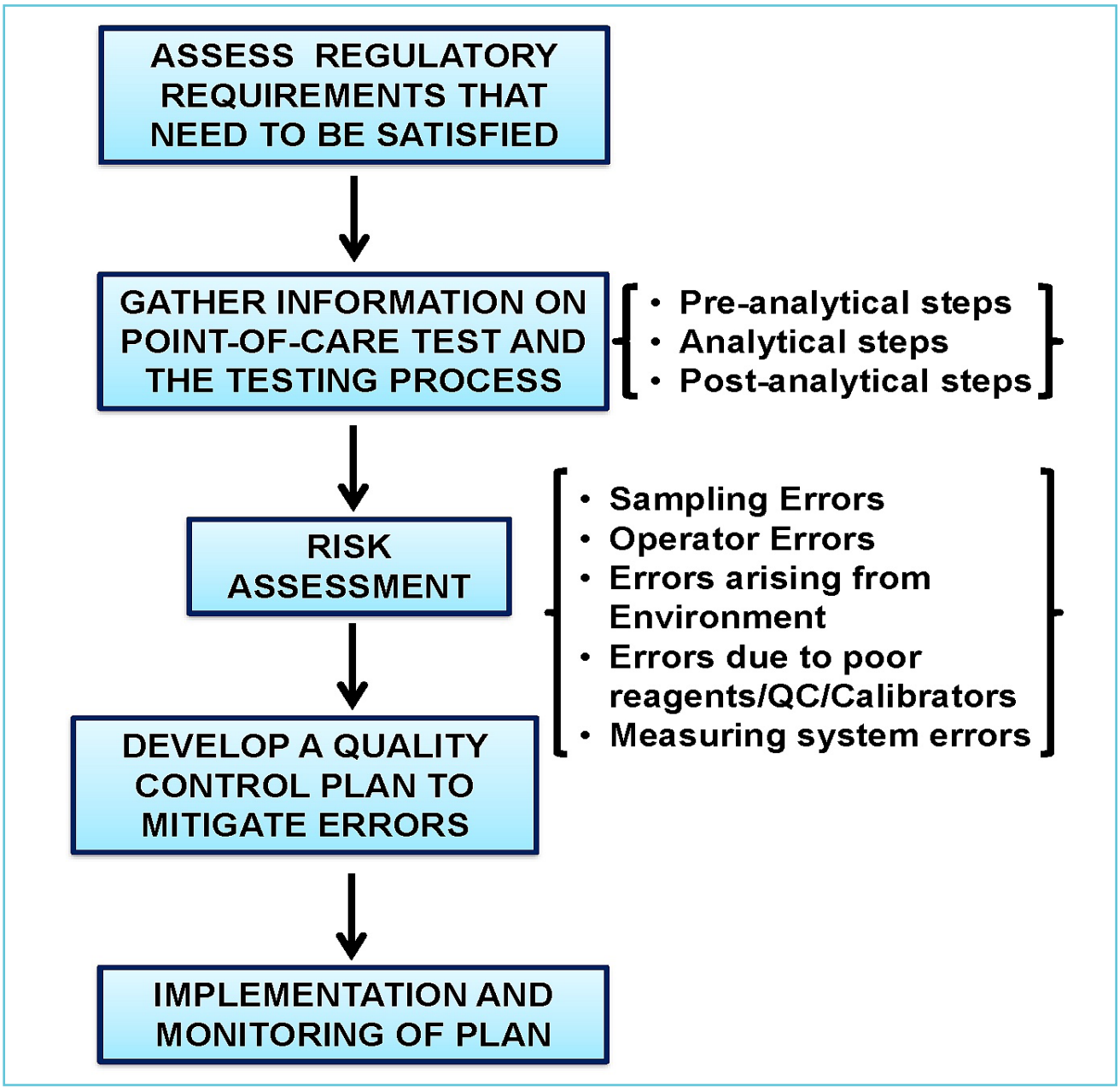
1. Reagents have barcoded expiration dates that prevent their usage if employed past this date.
2. Instrument lockout features prevent operator usage if the QC has failed or has not been run.
3. Instrument usage requires an operator-specific code ensuring qualified operators are testing patients.

4. Sensors in the instrument can detect air bubbles or clots and will not run patient samples unless this has been corrected.
5. For qualitative tests (e.g. pregnancy kit), a correct QC run is confirmed by the development of a strongly visible line.

The development of the IQCP involves the following steps (Summarized in Figure 2):[11]

1. Assessing any regulatory or accreditation requirements that need to be satisfied.
2. Gathering information about the instrument and the testing process for the analyte (s) from the manufacturer.
3. Risk Assessment - mapping the process to identifying procedural weaknesses.

Figure 2 Schematic showing the thought process in developing an IQCP (11)



4. Developing a Quality Control Plan to mitigate errors identified in the risk assessment.
5. Implementation and monitoring the Quality Control Plan to ensure that it is always appropriate, making adjustments as necessary.

D. Ensuring there is accurate documentation of all aspects of laboratory testing

Accurate documentation is important in ensuring the correct result is associated with the correct patient but with respect to QC, EQA, instrument maintenance, and performance improvement exercises instills a culture of accountability and therefore is an important aspect of any quality management system. It also helps provide potential metrics for service assessment and performance improvement.

CONCLUSION

Best laboratory practices are the cornerstone of diagnostic testing and essential for patient care and therefore important whether testing is performed inside or outside a hospital setting. Following best laboratory practices have highlighted problems in workflow and/or diagnostic processes that would have otherwise been missed. Furthermore, because the nature of POC testing involves a diverse personnel with different educational backgrounds, it is essential to educate healthcare professionals in these best laboratory practices to keep up pace with the extensive proliferation of POC testing and their increasing reliance as integral components of the patient's treatment.

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POCT accreditation ISO 15189 and ISO 22870: making the point

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ABSTRACT

ISO 22870 lists specific requirements for the quality and competence of point-of-care testing (POCT), which are intended for medical laboratories in conjunction with ISO 15189. POCT characteristics include the availability of a large number of devices 24 h/day, a variety of analytical methods, clinical settings inside and outside the hospital, and general non-laboratory staff. ISO 22870 accreditation for adequate POCT management therefore poses a challenge for laboratory medicine, which is charged with leading and coordinating POCT with a multidisciplinary committee. La Paz University Hospital has a complex multitest and multisite network that has been accredited since 2017. In our experience, the particularly crucial areas for POCT accreditation are method performance verification, internal and external quality assurance, staff training and competency, and continuous improvement. ISO 22870 and ISO 15189 accreditation have led us to improve numerous areas regarding the total testing process and, consequently, our patients' results.

1. ISO 15189 AND ISO 22870 ACCREDITATION

ISO 15189 specifies requirements for quality and competence in medical laboratories and can be employed by medical laboratories to develop their quality management systems and assess their competence [1]. ISO 22870 provides specific requirements applicable to point-of-care testing (POCT) and is intended for use in conjunction with ISO 15189 [2]. ISO 22870 applies when POCT is performed in a hospital, clinic, or healthcare organisation providing ambulatory care.

Neither ISO 15189 nor ISO 22870 should be considered goals in and of themselves but rather should be employed to confirm or recognise the competence of medical laboratories by regulatory authorities and accreditation bodies for the benefit of clinicians and patients.

2. TIMELINE FOR ISO 15189 AND ISO 22870 ACCREDITATION AT LA PAZ UNIVERSITY HOSPITAL

La Paz University Hospital is a tertiary public hospital located in Madrid (Spain) and is a referral centre widely recognised for its range of specialisations. The hospital is one of the largest in Spain, with approximately 1300 beds in 4 buildings, with several satellite facilities providing specialist services and 23 primary healthcare centres.

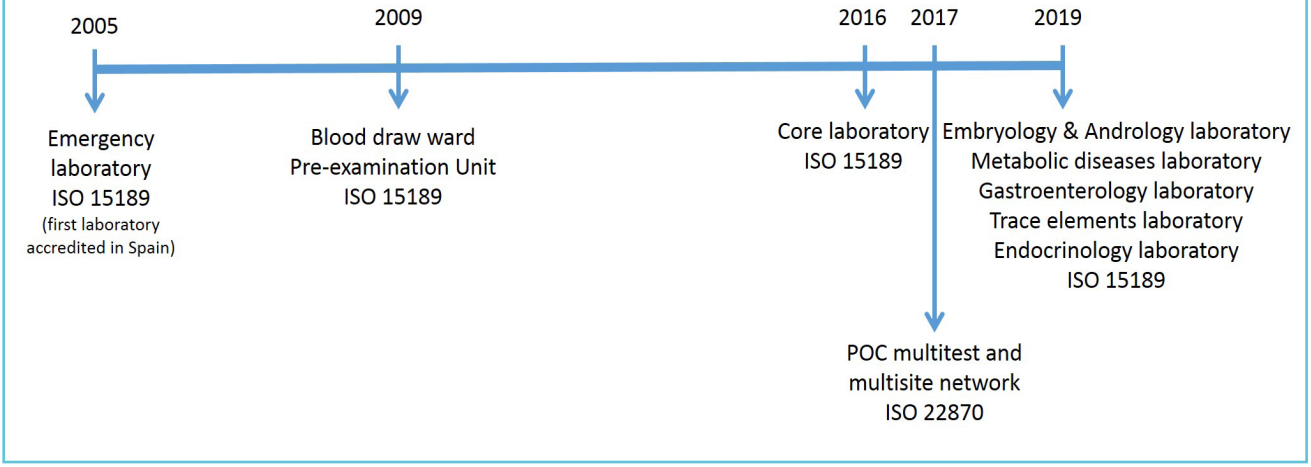
The Laboratory Medicine Department covers various areas, which have been accredited since 2005 (Figure1).

3. POINT-OF-CARE MULTITEST AND MULTISITE NETWORK ACCREDITATION

The POCT Unit of the Laboratory Medicine Department has led the hospital's POCT network over the last 22 years. The core of the POCT Unit includes the POCT Director, the POCT Coordinator and the head of the Quality section. There is also a multidisciplinary POCT committee, which is responsible for making decisions on a wide range of POCT-related topics and consists of the hospital's Board of Directors, hospital administration representatives, physicians and nursing personnel from medical and surgical services and staff from the information technology department, the laboratory medicine team and the POCT Unit.

POCT management has always been conducted in accordance with the requirements of ISO 22870

Figure 1 Timeline for ISO 15189 and ISO 22870 accreditation in La Paz University Hospital



for all the magnitudes included, and considering the previous experience with ISO 15189 in other laboratory areas. Figure 2 illustrates the development in this regard.

The POCT network currently includes 30 ABL90 Flex (Radiometer®) blood gas analysers, 2 DCA Vantage (Siemens®) glycated haemoglobin devices, 266 Accu-Chek Performa (Roche Diabetes®) nonc-onnected glucometers, one Sweat-Chek (Werfen®) sweat test device and 7 recently installed Accu-Chek Inform II (Roche Diagnostics®) connected glucometers (Table 1).

At this time, only the 3 nonconnected glucometers employed in the blood draw ward have been included in the accreditation scope. The lack of connectivity and the large number of devices located in numerous clinical settings are important limitations in meeting the requirements.

4. KEY POINTS AND CHALLENGES IN ISO 22870 ACCREDITATION

As with ISO 15189, ISO 22870 focuses on quality assurance and competence; however, POCT has particular characteristics, including a large number of devices available 24 h/day, various analytical methods, clinical settings inside and outside the hospital and general non-laboratory staff [3]. Adequate POCT management therefore poses a challenge for laboratory medicine, which is charged with leading and coordinating POCT with a multidisciplinary committee as a specific requirement of ISO 22870 accreditation [2] [4].

Globally, the ISO 22870 accreditation requires compliance with all the steps before implementing a new test and with the required activities to perform after its incorporation in clinical practice (Figure 3). Due to the particular characteristics of POCT, the following areas are particularly crucial: method performance verification, internal and external quality assurance, staff training and competency and continuous improvement [5][4], all of which significantly affect the quality assurance of patient results.

Method performance verification

ISO 22870 requires verification of the main analytical performance of the methods according to the specifications established by laboratory medicine, such as imprecision and systematic error. When implementing a new analytical

Figure 2 Timeline for ISO 22870 accreditation in La Paz University Hospital

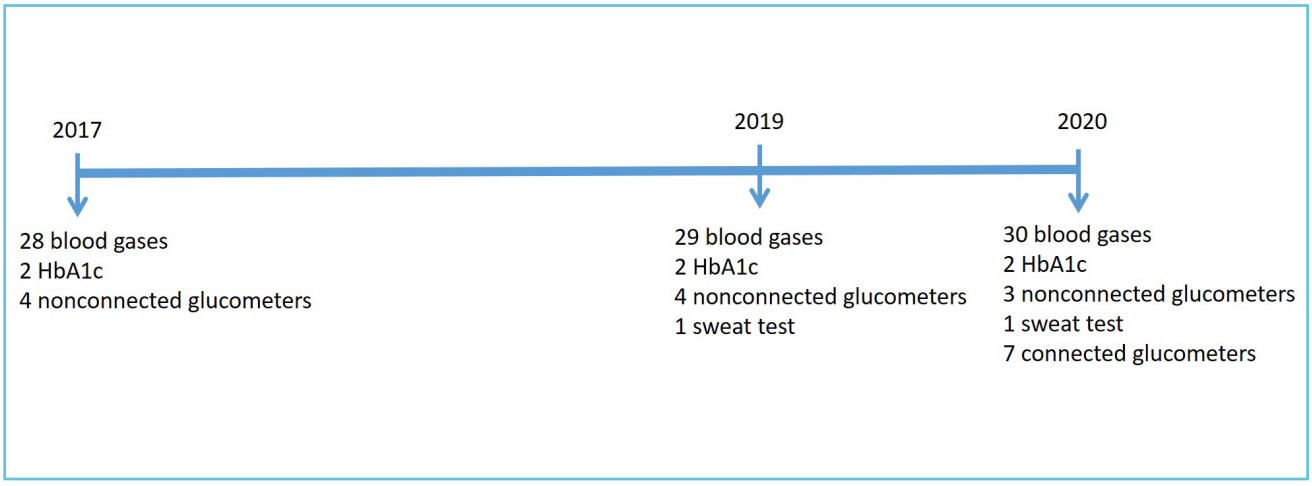
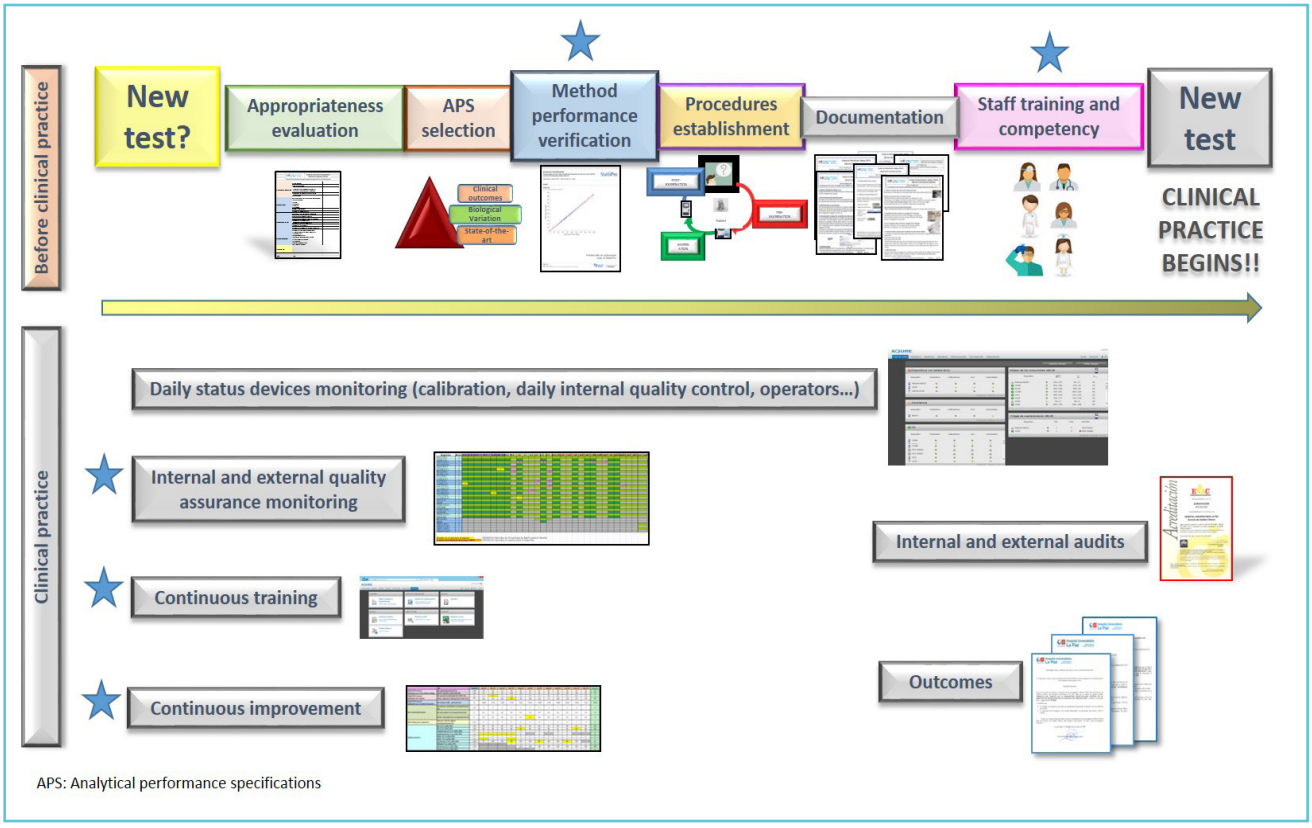


Table 1 Current POCT network at La Paz University Hospital

POCT (n)	Clinical setting	Analysers
Blood gases (30)	Emergency Laboratory	2
	Preanalytical Unit	2
	Delivery Room	2
	Paediatric Emergency Department	1
	Neonatal ICU Department	3
	Paediatric ICU Department	1
	Paediatric Reanimation and Surgery Unit	1
	Paediatric Haemodynamic Unit	1
	Emergency Department	2
	Coronary Care Unit	1
	Pulmonology Department Doctor's office	1
	Pulmonology Department	1
	Nephrology Department	1
	ICU Department 1	1
	ICU Department 2	1
	Burn Unit	1
	Reanimation Unit 1	1
	Reanimation Unit 2	1
	Reanimation Unit 3	1
	Surgery Suite 1	1
	Surgery Suite 2	1
	Surgery Suite 3	1
	Cantoblanco Hospital	1
	Carlos III Hospital	1

HbA1c (2)	Adult Diabetes Unit	1
	Paediatric Diabetes Unit	1
Nonconnected glucometers (266)	84 different departments in the hospital	266
Sweat Test (1)	Paediatric Pulmonology Unit	1
Connected glucometers (5)	Neonatal ICU Department	3
	Paediatric ICU Department	1
	Paediatric Diabetes Unit	1
	Burn Unit	1
	Blood Draw Ward	1

Figure 3 Steps before and after implementing a new test in clinical practice



method, verification of the interchangeability of patient results is important for assessing the method's clinical impact on patient care. POCT commonly involves a large number of devices installed in different locations. A patient can be treated in several clinical settings, such as the emergency department, intensive care unit, and internal medicine. Consequently, the interchangeability of patient results should be previously verified among all POCT devices and against the central laboratory methods [6][7].

In our hospital, we evaluate the analytical performance of a POCT analyser following the Clinical Laboratory Standards Institute protocols. We then assess the interchangeability of patient results with the other POCT and laboratory analysers employed for the same measurand in clinical practice [7].

Internal and external quality assurance

To evaluate internal quality control on a daily basis and monitor the internal and external quality assurance periodically in accordance with ISO 22870 requirements, the connectivity of POCT devices is helpful. When a large number of devices are included in the POCT network, this connectivity becomes indispensable [7]. On the whole, POCT data management systems are improving; however, there remain some limitations, such as the setting of the analytical performance specifications established by the laboratory directly in the analyser and the inability to automatically obtain reports with the imprecision and systematic error results for each measurand at each level from each device. This situation implies that laboratory medicine needs to develop manual procedures to collect and assess this important information, which, in our case, entails the management of more than 4000 results each month. We group and record the internal quality control and external quality assurance results in a manual dashboard to be evaluated according to our analytical performance specifications as a whole [8]. All deviations are evaluated, and the corresponding corrective actions are taken if necessary (e.g., replace a POCT analyser, remove a defective batch of glucose strips).

Staff training and competency

According to the ISO 22870 requirements, all operators need to be trained before using a POCT device. The particular POCT challenge here when compared with a central laboratory is that the personnel are generally non-laboratory, and there could be a large number of staff with a high rate of turnover [3]. Connectivity and POCT data management systems are once again an essential aspect of this situation [8].

In our hospital, all operators undergo initial training following the particular program established by the laboratory, after which the training is recorded, and the operator becomes an active user in the data management system to use the respective POCT analyser. We also provide online continuous training for the staff who perform POCT after starting the use of an analyser in clinical practice. Based on this training and in collaboration with the clinical departments/units, we annually reassess the competence of all operators, following the ISO 22870 requirements [8].

It is important to document all measurement procedures for the staff in the various clinical settings and in laboratory medicine, including internal quality control, calibrations and other procedures [4]. In our hospital, the latest version of these documents is available to all staff from any computer in the hospital [8].

Continuous improvement

In POCT (and specifically with a complex network such as ours), it is especially important to properly manage the indicators in accordance with ISO 22870 [4]. We select and periodically review the key performance indicators that are

representative of the various aspects of the global POCT process, which is useful for identifying opportunities to improve and evaluate the laboratory's contribution to patient care [9][10].

Table 2 shows the various areas included in our improvement dashboard.

The average of the key performance indicator results from all clinical settings is recorded in the improvement dashboard on a monthly basis. Both the average and each deviation in each particular clinical site below the target is reviewed, and corrective action is taken when necessary (providing more training for specific staff, performing new procedures for preventing pre-examination errors, etc.).

5. PATIENT CARE OUTCOMES

All of the above tasks related to laboratory medicine and POCT accreditation are performed in the service of patient care, and their impact should therefore also be evaluated. In our hospital, we implement and conduct several projects in collaboration with other professionals in various clinical settings, such as in

Table 2 Improvement dashboard with key performance indicators

	Objective of the evaluation	Key performance indicators
1. Global POCT process	Adequate use of POCT in each clinical setting	1.1. Percentage of the tests reported in LIS over the tests performed in POCT analysers
	Duplicate test requests to laboratory and POCT from the same clinical setting	1.2. Percentage of the tests reported in LIS by laboratory over the tests reported in LIS by POCT from the same clinical setting
	Use of material resources	1.3. Difference between the number of tests considering the consumables used and the tests performed in POCT analysers
2. Extra-examination phase	Sample and analyser management by POCT operators	2.1. Percentage of the tests with pre-examination errors (blood gases) or instrument alerts (glucometers) over the total tests performed in POCT analysers
	Patient identification by POCT operators	2.2. Percentage of the tests with patient identification errors (electronic medical record ≤3 digits) over all the tests reported in LIS by POCT

3. Examination phase	Fulfilment of analytical performance specifications established by laboratory	3.1. Percentage or number of results of variation coefficients within analytical performance specifications over the total results 3.2. Percentage or number of results of total errors within the analytical performance specifications over the total results
4. Staff training and competency	Personal identification strategy by POCT operators to ensure that only trained operators use the POCT analysers	4.1. Percentage of the tests performed by the POCT operator with the highest activity over all the tests performed in every clinical setting

the Pulmonology and Nephrology Departments [11][12]. These projects include clinical, operative and economic outcomes to gain an overview of the impact of POCT in clinical practice.

6. CONCLUSIONS

In our experience in La Paz University Hospital, ISO 15189 and ISO 22870 accreditation has led us to improve numerous areas regarding the total testing process. Due to the particular characteristics of POCT, the particularly crucial areas for ISO 22870 accreditation are method performance verification, internal and external quality assurance, staff training and competency, and continuous improvement, all of which have an effect on the quality assurance of patient results.

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Utilizing point-of-care testing to optimize patient care

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ABSTRACT

Background

Point-of-Care Testing (POCT) is clinical laboratory testing conducted close to the site of patient care. POCT provides rapid turnaround of test results with the potential for fast clinical action that can improve patient outcomes compared to laboratory testing.

Methods

Review the advantages of POCT and discuss the factors that are driving the expansion of POCT in modern healthcare

Results

Portability, ease-of-use, and minimal training are some of the advantages of POCT. The ability to obtain a fast test result and the convenience of testing close to the patient are increasing the demand for POCT. Healthcare is finding new opportunities for growth in the community and POCT is facilitating this growth.

Conclusions

This article will review the advantages of POCT and how POCT is complimenting patient care in a variety of settings.

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INTRODUCTION

Point-of-Care Testing (POCT) is clinical laboratory testing conducted close to the site of patient care. (1) There are many POCT devices available for a variety of acute and chronic illnesses: glucose meters, hemoglobin A1c and ketones for diabetes; hemoglobin/hematocrit and gastric or fecal occult blood tests for anemia and bleeding; erythrocyte sedimentation rate and C-reactive protein (CRP) for inflammation; urine and whole blood human chorionic gonadotropin (hCG) for pregnancy, luteinizing hormone (LH) for ovulation, follicle stimulating hormone (FSH) for menopause, premature rupture of membranes (PROM) and fern test for delivery, semen counts for male fertility; urine dipsticks, urine and whole blood creatinine, urea, and microalbumin for renal function; cholesterol, HDL, LDL and triglycerides for lipids; troponin and brain natriuretic peptide (BNP) to diagnose myocardial infarction and manage heart failure; prothrombin (PT), international normalized ratio (INR), activated clotting time (ACT) and activated partial thromboplastin time (aPTT) to assess coagulation; urine drugs of abuse testing for addiction and emergency management; blood gas, electrolytes, basic metabolic and comprehensive chemistry panels; rapid streptococcus, mononucleosis, human immunodeficiency virus (HIV), helicobacter pylori; amines and pH for bacterial vaginosis, respiratory syncytial virus (RSV), influenza, and most recently SARS COVID-2 virus tests. The menu of POCT has grown rapidly over the past 10 – 15 years and continues to expand continuously with the introduction of new tests. The global POCT market is expected to exceed US $44.6 Billion by 2025 with a compound annual growth rate of 9 %.(2)

POCT are simple devices or visually interpreted dipsticks and kits. POCT is low maintenance and easy to use. A majority of POCT is waived complexity under the US Clinical and Laboratory Improvement Amendments of 1988 (CLIA), which have minimal requirements for testing. (3) CLIA waived POCT requires no performance validation prior to routine patient testing. There is no formal operator training and competency required. Operators must only follow manufacturer instructions for use. So, CLIA waived tests can be performed by non-laboratory staff with only a high school education and minimal test orientation. This allows for rapid implementation when needed. Modern POCT devices have computerized data management that collects the operator and patient ID and can transmit this information with the test result to the electronic medical record. POCT data management and operator/quality control lock-out features enhance regulatory compliance.(4, 5) POCT is portable allowing the test to be transported easily to the patient. POCT utilizes unprocessed urine and whole blood, so capillary fingerstick samples can be utilized. This facilitates testing at locations where phlebotomy isn't available.

POCT SETTINGS

POCT disrupts the current health care model where a physician sees a patient, orders a test, the patient has blood collected, the sample is sent to a lab, later results are reported back to the physician, the physician acknowledges the result and takes clinical action. With the current model turnaround of test results depends on the distance to transport a specimen to a laboratory and the speed of laboratory instrumentation. Delays can occur and results may not be delivered for several hours or days depending on the test and the complexity of laboratory workflow.

POCT brings the laboratory to the patient, simplifies the testing process and shortens the time to clinical action.

The convenience of POCT and the potential for rapid turnaround of test results find applications for POCT in a variety of healthcare settings. Historically, POCT was first implemented on hospital nursing units to allow for rapid management of acute inpatients in the intensive care units, operating rooms, and emergency departments. But outpatient use of POCT in physician offices and clinics soon followed. POCT in the clinic allows physicians to counsel patients and make treatment adjustments while the patient is being seen.

Currently, POCT has expanded beyond the clinics and is being used by school nurses and emergency medical staff at sporting events, concerts, and festivals. POCT is supplied in medical transport vehicles, helicopters, and ambulances. POCT is available on cruise ships, trains, commercial airlines, and is packed on travel tours, expeditions, and POCT (blood gas analyzers) has even been taken to the top of Mount Everest. POCT has been deployed by governments in military field hospitals, disaster relief, and medical aid to remote areas of developing countries. Exposure to extremes of temperature, humidity and other environmental conditions is a challenge in some settings. Storage and testing outside of controlled hospital or clinic conditions is a consideration in managing the quality of test results.

PATIENT-CENTERED CARE

Healthcare is moving toward patient-centered care which empowers the patient to take a role in their care. Recent regulatory changes in the US give patients the right to access their personal health information under the Health Insurance Portability and Accountability Act (HIPAA). Amendments to CLIA in 2014 allow laboratories to give completed test reports to the patient or their representative. The final HIPAA rules were issued jointly by the Centers for Medicare & Medicaid Services (CMS), the Centers for Disease Control (CDC), and the Office of Civil Rights (OCR) which is the agency that enforces HIPAA. Kathleen Sebelius, the Department of Health and Human Services (DHHS) Secretary summarized the impact of patient access to laboratory test reports, “Information like laboratory results empower patients to track health progress, make decision with healthcare professionals and adhere to treatment plans.”(6)

Patient portals are websites that healthcare institutions have developed as a response to the HIPAA regulatory changes. On the patient portal, patients can see their laboratory results, ask their caregiver questions, request new appointments, view personal medical information, and pay bills. Some institutions are even providing full access to the physician clinical notes in the medical record. Patient portals are a one-stop shop for the patient’s healthcare needs. POCT results as well as laboratory results are visible. While physicians have been the traditional client of the laboratory, our test results and comments that accompany those results, need to change so that the comment is understandable and interpretable by the general consumer without a medical background. We need to rethink common abbreviations like QNS (quantity not sufficient) or technical terms like icterus in lieu of common descriptors like “insufficient sample volume to perform test” or “bilirubin interference”.

With the recent COVID pandemic more emphasis is being placed on telehealth and remote healthcare. Patient portals are just one means of connecting physicians with patients who may be on quarantine or working from home. POCT plays a role in these changing healthcare models. Home testing devices can download results into the patient’s medical record for the physician to review. Patient self-testing devices like PT/INR and glucose meters are available, but

data from monitoring devices like continuous glucose monitors, blood pressure, pulse oximeters and even weight from digital scales can also be downloaded to monitor the patient remotely. Video conferencing can monitor the condition and demeanor of the patient, assess for overall status, and even take size measurements to assess wound recovery. Wearable devices and health applications in smart watches can monitor temperature, pulse, and other parameters to warn of potential fever, or alert to ovulation for fertility cycles. More health information is available to physicians remotely than ever before.

CHANGING HEALTHCARE MODELS

Delivery of healthcare is changing to better meet patient needs. People are busier than ever during the COVID pandemic, working from home, virtual schooling their children, on top of the daily responsibilities of cooking, cleaning, and maintaining the house. Getting a doctor appointment may be challenging with fewer appointments available and the risk of contact with other patients in the waiting rooms. So, doctor-on-call services are becoming more popular. These services allow the patient to rest where they are while a doctor or nurse practitioner comes to them. Originally developed in partnership with hotel concierge to provide service for tourists or visitors who may get sick while traveling and not know where to turn. Now, phone applications are available to place a request (similar to calling an uber or lyft car service) where the health problem is described, and the doctor-on-call responds with an estimated time of arrival. The doctor-on-call goes to the patient's hotel room, home or apartment, takes a medical history, performs a basic physical exam, and offers starter packs of medications until the patient gets home or can have a pharmacy deliver a full prescription. POCT is offered by the doctor-on-call with tests such as rapid strep, influenza, pregnancy, urine dipsticks. With the recent COVID pandemic, this service can even collect nasal swabs to deliver for laboratory testing while the patient quarantines at home or in their hotel room.

Pharmacies are also taking a greater role in healthcare. People often wake up not feeling well but cannot get an appointment the same day to see their routine doctor. So, many pharmacies are opening clinics where the patient can sign-up for a same day appointment and wait in their car until called in for their appointment. This decreases the contact between patients in a waiting room. These pharmacy clinics provide a variety of services including pre-employment, sports and school physicals, immunizations, allergies, rashes, bites, screening for sexually transmitted infections, travel medicine, diabetes screening, pregnancy, and smoking cessation. Some even have EKG and X-ray machines available on-site to assess for conditions, sprains, and fractured bones. These clinics offer a range of POCT including PT/INR, influenza, glucose and hemoglobin A1c, urinalysis, rapid streptococcus, mononucleosis, pregnancy and even molecular POCT for SARS CoV-2. The pharmacy clinic performs phlebotomy and can collect specimens to send out for other tests not available on-site. Some of these clinics are even being run by larger medical institutions as a means of community outreach and to provide for care of lower acuity conditions as an outpatient rather than an emergency room visit. Some pharmacies and healthcare institutions are even offering drive-thru healthcare services for collection of nasal swabs for SARS CV-2 testing and as flu vaccination centers.

CONCLUSIONS

POCT is an increasingly popular means of providing laboratory testing with rapid turnaround of test results close to the patient. A wide menu of POCT is currently available and new tests are

continuously being introduced on the market. POCT is utilized in a variety of healthcare settings and is taking on new roles with the recent COVID pandemic. Doctors-on-call and pharmacy clinics are just two examples how healthcare is connecting with the community to drive patient-centered care. The patient is in the driving seat, taking charge of their health and demanding healthcare services that meet their needs at their convenience and timeframe. The future of POCT promises new sensors, wearable devices and smart technologies that are less invasive and can better connect the patient with their physician. The convenience and ease-of-use will find new POCT applications and develop novel ways that laboratory diagnostics can improve patient outcomes in the future.

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In this issue: POCT – making the point

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POCT: an inherently ideal tool in pediatric laboratory medicine

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ABSTRACT

Point of care testing (POCT) is important in the provision of timely laboratory test results and continues to gain specific appreciation in the setting of pediatric healthcare. POCT platforms offer several advantages compared to central laboratory testing, including improved clinical outcomes, reduced time to diagnosis, length of stay, and blood volume requirements, as well as increased accessibility. These advantages are most pronounced in acute care settings such as pediatric emergency departments, intensive care units, and in remote settings, wherein rapid patient assessment and prognostication is essential to patient outcomes. The current review provides an overview and critical discussion of the evidence supporting clinical implementation of POCT systems in pediatric clinical decision-making, including but not limited to the diagnosis of viral and bacterial infection, identification of critical glucose and electrolyte dysregulation, and prognostication of post-operative inpatients.

Important considerations for test result reporting and interpretation are also discussed, including analytical concordance between POCT systems and central laboratory analyzers as well as availability of pediatric reference intervals for key analytes on POCT systems. Notably, a paucity of evidence-based pediatric reference intervals for test interpretation for critical care parameters on POCT platforms is highlighted, warranting further study and unique consideration prior to clinical implementation.

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BACKGROUND

Point of care testing (POCT) refers to laboratory testing performed in near-patient settings as opposed to the central laboratory. Narrowing the clinical-laboratory interface, POCT has become increasingly important in the provision of accurate and timely laboratory test results in both acute and remote patient settings. Longer turnaround-time (TAT) poses a significant barrier to rapid test interpretation, lengthening the time to appropriate clinical decision-making with known patient impact (1). Several reports have demonstrated both clinical and economic benefits to the implementation of POCT systems, including reduced TAT, length of stay, mortality, and enhanced cost effectiveness in a variety of clinical settings (2). While clinical laboratories were initially hesitant to adopt such technology due to concerns regarding analytical performance, increasing data suggests improved analytical concordance between common laboratory-based instruments and newer POCT platforms for several analytes, providing further support to their reliability for direct clinical implementation. Recent developments in POCT platforms have also expanded available assay menus to include key chemistry and immunoassay parameters, such as troponin and creatinine, further increasing their potential clinical utility.

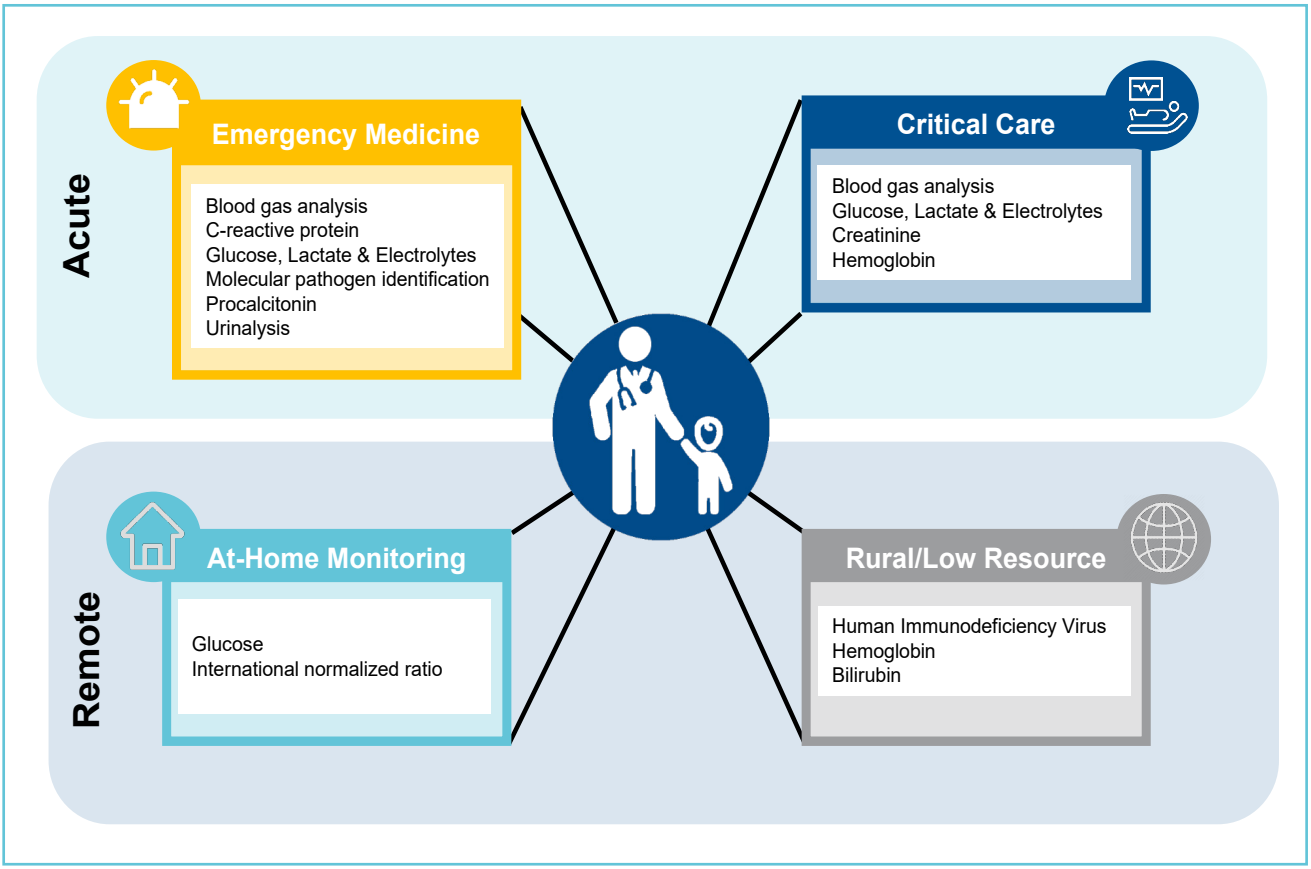
The clinical implementation of POCT platforms in pediatric institutions presents unique advantages as well, including smaller sample volume requirements. This is particularly true for emergency and critical care departments wherein rapid patient assessment and prognostication is essential to patient outcome. In this review, we will discuss the current state of POCT in pediatric healthcare centres, including its application in emergency, intensive care, and remote settings, and discuss unique considerations required for test interpretation (e.g. pediatric reference intervals) on POCT systems in children and adolescents (Figure 1).

ACUTE SETTINGS

Pediatric emergency medicine

Rapid assessment and diagnosis of acute conditions is essential in emergency departments (EDs) to ensure appropriate triage, timely intervention, and to prevent unnecessary hospital admission. As POCT systems evolve to include more complex testing menus, their value in pediatric emergency medicine is being increasingly recognized and supported. Fever is one of the main clinical presentations requiring consultation in pediatric emergency medicine. In febrile pediatric patients, it is essential to rapidly diagnose the infection source (e.g. bacterial or viral) as well as identify patients at high risk of serious bacterial infection. C-reactive protein (CRP), a positive acute phase reactant, is a valuable biomarker in the rapid identification of inflammatory processes. While most commonly measured by laboratory-based chemistry analyzers, few studies have evaluated the clinical and economic impacts of implementing POC CRP testing in pediatric EDs. In a study of 68 febrile pediatric patients, the availability of real-time POC CRP results resulted in a significant drop in ED consultation and medical intervention, without significant change in patient outcome (3).

Figure 1 Clinical utility of POCT in pediatric healthcare settings



Additionally, in a large prospective study of 283 well-appearing febrile infants, strong analytical concordance was observed between POC QuikRead go® and laboratory-based Abbott ARCHITECT platforms (4), resulting in accelerated diagnostic management of febrile patients, optimized ED patient flow, and substantially reduced length of stay (4). These findings are supported by other studies reporting decreased length of stay (5) as well as reduction of immediate antibiotic prescribing post-implementation of POC CRP testing (6,7). In addition to CRP, procalcitonin (PCT), a 116-amino acid protein produced by parafollicular cells, has gained considerable appreciation in the literature as an ideal marker of bacterial infection due to its rapid concentration peak post-endotoxin exposure (8). Recent evidence supports POC PCT testing in initial ED assessment of young febrile infants to improve early recognition of bacterial infection (9,10). However, its advantage over CRP in a POCT setting is still unclear and further research is warranted. In addition to PCT and CRP, POCT for direct molecular pathogen identification, including respiratory syncytial virus (RSV) and influenza A/B, has become increasingly adopted in pediatric EDs. Several reports suggest excellent analytical and clinical performance of both PCR and antigen-based POC assays for molecular pathogen identification in pediatric settings. Side-by-side comparisons of antigen-based respiratory syncytial virus (RSV) and influenza A/B assays relative to laboratory-based nucleic acid amplification tests have reported excellent analytical concordance in pediatric ED settings (NPV>90%, PPV>89%) (11). Subsequent clinical advantages have been observed post-implementation, including reduced length of stay (12), improved

hospital workflow (13,14), cost effectiveness (15), as well as decreased laboratory investigations and antibiotic/antiviral ordering in peak flu season (16), providing further rationale for clinical implementation.

Finally, it is important to note that urinalysis and blood gas analysis also play important roles in pediatric ED assessment. Rapid testing of blood gases, glucose, lactate, ionized calcium, and electrolytes on POCT systems is an integral component to the assessment of children presenting to the ED with acid-base disturbances, tissue damage, and dyselectrolytemias. Indeed, the implementation of POCT blood gas analyzers in EDs has been shown to shorten the laboratory process, allowing for quicker discharge with proper training and education (17). Dipstick and automated urinalysis at the POC have also demonstrated significant value in the identification of urinary tract infection (UTI), particularly in young children (18–20). However, rapid identification of pyuria by urine dipstick in children has been correlated to unnecessary antibiotic exposure, suggesting diagnostic accuracy of urine dipstick is suboptimal and waiting for culture results should be considered prior to antibiotic prescription (21). Identification of hematuria via urinalysis at the POC has also demonstrated clinical value in the assessment of kidney disease as well as urinary or renal blockages/obstructions in pediatric ED settings (22).

Pediatric critical care units

While increasing implementation of POCT systems in pediatric EDs is evident, the value of POCT in pediatrics is most clearly demonstrated in intensive care units (ICU), wherein rapid TAT and test result interpretation is integral to appropriate patient diagnosis and management. Particular analytes of interest in this clinical context include blood gases, glucose, and electrolytes, as discussed below.

Blood gas analysis is often used as a metric of overall metabolic function and health, wherein acid-base disturbances are common among critically ill patients. As frequent blood gas and pH assessments are essential for patient management in pediatric ICUs (PICUs), POCT provides an ideal service to ensure rapid result reporting and interpretation. Several analytical and clinical evaluations of POC blood gas instruments in ICU departments have been reported. Specifically, analytical evaluations of the i-STAT (Abbott Diagnostics) and epoc (Siemens Healthineers) systems have demonstrated excellent concordance with the central laboratory for main blood gas parameters (pH, pCO2, and pO2; r>0.99) in pediatric settings (23,24). Several clinical benefits have also been observed post-implementation, including improved cost-effectiveness (25), quality of care (25), and significant reductions in red blood cell transfusions in low-birth weight infants, which are often required due to phlebotomy-induced anemia (26). It is also important to note that blood gas analyzers can be prone to interferences. The use of syringes with minimal liquid heparin is recommended to mitigate this effect, although more research is required to compare analytical performance when using liquid and dry balanced heparin syringes (27).

Glucose dysregulation is very common in critically ill patients and is associated with adverse outcomes, including organ failure and mortality (28). This is particularly important for patients in the neonatal intensive care unit (NICU) wherein glucose dysregulation is highly prevalent and close monitoring is required. Indeed, the neonatal period is characterized by a normative phase of transitional hypoglycemia; however, prolonged periods of critically low blood glucose can induce serious complications, such as cerebral ischemia, seizures, long-term neurodevelopmental damage, and mortality (29,30). As hypoglycemia often presents asymptomatically, laboratory-driven investigation is critical

to prevent unnecessary and adverse outcomes. Consequently, the American Academy of Pediatrics recommends serial blood glucose monitoring in both symptomatic and asymptomatic neonates at increased risk of glucose dysregulation. In addition, hyperglycemia is common in ICU patients, resultant primarily from physiologic stress caused by surgery, respiratory distress, and/or sepsis. Numerous studies have therefore assessed potential clinical advantages of implementing POCT systems for glucose measurements in NICUs and PICUs (31–33). In addition, studies have also sought to assess the analytical performance of POCT devices. For example, modern POCT devices, such as the StatStrip (Nova Biomedical) (31) and iSTAT (Abbott Diagnostics) (33,34), have demonstrated excellent concordance with central laboratory blood glucose assessments in critical care settings. Despite reported concordance, it is important to consider specimen type in test interpretation (e.g. capillary/venous whole blood, plasma, serum), particularly when both POC and laboratory-based analyzers are being used in patient monitoring.

Electrolytes are vital to maintaining whole-body homeostasis required for regular metabolic functioning. Due to a number of inducing factors, such as chronic disease (e.g. respiratory disease, renal failure) (35), inappropriate intravenous administration (36), acute critical conditions (i.e. sepsis, severe burns, trauma, brain damage, heart failure) (37), or major surgery (38), patients in the ICU often present with electrolyte imbalances. This dysregulated state often goes undetected and has been associated with a five-fold increased risk of mortality in such patients (35). Given the high prevalence and potential clinical severity of electrolyte abnormalities, POCT offers unique advantages in mitigating avoidable poor outcomes in ICU patients, by reducing TAT and subsequently leading to more rapid test interpretation. Indeed, several studies have evaluated the analytical accuracy of POC analyzers compared to central laboratory systems in electrolyte assessment. For example, acceptable clinical concordance between both the i-STAT (Abbott Laboratories; (34)) and Xpress analyzer (Nova Biomedical; (39)) with central laboratory instruments have been observed. However, other reports have demonstrated a significant bias in key electrolytes reported at the POC in ICUs (40,41). Several factors may contribute to the disparities observed in POC versus central laboratory testing, such as differing sample matrices (i.e. whole blood versus serum/plasma) and interferences in POC devices (e.g. heparin). Further research is needed to evaluate analytical performance of new instruments as they are developed. Importantly, no studies have assessed the clinical impact of electrolyte POCT in NICU and PICU patients; thus, this warrants further investigation to delineate their role in these clinical settings.

Peri- and post-operative patient management

POC instruments have also demonstrated clinical value in the peri- and post-operative setting, particularly in the measurement of creatinine, lactate, and hemoglobin. It is well appreciated that post-operative pediatric patients undergoing major cardiac surgery are at disproportionately higher risk of developing acute kidney injury (AKI), especially those on cardiopulmonary bypass (42). Recent developments in POCT have enabled measurement of known AKI marker, creatinine, with anticipated value in this setting. Few reports have assessed the analytical and clinical performance of POC creatinine testing in post-operative patients. In a study of 498 infants admitted to the PICU following cardiac surgery, Kimura et al. observed an excellent correlation between ABL800 (Radiometer) POCT platform (whole blood) and a central laboratory (serum) analyzer (r=0.968) (43). However, the clinical significance of creatinine measured at the POC

relative to laboratory-based settings was not conclusive. Specifically, despite encouraging analytical concordance, the incidence of AKI diagnosis among patients differed significantly across platforms, with POCT demonstrating significantly higher identification rates. Differential clinical outcomes may be partially due to improved detection of abnormal creatinine levels at the POC as a result of increased test frequency as compared to the central laboratory. However, with repeated testing, there is also an increased risk of misidentifying elevated creatinine (43). As Kimura et al. were the first to assess creatinine POCT in pediatrics, future research is warranted to elucidate both the analytical performance and clinical utility in this setting. In addition to creatinine, lactate assessment at the POC has demonstrated value as a predictor of morbidity and mortality in post-operative pediatric patients (44). Increasing reports have highlighted particular value following congenital heart surgery (CGS), wherein tissue oxygen delivery is compromised and often complicated by liver and renal dysfunction (45). Serial lactate testing is thus considered standard practice following CGS, and is often performed on POCT systems due to lower TAT and demonstrated analytical concordance with laboratory-based analyzers (46,47). Additionally, post-operative goal-directed therapy for blood lactate assessment via POCT resulted in a significant drop in overall mortality in NICU patients (48). However, it is important to note that some studies evaluating POC lactate testing have demonstrated reduced reproducibility at low concentrations (47) and systemic biases relative to the central laboratory (46,47). Clinical laboratories should ensure to monitor POC lactate performance relative to central laboratory testing, particularly if both are being used for patient assessment. Finally, hemoglobin is frequently ordered in the perioperative setting (49) as anemia is extremely common herein and is associated with increased complications, including mortality (50). To ensure timely clinical decision-making regarding potential transfusions, several studies have evaluated the analytical performance of hemoglobin testing on POCT systems in the peri-operative setting. A formative study by Spielmann et al. evaluated the analytical performance of arterial hemoglobin measurement across several POCT platforms in a cohort of pediatric patients undergoing major surgery. Specifically, blood was drawn from an arterial catheter several times during surgery and subsequently assessed on four POCT platforms (GEM Premier 3000, ABL 800, GEM OPL, HemoCue B-Hemoglobin) and compared to a central laboratory analyzer (Sysmex XE 2100) (51). All POCT devices demonstrated excellent concordance ($r>0.95$) and minimal bias (<1%) with respect to the reference method (51). These findings are supported by other studies assessing the accuracy, precision, and practicality of capillary hemoglobin measurement on three POC devices (capillary hematocrit, HemoCue Hb210+, and i-STAT,) relative to central laboratory measurement, demonstrating acceptable concordance ($r>0.91$) (52). Reported analytical comparability is encouraging, especially given differences in analytical methodology across testing platforms. Specifically, most POCT platforms indirectly calculate hemoglobin levels based on hematocrit measurement, whereas central laboratory analyzers often employ flow cytometry. Importantly, no studies have assessed the clinical advantages of implementing POC hemoglobin testing in this setting and thus further clinical evaluations are warranted.

REMOTE SETTINGS

In addition to the assessment of critical conditions in emergent settings, at-home monitoring of chronic conditions and patient assessment in remote or rural settings through POCT systems presents unique advantages in the pediatric population.

At-home monitoring of chronic conditions

One key example of at-home use of POCT systems is glucose management in diabetic patients. User-friendly glucometers were among the first POCT devices developed and approved by regulatory bodies to monitor diabetic patients outside of the hospital. While it was previously recommended by the National Institute for Health and Care Excellence that diabetic patients undergo 4–10 finger prick measurements per day to adequately manage their condition (53), the development of continuous glucose monitors (CGM) has revolutionized glucose management. These systems exploit various physiochemical principles (i.e. glucose-oxidase, fluorescence, skin dielectric properties, etc.) to provide real-time measurements every 1–5 minutes. Numerous companies have developed wearable, minimally invasive CGM devices, which can be worn for up to several days to weeks at a time: Dexcom (G4 Platinum, G5 Mobile), Medtronic (Enlite Sensor, Guardian Sensor 3), Abbott (Navigator II, FreeStyle Libre), and Senseonics (Eversense). Several studies have evaluated the analytical accuracy of CGM instruments compared to the central laboratory, and have demonstrated generally good concordance (54,55), underscoring their unique value. However, the role of the clinical laboratory in monitoring and reporting glucose values as determined by CGM is unclear and warrants further consideration. Another common application of at-home POCT in pediatrics is international normalized ratio (INR) monitoring in patients who require long-term oral anticoagulation (e.g. warfarin) therapy. Warfarin is the preferred anticoagulant used in pediatrics and has become increasingly important due to increased survival of children with severe conditions at higher risk of thrombolytic events (e.g. congenital heart disease). INR monitoring requires daily laboratory testing and thus POCT offers an opportunity for pediatric patients in remote regions to adhere to a proper monitoring schedule. Few studies have assessed the clinical and analytical performance of POC INR testing. In terms of analytical performance, one study evaluating the CoaguChek XS system reported high analytical concordant relative to a central analyzer (r =0.95) (56). Additional clinical evaluations have suggested this system to be suitable for pediatric assessment (57), observing increased savings in both time (>1 hour) and cost per INR test, compared to traditional care (58).

Rural or low-resource settings

Another emerging application of POCT is rural settings where a central laboratory is inaccessible. For example, early infant diagnosis of human immunodeficiency virus (HIV) is particularly challenging in rural areas of sub-Saharan Africa, where infection rates are high and centralized testing can lead to substantial delays in diagnosis and treatment (59). Early intervention can be critical in reducing HIV-associated morbidity and mortality, and POCT has demonstrated value in this regard (59–61). In addition, the prevalence of sickle cell disease (SCD) is an ongoing concern in countries without access to newborn screening programs, wherein undetected SCD is strongly associated with under-five mortality (62). POCT may offer a unique advantage in these regions. Indeed, studies that have implemented POCT for the detection of sickle hemoglobin are encouraging. Excellent sensitivities (>93%) and specificities (>99%) using the HemoTypeSC POC device in children screened for SCA have been reported (63,64). Additional large-scale studies are needed to confirm the clinical advantage of POCT implementation in this scenario. Lastly, newborn infants are also at an increased risk for jaundice, which is characterized by increased bilirubin concentrations (65). Timely diagnosis of newborn jaundice is critical and a routine component of neonatal assessment in modern tertiary hospitals. Left untreated, newborn jaundice can result in neurological damage and death

in severe cases. Several POCT systems have recently been designed to measure bilirubin and have demonstrated excellent concordance with the central laboratory (66,67), thereby offering immense clinical potential in remote settings.

UNIQUE INTERPRETATIVE CONSIDERATIONS IN PEDIATRIC POCT

Given the clinical indications discussed above, it is clear that POCT provides clinical value in both acute and remote pediatric settings, ensuring timely test result reporting. However, while studies suggest good to excellent analytical performance of these devices as compared to central laboratory analyzers, an equally important consideration is test result interpretation. Reference intervals, defined as the 2.5th and 97.5th percentiles derived from a reference population, are important health-associated benchmarks that are used to flag abnormal laboratory test results and alert clinicians of the potential need for follow-up and/or treatment. Unfortunately, while most analytical platforms (including POCT devices) provide reference intervals for test interpretation in their package insert, they are primarily based on adult populations and do not include pediatric recommendations. This is likely resultant from challenges encountered in pediatric reference interval establishment, including extensive resources required for recruitment, higher sample size needed to adequately reflect age- and sex-specific changes during growth and development, as well as ethical considerations limiting resampling opportunities (68). These unique challenges have often led to the implementation of adult-based reference intervals for pediatric test result interpretation, which may cause significant and adverse clinical outcomes. To address this evidence gap, several initiatives have been developed, including the Canadian Laboratory Initiative on Pediatric Reference Intervals (CALIPER) (69), the Harmonising Age Pathology Parameters in Kids (70), Children's Health Improvement through Laboratory Diagnostics (71), KiGGs study (72), and Lifestyle of Our Kids program (73). However, most of these initiatives focus on biochemical and immunochemical assays available on central laboratory analyzers. Establishment of pediatric reference intervals on POCT systems is further complicated due to rapid pre-analytical requirements, preventing specimen storage and batch testing. This has led to an immense gap in the literature with practically no studies developing reference intervals on POCT systems for pediatrics, despite their growing clinical value. Future pediatric reference interval studies in this area should focus on important covariates, such as age, sex, and specimen type. Importantly, as discussed above, unique physiological dynamics influence biochemical markers (e.g. glucose), particularly in early life, requiring close consideration of key covariates and age-specific interpretation. This further emphasizes the necessity for robust, evidence-based reference intervals that adequately capture dynamic changes in analyte concentration that occur throughout pediatric growth and development. Recently, CALIPER has expanded the utility of their database to include critical care parameters on a common POCT system (Radiometer ABL90 FLEX Plus) (74) and plans to continue completing studies on alternate POCT platforms to close this evidence gap. Taken together, clinical laboratories and clinicians should recognize the limited evidence surrounding pediatric normative values for key parameters on POCT systems and the potential impact on clinical decision-making.

Another important distinction of note is that some parameters commonly assessed in acute care on POCT systems (e.g. glucose, electrolytes, pH) have associated critical values or cut-offs to define extremely abnormal values warranting immediate follow-up and clinical action. Unfortunately, these decisionlimits are also commonly based on clinical evidence in adult populations (75). New studies are needed to

develop evidence-based reference intervals and critical values for POCT platforms in children and adolescents as implementation and usage of POCT devices continues to grow in pediatric settings.

CONCLUSION

In conclusion, current POCT systems offer a unique set of advantages in pediatric healthcare provision, particularly in acute and remote settings. Evidence to date supports several key benefits to patient care, including reduced length of stay, improved time to diagnosis, improved acute condition outcomes, improved condition management, and reduced cost of hospital admission. With proper education and training, additional administrative and economic advantages have also been reported, including improved staff satisfaction and clinical workflow efficiency. However, not all POCT systems are created equal and differences between POCT systems and central laboratory analyzers continue to be reported and may sometimes require device-specific test interpretation. In addition, pediatric reference interval studies are lacking for POCT systems, compromising the accuracy and standard of test result interpretation in infants, children, and adolescents. Further studies are needed to establish pediatric reference intervals and/or critical values as new POCT systems are developed. Taken together, while implementation of POCT systems in emergency, critical care, and remote settings has demonstrated major clinical value in pediatrics, close consideration of their analytical (e.g. comparison to central laboratory) and post-analytical (e.g. test result interpretation) requirements is needed prior to clinical implementation.

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In this issue: POCT – making the point

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Point of care testing of serum electrolytes and lactate in sick children

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ARTICLE

Objective

To evaluate the electrolyte and lactate abnormalities in hospitalized children using a point of care testing (POCT) device and assess the agreement on the electrolyte abnormalities between POCT and central laboratory analyzer with venous blood.

Methods

This observational study recruited hospitalized children aged 1 month to 12 years within two hours of admission. A paired venous sample and heparinized blood sample were drawn and analyzed by the central laboratory and POCT device (Stat Profile Prime Plus-Nova Biomedical, Waltham, MA, USA) for sodium and potassium. Lactate was measured on the POCT device

only. The clinical and outcome parameters of children with electrolyte abnormalities or elevated lactate (>2mmol/L), and the agreement between POCT values and central laboratory values were assessed.

Results

A total of 158 children with median (IQR) age 11 (6-10) months and PRISM score 5 (2-9) were enrolled. The proportion of children with abnormal sodium and potassium levels, and acidosis on POCT were 87 (55.1%), 47 (29.7%) and 73 (46.2%), respectively. The interclass coefficient between POCT and laboratory values of sodium and potassium values was 0.74 and 0.71 respectively; P<0.001. Children with hyperlactatemia (81, 51.3%) had higher odds of shock (OR 4.58, 95% CI: 1.6-12.9), mechanical ventilation (OR 2.7, 95% CI 1.1-6.6, P=0.02) and death (OR 3.1, 95% CI 1.3-7.5 P=0.01) compared to those with normal lactate.

Conclusion

POCT can be used as an adjunct for rapid assessment of biochemical parameters in sick children. Lactate measured by POCT was a good prognostic indicator.

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INTRODUCTION

Point-of-care testing (POCT) is being increasingly used in the emergency department (ED) and the intensive care unit (ICU) to enable the rapid assessment of biochemical, microbiological and radiological evaluations both for single-point assessments and serial monitoring of sick patients[1,2]. POCT for blood tests circumvents several steps in central laboratory testing including specimen transportation and processing, resulting in faster turn-around time preventing unnecessary delay in clinical decision[1]. These tests require significantly less blood making them a good option for pediatric patients[3]. Early recognition and management of common electrolyte abnormalities are important in the final outcome of the patient[4]. Critical illness may trigger an acute phase response which is associated with several metabolic, electrolyte and acid-base derangements[4]. The presence of these disorders typically reflects the underlying pathology and may be associated with poor outcomes[5].

Measurement of electrolytes and lactate using a POC blood gas analyzer has shown good agreement with a central laboratory analyzer in several studies[6,7], although others have raised concerns regarding their accuracy and reliability[8,9]. This study was planned in the pediatric department of a tertiary hospital with the aims to assess the proportion of electrolyte and lactate abnormalities in hospitalized children using a POCT device and check the agreement between the electrolyte abnormalities measured by POCT device and venous blood analyzed in the central laboratory.

METHODS

The study was conducted in the pediatric department of a tertiary hospital after permission from the ethics committee of the institute between March-July 2019. Children aged 1 month to 12 years admitted to the pediatric emergency department were assessed for enrollment after parental consent. Criteria for hospitalization were defined based on emergency or priority signs as per Facility based-Integrated Management of Maternal, Neonatal and Child Illnesses (F-IMNCI), which were respiratory distress, cyanosis, shock, coma, seizures, altered sensorium, lethargy, poisoning, bilateral pedal edema, bleeding and anemia requiring transfusion[10]. In addition, as per the unit's protocol, any patient requiring a surgical intervention, jaundice with decompensation, unexplained fever for seven days, acute flaccid paralysis or poisoning were also admitted. Children with known tubulopathy, severe

acute malnutrition, diarrhea and chronic malabsorptive states who were predisposed to develop disease related electrolyte abnormalities were excluded from the study.

Clinical history and examination were noted on a predesigned Performa. PRISM III score[11] was used to assess the severity of illness. The duration of hospitalization and disposition (death/discharge/abscond/left against advice) was recorded. A concurrent two mL venous sample for serum analysis and 0.5 mL heparinized venous blood sample were drawn within two hours of admission after stabilization. The serum sample was analyzed in the central laboratory for case-based management which included measurement of blood urea, creatinine, sodium and potassium. The Stat Profile Prime Plus (Nova Biomedical, Waltham, MA, USA) blood gas analyzer using whole blood co-oximetry technology was used for POCT for blood pH, bicarbonate, blood oxygen, carbon dioxide, lactate, sodium and potassium. The proportion of children who had abnormal electrolytes, blood-gas disturbances or elevated lactate on POCT analysis was recorded. An agreement of POCT values was validated with the concurrently sampled venous blood values. The normal range of sodium and potassium were considered as 135-145 meq/L and 3.5-5.5 meq/L, respectively. The upper limit of normal for BUN was 18mg/dL[12], and for lactate 2mmol/L[13]. A difference of up to 4 mEq/L for sodium and 0.5 mEq/L for potassium between the central laboratory and POCT were considered acceptable as per the United States Clinical Laboratory Improvement Amendment (US CLIA) 2006[14].

Sample size: Sample size was calculated using a study by Naseem *et al*[15] where electrolyte abnormality was seen in 84% children aged 1 mo-12 yr admitted to the pediatric ICU. The sample size at 5% error and 90% CI was 146 children.

Statistical analysis

All analyses were performed using Stata version 15.1 for Windows (Stata Corp., College Station, TX, USA). Quantitative variables were expressed as mean/median and Standard deviation/IQR, and qualitative variables were expressed as proportions (%). A p-value <5% was considered to be statistically significant. Data distribution was checked by Normal probability plot and Kolmogorov-Smirnov normality test. For the comparison of two groups, student's *t*-test was used if following normal distribution, otherwise Mann Whitney U-test was used. Paired t-test was used to test the mean difference between two sets of observations. Intraclass correlation coefficients (ICC) were calculated to determine the agreement between POCT and venous blood values. Qualitative variables were compared between the two groups using Chi-square test or Fisher's exact test. For the comparison of more than two groups One-way analysis of variance followed by Bonferroni correction for multiple comparison was applied. Pearson's correlation coefficient between study variables were calculated along with the assessment for the significance of these correlations. Odds Ratios (95% CI) were calculated for study variables associated with outcome.

RESULTS

A total of 197 children were screened, out of which 25 with diarrhoea, 4 with malabsorption, 7 with severe acute malnutrition and 3 with renal tubular acidosis were excluded. A total of 158 (66.4% boys) children with median (Q1,Q3) age of 11 (6-10) months were included in the study with outcomes available for 138 children, as others were still admitted at the end of study period. BUN and serum creatinine measurements were available for 28 children.

The disease wise distribution and proportion of electrolyte abnormalities is shown in Table 1.

Table 1 Demographic and laboratory parameters of the study group (n=158)

Parameter	Value n (%)
Diagnosis#	
Pneumonia	56 (35.4%)
Sepsis	32 (20.2%)
CHD	32 (20.2%)
Shock	25 (15.8%)
Seizures	18 (11.4%)
Meningitis	6 (3.8%)
Liver failure	5 (3.2%)
Others	9 (5.7%)
Outcome (n=138)	
Discharge	100 (72.5%)
Leave against advice	6 (4.3%)
Death	30 (21.7%)
Abscond	4 (2.9%)
Acidosis	73 (46.2%)
Alkalosis	3 (1.9%)
Elevated Lactate	81 (51.3%)
Ventilated	28 (17.7%)
†Duration of stay (d)	7 (4-10)
†Duration of mechanical ventilation (hr)	22 (18-25.7)
PRISM III, score*	5 (2-9)
‡pH	7.32 (0.15)
†Bicarbonate (mEq/L)	16.9 (12-20)

†Median (IQR); ‡Mean (SD); #the percentage of diagnoses adds to more than 100 as few patients had more than one diagnoses. CHD- congenital heart diseases; POCT- point of care testing; PRISM pediatric risk of mortality.

Hyponatremia and hypernatremia was found in 58 (37.7%) and 9 (5.7%) of the serum samples while hypokalemia and hyperkalemia was seen in 13 (8.3%) and 24 (15.2%) of the samples. The agreement between the laboratory and POCT device values (n=152) was good for all the above parameters as shown in Table 2.

The difference between sodium and potassium serum and gas values for different electrolyte ranges is also shown in Table 2. There was no significant difference in the proportion of sodium abnormalities between patients with PRISM III score >10 and <10 (P =0.16).

The odds of mechanical ventilation were not increased with abnormal sodium (OR 1.06 95% CI 0.4-2.4, P=0.87) or abnormal potassium (OR 1.3 95% CI 0.5-3.4, P=0.55).

The odds of death were not increased with sodium (OR, 95% CI 1.1, 0.5-2.5; P=0.79) and potassium abnormalities (OR, 95% CI 2.2, 0.89-5.7; P=0.08).

Table 2 Agreement between laboratory and POCT device biochemistry

Parameter	Laboratory value, mean (SD)	POCT value, mean (SD)	Interclass correlation (95% CI)	Mean difference (95% CI)	*P* value
Sodium (meq/L)	136.20 (7.3)	133.6 (7.1)	0.74 (0.64-0.84)	-2.56 (-3.64, -1.48)	**≤0.001
Potassium (meq/L)	4.60 (0.9)	3.94 (0.8)	0.71 (0.60-0.80)	-0.66 (-0.59, -0.73)	**≤0.001
Sodium >145 meq/L	152.86 (11.7) (n=9)	149.46 (3.1) (n=9)	-	-3.4 (-12.85, 6.05)	0.41
Sodium 135-145 meq/L	137.02 (2.1) (n=91)	138.62 (2.0) (n=71)	-	0.41 (-0.65, 1.47)	0.43
Sodium <135 meq/L	130.21 (3.0) (n=58)	128.94 (3.9) (n=78)	-	-1.27 (-2.41, -0.13)	*0.03
Potassium >5.5 meq/L	6.70 (0.4) (n=24)	5.90 (0.4) (n=8)	-	-0.80 (-1.38, -0.23)	*0.02
Potassium 3.5-5.5 meq/L	4.51 (0.05) (n=121)	4.03 (0.04) (n=111)	-	-0.48 (-0.6, -0.37)	**<0.001
Potassium <3.5 meq/L	2.89 (0.15) (n=13)	2.75 (0.15) (n=39)	-	-0.14 (-0.51, 2.3)	0.42

*POCT: point of care testing; mean difference = POCT - laboratory value; *P<0.05; **P ≤0.01.*

Patients with sepsis had higher odds of abnormal serum sodium compared to those without (OR, 95% CI 3.0, 1.3-6.7; P=0.006), unlike patients with CHD (OR, 95% CI 0.97, 0.4-2.1; P=0.95).

The odds of potassium abnormality were not significant in those with sepsis (OR 1.0, 95% CI 0.4-2.7, P=0.87) and or CHD (OR, 95% CI 1.3, 0.5-3.3, P=0.52).

The median (Q1, Q3) of lactate by POCT was 2.1 (1.3-3.4) mg/dL, range 0.8-17.2. Table 3 shows differences in various clinical and biochemical parameters in patients with or without hyperlactatemia. Children with hyperlactatemia had higher odds (OR, 95% CI) of shock (4.58, 1.6-12.9, P=0.002), acidosis (2.9, 1.51-5.59, P=0.001), mechanical ventilation (2.7, 1.1-6.6, P=0.02) with longer duration of ventilation (P=0.01) and death (3.1, 1.3-7.5 P= 0.01) compared to those with normal lactate.

Lactate levels had significant positive correlation with PRISM III score (r=0.45, P<0.001), while it negatively correlated with duration of stay (r=-0.14, P=0.09).

Table 3 Comparison of clinical parameters between normal and raised lactate (N=158)

Parameter	Normal lactate, n(%) (n=77)	Hyperlactatemia, n(%) (n=81)	*P* value
†Age (Months)	11 (4.5,66)	10 (3,39)	0.78
§Death	(n=64) 8 (12.5%)	(n=74) 22 (29.7%)	**0.01
Shock	5 (6.5%)	20 (24.7%)	**0.002
Sepsis	13 (16.9%)	19 (23.5%)	0.94
CHD	15 (19.5%)	17 (20.9%)	0.87
Ventilation	8 (10.4%)	20 (24.7%)	*0.02
Acidosis	25 (32.5%)	48 (59.3%)	**0.001
†Duration of stay (d)	7 (4-10)	7 (4,10)	0.24
†PRISM III	4 (2,7)	6 (2;11)	**<0.001
†Duration of ventilation (hr)	22 (18-40)	22 (18-25)	**0.01
‡pH	7.35 (0.11)	7.29 (0.18)	0.19
‡Bicarbonate (mEq/L)	17 (5.7)	15.4 (6.4)	**0.009

*†Median (Q1,Q3); ‡Mean (SD); §Data not available in still admitted patients;*P<0.05;** P ≤0.01; CHD- congenital heart diseases; PRISM pediatric risk of mortality.*

DISCUSSION

The present study showed good agreement between the central laboratory and POCT for sodium and potassium. Lactate estimation by POCT was found to significantly predict illness and poor outcome.

The agreement between the laboratory and POCT device results for sodium is similar to earlier studies[1,6,16], including one which used a similar method (ChemSTAT, Instrumentation Laboratories)[16]. Similar results were also reported for potassium earlier[6,16] and better agreement by other studies[1,9]. It is postulated that the dilution and interaction of heparin in blood gas samples may decrease the electrolyte concentration in comparison to serum samples, as seen in the present study and also reported earlier[9,17]. There may be variability due to manually heparinizing the syringes for blood gas analysis which can introduce bias with the measurement of positively charged ions on a gas analyzer[3].

The mean difference between the laboratory and POCT device sodium values was within the acceptable US CLIA limits[14] for all ranges of sodium, unlike for potassium which was >0.5 mmol/L in the higher range. Hemolysis during collection of serum samples was potentially responsible for the higher serum potassium values. Studies have shown good association between lactate measured by serum and blood gas analyzers[7,13,18,19] and handheld POC devices[20].

A systematic review of over 3000 adult and pediatric patients demonstrated an advantage to measuring lactate in reducing mortality and duration of hospitalization in emergency settings[21]. Blood lactate levels at admission has consistently shown to be associated with mortality in sick children[16,21].

However, unlike adults, sampling of sick children may be challenging in the emergency department and in states of shock. A significant percentage of children had hyperlactatemia as assessed by POCT in this study which was a predictor of severity of illness, outcome and need for ventilation, thus signifying its prognostic importance in both sepsis and non-sepsis conditions. A similar study demonstrated the role of POC measured lactate as a strong predictor of mortality in children with severe febrile illness[22].

The reliability and advantage of clinical risk prediction of POC lactate was also concluded in umbilical cord samples (for perinatal hypoxia) compared by two separate handheld POC devices, blood gas machine and plasma lactate levels[23]. Arterial sample for lactate measurement which is considered as ideal for lactate measurement may be difficult and painful to obtain in sick children in the emergency. Venous lactate values have shown excellent agreement with arterial lactate during initial phase of sepsis in children[24]. Therefore, the utility of estimation of venous lactate by POCT device is further reiterated.

The present study was not powered sufficiently to conclude agreement between gas and blood samples, but showed acceptable difference for measurement of sodium and potassium at normal and extreme ranges. A lack of follow-up data of electrolyte measurements in the study population was a limitation. The serum lactate values were not measurable due to logistic issues and thus no comparison between POCT and laboratory lactate values could be made. There was no cost-effectiveness analysis for POCT in this study.

To conclude, POCT can be employed as an adjunct in the ICU and ED for rapid assessment of electrolytes, including lactate, which requires a smaller blood sample, and allows for quicker results, enabling faster decision making in sick children.

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What is already known?

1. Electrolyte abnormalities are common in sick children
2. Elevated lactate levels are associated with poor clinical outcomes
3. There is an increasing use of point-of-care devices for different laboratory parameters

What this paper adds?

1. Point-of-care devices measured electrolytes in sick children with good correlation to serum values
2. Lactate measured by POCT was a good prognostic indicator for poor clinical outcomes

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In this issue: POCT – making the point

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Training and competency strategies for point-of-care testing

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ARTICLE

The increased availability and use of POCT are being influenced by many factors, such as; industry trends to move towards patient-centered care and health-care decentralization, the increasing prevalence of infectious diseases also including the current use of Rapid SARS-CoV-2 Testing, a growing incidence of life-style diseases such as diabetes, heart disease, and hypertension, as well as advances in in-vitro diagnostic medical technologies. The use of POCT can increase the efficiency of services and improve outcomes for patients. However, the variability of the testing environment and conditions as well as the competency of staff performing the tests may have a significant impact on the quality and accuracy of POCT results.

A majority of the staff who perform POCT are not trained laboratory staff and may not be as knowledgeable about the processes involved in testing, such as

patient preparation, sample collection, management of equipment and supplies, instrument calibration and maintenance, the performance of the test, quality control, interpretation of the results, and reporting/documentation of results in each patient's context. Therefore, staff performing POCT must have the proper training and experience to ensure test results are accurate and reliable.

This short communication outlines the specific requirements for staff training based on international standards which need to be considered to ensure the quality of test results and describes competency criteria required for compliance with POCT.

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INTRODUCTION

Point-of-Care Testing (POCT) is rather broad in scope and covers any diagnostic tests performed near or at the site of a patient where a specimen is collected and outside of the conventional clinical laboratory, whether it is performed in a physician's office, emergency department, intensive care unit, operating room or an ambulatory care clinic. These tests are waived under the Clinical Laboratory Improvement Amendments (CLIA) of 1988 in the US and can be molecular, antigen, or antibody tests (1). POCT ranges between three levels of complexity, from simple procedures such as glucose testing, moderate-complexity procedures (including provider performed microscopy procedures), or high-complexity procedures such as influenza testing. Health care professionals delivering POCT usually use test kits, which may include hand-held devices or otherwise transported to the vicinity of the patient for immediate testing at that site (e.g. capillary blood glucose) or analytic instruments that are temporarily brought to a patient care location in a hospital to read blood, saliva, or urine samples (2-4). The primary advantage of POCT is the faster turn-around time for results. They provide results within minutes (depending on the test) rather than hours leading to a possible change in the care of the patient in various settings such as physician offices, urgent care facilities, pharmacies, school health clinics, long-term care facilities, and nursing homes, temporary locations, such as drive-through sites managed by local organizations (5). An additional advantage is that these tests often require less sample volume than tests performed in the laboratory.

The recent and ongoing changes in clinical laboratory technology have a great impact on laboratory staff needs. POCT is usually performed by non-laboratory trained individuals such as licensed practical nurses, registered nurses, nurse aides, physicians, residents, students, technical assistants, respiratory therapists, emergency technicians, and pharmacists among others.

There are many "official" and professionally based standards and guidelines that define how POCT should be implemented, managed and the performance quality checked and maintained. Most professionally based guidelines follow a similar template and provide similar information which includes specific references to staff training and competency assessment (6-10). Organizations that have a central biomedical laboratory are to use these standards in POCT - specific requirements for quality and competence based on ISO 22870:2016. This standard is intended to be used in conjunction with ISO 15189:2012 and applies when POCT is carried out in a hospital, clinic, or healthcare organization providing ambulatory care. Patient self-testing in a home or community setting is excluded, but elements of this document can be applied. Table 1 lists selected International Organization for Standardization (ISO) standards to be considered associated with the POCT training and competency assessment requirements (11-18).

Table 1 International standards define or are associated with medical laboratory and POCT competency and training

Standard	Definition	Scope of the document
ISO 17593:2007	Clinical laboratory testing and in-vitro medical devices – requirements for in vitro monitoring systems for self-testing of oral anticoagulant therapy.	• specifies requirements for in *vitro* measuring systems for self-monitoring of vitamin-K antagonist therapy, including performance, quality assurance, and user training and procedures for the verification and validation of performance by the intended users under actual and simulated conditions of use. • pertains solely to PT measuring systems used by individuals for monitoring their vitamin-K antagonist therapy, and which report results as international normalized ratios (INR).
ISO 15189:2012	Medical laboratories – particular requirements for quality and competence.	• specifies requirements for quality and competence in medical laboratories. • can be used by medical laboratories in developing their quality management systems and assessing their competence. It can also be used for confirming or recognizing the competence of medical laboratories by laboratory customers, regulating authorities, and accreditation bodies.
ISO 15197:2013	In vitro diagnostic test systems — Requirements for blood-glucose monitoring systems for self-testing in managing diabetes mellitus.	• specifies requirements for *in vitro* glucose monitoring systems that measure glucose concentrations in capillary blood samples, for specific design verification procedures, and the validation of performance by the intended users. These systems are intended for self-measurement by laypersons for the management of diabetes mellitus.

		• applies to manufacturers of such systems and those other organizations (e.g. regulatory authorities and conformity assessment bodies) having the responsibility for assessing the performance of these systems.
ISO 22870:2016	Point-of-care testing – requirements for quality and competence.	• gives specific requirements applicable to point-of-care testing and is intended to be used in conjunction with ISO 15189. The requirements of this document apply when POCT is carried out in a hospital, clinic, and by a healthcare organization providing ambulatory care. This document can be applied to transcutaneous measurements, the analysis of expired air, and *in vivo* monitoring of physiological parameters. • patient self-testing in a home or community setting is excluded, but elements of this document can be applied.
ISO/TS 22583:2019	Guidance for supervisors and operators of point-of-care testing (POCT) devices.	• gives guidance for supervisors and operators of POCT services where POCT is performed without medical laboratory training, supervision, or support. It includes the key components that should be considered to provide safe and reliable POCT results.
ISO/TS 20914:2019	Medical laboratories — Practical guidance for the estimation of measurement uncertainty.	• provides practical guidance for the estimation and expression of the MU of quantitative measurand values produced by medical laboratories. Quantitative measurand values produced near the medical decision threshold by POCT systems are also included in this scope. This document also applies to the estimation of MU for results produced by qualitative (nominal) methods which include a measurement step.

		It is not recommended that estimates of MU be routinely reported with patient test results but should be available on request.
ISO 15190:2020	Medical laboratories — Requirements for safety	• specifies requirements to establish and maintain a safe working environment in a medical laboratory. As with all such safety guidelines, requirements are set forth to specify the role and responsibilities of the laboratory safety officer in ensuring that all employees take personal responsibility for their safety at work, and the safety of others who can be affected by it.

ISO: The International Organization for Standardization; PT: prothrombin time; POCT: Point-of-Care Testing; MU: measurement uncertainty.

A well-organized POCT program requires both thoughtful planning as well as ongoing oversight and supervision (19-21). Joint Commission International (JCI) specifies that a qualified individual is responsible for the oversight and supervision of the point-of-care testing program (Standard AOP.5.1.1) (22). Leadership may be involved in the planning process by identifying and approving the resources dedicated to the POCT program as well as the policies and procedures related to management and oversight of the program (23,24). When considering the tasks conducted by individuals who do not have technical skills and training, it is important to note that many countries have licensure laws that preclude the conduct of certain testing procedures by non-technical staff (25,26). CLIA requirements in the US, as they relate to moderate- and high-complexity tests, do not allow the use of non-technical staff for certain testing procedures (27). The College of Physicians and Surgeons of Alberta provides detailed recommendations for the use of POCT outside of an accredited laboratory which includes documentation, non-technical staff training, quality control, etc, in a guideline (28).

TRAINING REQUIREMENTS FOR POINT-OF-CARE TESTING

A majority of the staff who perform POCT are not trained laboratory staff members and may not be as knowledgeable about the processes involved in testing, such as patient preparation, sample collection, instrument calibration, instrument maintenance, and quality control. Therefore, staff performing POCT must have the proper training and competency assessment to ensure test results are accurate and reliable (29,30).

Alternatively, laboratory staff may take responsibility, if preferred, for some of the POCT activities, such as managing instrument maintenance and acting on instrument failures. Before training for POCT, each staff member must have qualifications verified with state or national authority requirements and accreditation agencies, if appropriate. For institutions performing POCT utilizing waived or non-waived testing, CLIA regulations require a high school diploma or equivalency in the US (31). Some state regulating agencies require a license and/or a specific level of professional qualifications for persons

performing laboratory testing in any setting, including point-of-care. Each qualified POCT user must complete initial training and orientation on each test method before initiation of testing and following any changes or update in instrumentation, kits, or test methods. Initial training must be completed before the user performing any patient testing and competence must be documented. This initial training must include direct observation, be documented, and the documentation retained in the individual's training record.

Following any changes or updates in methodology, training of personnel in the new methodology must occur and be documented before performing patient testing. All training must be performed by a qualified individual such as a certified laboratory technical staff or the manufacturer/company representative and the competency of the tester verified before performing patient testing. A qualified trainer must have been trained and demonstrated competency for all methods for which training is being conducted (32).

COMPETENCY ASSESSMENT REQUIREMENTS FOR POINT-OF-CARE TESTING

Competency confirms the effectiveness of training. Assessment of competency is an evaluation of training and verifying that training is applied to test performance. Following initial training and competency, the standards require that staff performing POCT must be re-assessed for competency at regular intervals to ensure the accuracy and reliability of results and the quality and safety of patient care. Re-training and competency re-assessment should occur if there are nonconformances or adverse events relating to patient testing. Competency assessment should include policies and procedures outlining the process for evaluating competency. As with all policies and procedures, the laboratory director must approve the process at the inception and following any major revision. All reviews and approvals are documented with signatures and dates. All policies and procedures must be periodically reviewed, annually or every two years (biennially), depending on regulatory and accrediting requirements, by the laboratory director or designee, and this review documented with the date of the review.

As with initial training, each employee that performs POCT must have competency assessed and documented after training and before performing patient testing. The documentation must be retained for each procedure the employee performs. If there is a change in test method or a new test added, initial training and assessment of competency must be completed and documented. For each employee performing POCT, an ongoing competency assessment must be completed at designated intervals for each test method that the employee performs. For CLIA compliance, competency must be assessed for each non-waived POCT at six months and 12 months following initial training and assessment annually thereafter. Evaluation of competency should include pre-analytic, analytic, and post-analytic phases of testing. For minimum compliance with POCT regulations, six procedures must be included within the competency assessment process for all employees performing non-waived POCT testing. Table 2 provides a summary of assessment procedures for POCT; including the requirement for operator training, proof of competency, quality control, and external quality assessment. Most authorities provide statements regarding POCT which include mandatory quality procedures as defined by regulation or specific policy.

Each of the required procedures will not be appropriate for every activity in a comprehensive competency assessment program. The procedures are applied as appropriate, evaluated

with an appropriate assessment tool, results evaluated, reviewed with the employee, and documentation is retained. Tools employed for competency assessment may include items such as checklists (for direct observation), case studies (problem-solving), quizzes (problem-solving), unknown sample testing (test performance), review of retained records, proficiency testing results, and any other appropriate mechanism for assessment of competency.

Like other processes in a laboratory, errors can happen at any phase of POCT. A study by Cantero, et. al. looked at the error rates during all phases

Table 2 **A staff training and education program, as appropriate, includes the following learning items of procedure and tools for assessment.**

All POCT operators must complete a comprehensive training program that includes an understanding of the purpose and limitations of the test and awareness of procedures and processes relating to all aspects of operating the device.

Procedure	Potential tools for assessment
Pre-analytic phase	
• **General background information**	
The context and clinical utility of POCT and the theoretical aspects of the measuring system	Review of the manufacturer's guides, standard operating procedure documents referring to the international and national quality standards, and training resources
• **Instrument and equipment**	
Direct observations of the use of POCT instruments and devices for ensuring readiness	Review of equipment/kit validation/verification to ensure they are performing as intended, inspection and validation of incoming materials and new lot numbers, verification of reference range for the population being tested (e.g. pediatric vs. adult)
Direct observations of the performance of instrument maintenance, calibration of equipment (instrument/reagent system) if required by the manufacturer, and function checks	Checklist and preventive maintenance records
Review of troubleshooting when an instrument fails	Checklist

Direct observations of reagent storage	Review of worksheets, inventory logs, expiration dates
• **Patient safety**	
Direct observations in the Specimen Collection and Preparation	Checklist for patient identification, patient preparation (e.g. fasting, lack of interfering drugs), proper specimen collection at the appropriate time (e.g. toxicology or therapeutic drug monitoring (TDM) tests), volume, handling, and processing by the manufacturer's instructions
Analytic phase	
• **Evaluation of the analytical performance**	
Assessment of test performance and limitations of the measuring systems	Checklist for unknown and previously analyzed specimens, internal blind testing samples, internal quality control, or external proficiency testing samples
Direct observations of routine patient test performance	Checklist
Post-analytic phase	
Monitoring the record-keeping and reporting of test results	Review of worksheets, permanent records (which may be the patient's chart or directly into an electronic medical record, if applicable) Logs for the length of time that records are retained (must comply with established best practice guidelines).
Direct observations of documentation and reporting requirements of test results	Review of arrangements/processes in place to respond to and act upon any critical POCT laboratory results. Checklist and review of worksheets
Review of response to results outside predefined limits	Checklist
Assessment of Quality Control Program	Review of quality control records, proficiency testing or EQA sample results, split samples
Assessment of problem-solving skills	Case study, quizzes, tests

Health and biosafety	
Direct observations of infection control	Review of implementation of a safety training program for employees who routinely work with blood or other infectious materials Review of worksheets related to the management of biological/medical waste disposal, logs for handwash practice, cleaning and disinfecting requirements for contaminated surfaces, supplies, and equipment Review of personal protective equipment when dealing with patients and testing of samples (e.g. gloves, gowns/coats) and evaluation and follow-up of workers after accidental exposure to blood and body fluids Review of the protocol for the management of patient adverse events/reactions (e.g. fainting),
Direct observations of risk assessment	Review of worksheets for performing a risk assessment to identify what could go wrong, such as breathing in infectious material or touching contaminated objects and surfaces. Checklist for implementing appropriate control measures to prevent these potentially negative outcomes from happening. Review of hazard assessment for the identification and mitigation of possible hazards that could be encountered when using the POCT device.

EQA: External Quality Assessment.

of testing in the central laboratory and the performance of POCT. A higher rate of pre-analytical errors was found to be associated with POCT compared to central laboratory testing (33). In this context, the organization needs to identify the risk points in the process where errors in POCT may occur and take action to mitigate those risks. Monitoring and evaluation of the risks in performing POCT are essential and must be included in the training program.

One of the biggest POCT challenges is keeping track of the training and competency assessments for a multitude of operators in different locations, many of whom are non-laboratorians (34). A list of POCT challenges is shown in Table 3. Every operator is required to have documented training on each device before reporting outpatient results. Ongoing assessments are performed at the first six months, and then annually thereafter. In a large healthcare organization,

this can include several device types and thousands of operators. Facilities that need to track a large number of POCT operators may decide to use an online training tool such as a learning management system (LMS). POCT management software can automate reminders to users who are due for their competency assessment. When devices are capable, the POCT management software can block users from using a device until their certification is valid (35).

Table 3 POCT management challenges

New instrument evaluation
Compliance of users
Testing environments
Data management
Managing inspections
Handling quality control failures
Correlations to core lab
Managing competency assessments

PERSONNEL QUALIFIED TO PERFORM COMPETENCY ASSESSMENT

Specifically, ISO 22870:2016 recommends that organizations should constitute a multidisciplinary POCT committee to oversee the PoCT service. The POCT management committee is responsible to designate staff performing POCT and implement a POCT operator training and competency assessment program. Competency assessment for personnel performing moderately complex testing (which is the majority of non-waived POCT) is the responsibility of the technical consultant. This is the requirement for CLIA compliance. The laboratory director may act as the technical consultant and may perform competency assessment if they also meet the personnel qualification requirements of education, experience, and training for the position to fulfill the responsibilities. Qualifications for a technical consultant or POCT are defined in 42 CFR §493.1411 (36). The qualified laboratory director will perform a competency assessment. Technical consultants are the only staff that does NOT require competency assessment annually.

The laboratory director bears the responsibility that all competency assessments are completed and that the testing personnel are competent and consistently report accurate test results. Competency assessment may also be performed by any person that would qualify as a technical consultant, but does not serve in that role. Testing personnel who are peers may serve in the role of assessing competency If the qualifications for a technical consultant are met.

SUMMARY

Growth in point-of-care tests which do not have to be performed by laboratorians may mean that more allied health personnel will be needed in hospitals, physicians' offices, and in organizations that do not have a central biomedical laboratory (e.g. long term care, home care, or a community pharmacy), but may have an agreement and work with a central biomedical laboratory that is offsite.

To ensure that POCT is performed safely and correctly, a clearly defined and well-structured approach to the management of POCT is required. Also, a robust strategy of training for personnel performing POCT must be in place for compliance with POCT, including specific requirements for POCT policies and procedures based on ISO 22870, staff training, and continuing education. Finally, a POCT program for training and competency assessment must be implemented and

the POCT operators must be periodically evaluated to ensure the program is meeting the educational needs of the staff performing POCT.

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In this issue: POCT – making the point

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Leading POCT networks: operating POCT programs across multiple sites involving vast geographical areas and rural communities

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ARTICLE

Few peer-reviewed publications provide laboratory leaders with useful strategies on which to develop and implement point of care testing (POCT) programs to support delivery of acute care services to remote rural communities, with or without trained laboratory staff on site. This mini review discusses common challenges faced by laboratory leaders poised to implement and operate POCT programs at multiple remote and rural sites. It identifies areas for consideration during the initial program planning phases and provides areas for focus during evaluation and for continued improvement of POCT services at remote locations. Finally, it discusses a potential oversight framework for governance and leadership of multisite POCT programs servicing remote and rural communities.

INTRODUCTION

Providing leadership for Point of Care Testing (POCT) programs across large geographical areas presents unique challenges whether in low and medium income regions of Africa or in remote locations of developed countries such as in some of the Canadian provinces and territories (1,2). There are few published reports in peer reviewed literature that laboratory leaders can draw on when contemplating laboratory service delivery by POCT to remote rural communities. Many published reports in this area focus on the provision of new services to such communities in order to address public health concerns and/or to support the needs of acute care and chronic disease management services not supported by on-site laboratories. Other major areas for focus of POCT research related to service delivery involve delivery of diagnostic testings at facilities that are located in relatively close geographic proximity to centralized clinical laboratories. These studies often compare outcomes and benefits of POCT service delivery models with centralized laboratory services, but yield conflicting results depending on the setting (3). An area left relatively unexplored from a research perspective is the delivery of laboratory services using POCT devices, to replace small on-site clinical laboratories. Many jurisdictions are exploring how POCT technologies can be leveraged to support acute care service needs but as an alternative to maintaining small core laboratories equipped with small to moderately sized autoanalyzers operated by laboratory staff. Potential POCT service delivery models in these instances can involve sole operation of POCT devices by non-laboratory operators or sharing models where both on-site laboratory and non-laboratory staff share use of devices. Drivers for both of these POCT service delivery models arise from difficulties with recruitment of medical laboratory technologists, excessive costs incurred through call-back, and difficulty with sustainability of small laboratories in rural communities from both financial and human resource perspectives. Clinical laboratories in these health centers generally serve small communities, and do not operate twenty-four hours per day, nor on all days. This leaves urgent and emergent testing needs arising during late evenings, nights and weekends to be done by call-back of laboratory staff and/or by arranging urgent transport of samples, or the patient to another center.

BENEFITS AND CHALLENGES

Benefits

For a review on the clinical benefit for POCT overall, the reader is directed to Florkowski et al. (3). Here we focus on use of POCT in remote settings, and Wong et al. (4) has published a recent review of economic and effecacy of POCT in remote settings in Australia. Possibly the greatest amount of published work examining benefits and challenges facing POCT service delivery to such populations were from studies done in Australia, which hosts possibly the largest POCT programs to remote rural communities (5,6). A wide variety of tests are available for use at the point of care and by a variety of different POCT technologies (7). Apart from blood glucose monitoring, some of the long standing POCT programs in rural settings involve testing for HbA1c (8) and urinary albumin testing (9) for chronic disease; cardiac troponin (10,11) and NT-proBNP (12,13,14), basic metabolic panels (11,13,14), blood gases (11,13,14), complete blood counts with differential (15,16), creatinine (8), urine test strips (17), or INR (11,13,14) for acute disease management; and others for infections disease screening and monitoring. These have brought about benefits including decreased mortality for acute coronary syndromes (10,12); improved diagnostic accuracy and patient triage, decreased patient transfers

to other hospitals, more rapid turn around time, and economic benefits (4,6,13,14,15,16,18); improved antibotic stewardship (15); and improved availability, assessibility and affordability of health care, especially to patients living in low and middle-income countries (19). Albiet in many of these instances the comparator for benefit was to be remotely available and no on-site laboratory.

Challenges

Providing clinical laboratory services by POCT to remote rural communities requires overcoming geographical and infrastructure challenges. Healthcare centers servicing these populations can be hours in travel time from the next laboratory (4). At times, transportation modes can be unreliable because of need to travel over ocean, by air, or over difficult terrain especially during severe weather and adverse climatic conditions. The dependability of the power grid and local infrastructure can be inadequate. Implementing new POCT technologies can present challenges for supply chains to deliver a continued supply of reagents, consumables and quality assurance materials to support services, and laboratory specimens for other tests from rural sites to testing centers outside (20). Providing a robust and safe system, especially if replacing an on-site laboratory, requires due consideration of the costs required to maintain supply chains, for travel and transportation, and for storage of supplies and consumables following delivery and waste disposal after use. These costs depend on the transportation mode used, and how consumables and supplies must be stored to assure stability and for convenient availability, and how wastes will be disposed of. Robust contingency is also required to address unexpected events, infrastructure failure, and equipment malfunction.

Each remote rural location has its unique workplace and community cultures. Furthermore, the burden of chronic and acute disease can be greater in these areas compared with urban areas and vary with ethnicity (4, 21, 22). Adding to this complexity is the more frequent need for patient transport to a larger facility. Such sites are also challenged by high staff turnover (11). Some sites may be more vulnerable to data breach, operate under inferior or inadequate quality standards, or encounter difficulty with integrating new technology (19). Prior to set up, consideration must be given to training systems to build and maintain local testing capacity by preparing on-site POCT operators (11).

Addressing increased staff turnover may require flexible and convenient solutions for ongoing and non-disruptive training of new operators. Consideration must also be given to the hidden burdens and costs of POCT (20, 15) created by how tests are used and reported locally, the distances patients need to travel for testing, the requirements for training and maintenance of competency of POCT operators, and to provide quality management and monitoring in compliance with local regulation and accreditation standards (23). Other burdens include increased workload for clinical staff and especially POCT operators (14), and increased use and possibly misuse of tests (11). Furthermore, there can be lack of trust in results (19); and challenges with quality assurance (15). Trustworthiness and ease of use improve the acceptance of POCT devices by healthcare workers. Consideration must be given to how local testing will be supported for reporting, interpretation of results, troubleshooting, and resolving issues related to quality assurance including identifying who will participate, how samples will be distributed and results reported back, and how corrective actions will take place (11, 23). These can be addressed by developing robust quality management systems to function within the diverse local operational contexts (24). Development of a robust system for management of POCT results

and quality assurance data involves accurate recording and transfer between the testing device and the several different electronic health records and laboratory information systems (25). Information technologies including web-based resources (on the internet or intranets depending on local connectivity challenges) can be applied to providing information on test interpretation and limitations, for tracking and communicating quality assurance activities, and for simple troubleshooting (23). Use of webinars for instruction and telephone hotlines for assistance are other approaches that can be helpful in supporting the needs of remote rural community POCT programs. Utilization management surveillance is an important part of demonstrating financial stewardship for use of testing materials. These challenges highlight the need for comprehensive oversight, a collaborative approach to change management, and implementation of a robust quality management system. A proactive approach is required to identify challenges such that robust solutions are available early.

MULTI-SITE POCT NETWORKS

Constructing multi-site networked POCT systems for servicing remote rural communities requires attention to the service delivery challenges outlined above but also through offering an organized framework for leadership and governance (26). Moreover, is the need to bring all components of materials management, human resources, finances, and quality management together with a focus on people and the way people interact with technologies and the supporting infrastructure (20, 27) within local cultural contexts. The main goal for high quality POCT programs is providing reliable testing information to inform evidence-based decisions and to support improved patient outcomes. Strategic planning towards achieving this end depends on prospective consideration of local factors at each site. This includes taking stock of the specific testing needs of local clinicians, the local environment, including the community and workplace cultures, in which testing will take place; patient triage and treatment processes influenced by laboratory tests; determining the frequency and type of clinical conditions commonly encountered and requiring prompt testing; and evaluating the competency and availability of those performing testing using POCT devices (27). Critical to the sustainability of a multicentre POCT network is the provision of appropriate technologies that are affordable, rapid, and easily used by non-laboratory healthcare professionals (4, 28). Maintaining the safety of POCT programs over networks requires robust quality management systems to support POCT device use. This includes robust routine quality assurance systems including regular internal quality control, external proficiency testing, and where required sporadic comparison against larger reference laboratories associated with the network, and internal audits to confirm compliance with standards and then externally by accreditation agencies. This review process is often conducted centrally.

Some jurisdictions have considered leveraging POCT technologies to address financial and human resource challenges as an alternative service delivery model to small on-site laboratories yet using excess capacity of the broader diagnostic testing network to address other testing needs. An example is the Hub and Spoke network models (29), and with test menus at specific sites determined based on *the right test at the right time* principle. In other words, developing local POCT testing menus and focusing on tests that provide benefit when results are available early, but leveraging centralized testing at large laboratories to meet other testing needs. In these situations the value of each test is evaluated with the care setting in mind and

considering the overall clincal and operational benefits to be delivered.

Much planning is required to effectively integrate POCT service delivery models into multiple and diverse local settings in a fair, resource conscious and standardized manner. For example, the Canadian province of Newfoundland and Labrador improved the efficiency and effectiveness of laboratory services delivery to its 23 rural community health centres by establishing a standard test menu after consulting with many rural physician groups (Table 1). This menu addressed urgent testing needs and defined the minimal level of testing that would be available to all, and provide a list of elective tests to address specific local needs. Some of these health centers were located at great distances from larger hospitals that had full service laboratories, and required in excess of two hours of travel by road and/or over open ocean. Consistent with *the right test at the right time* principle, the rural on-site STAT menu was developed to meet the needs for urgent acute care decision making, while most routine laboratory samples were stabilized for transport and testing at larger full service laboratories. This standardized approach to test menu development but allowing local customization has been safely operating for over 5 years, and the entire test menu can be supported by POCT technologies. It is a false notion that POCT can replace the need for continued investment of resources to developing centralized laboratories (20). In networked systems broader infrastructure at large centers facilitate operation of quality management programs, and other functions for maintaining the system's integrity. In its second list of essential *in vitro* diagnostic tests (30), World Health Organization established 46 tests for use in routine patient care and 69 others for

Table 1 Standard test menu for STAT and urgent tests

Category 1 tests	Category 2 tests
Electrolytes (Sodium, Potassium, Chloride)	Amylase
Creatinine	Blood gases
Glucose	Urea
Cardiac Troponin	PT/INR
Urinalysis	D-dimer
Pregnancy Screen (urine)	Liver tests (Albumin, ALT, ALP, Total Bilirubin)
Complete Blood Count with differential	Ethanol (Breath samples)

Test menus were available to rural community health centers provided that STAT turn around time is not provided by a nearby larger site with a central lab; the test ordering frequency justified on-site testing over transport; and there is on-site expertise for specimen collection and interpretations of the test results.

All sites with emergency rooms that were staffed by a physician receive Category 1 test menus. Category 2 tests are allocated based on other conditions being met.

detection, diagnosis and monitoring of specific diseases. These can also be used to inform decisions on local test menu scope to remote rural areas.

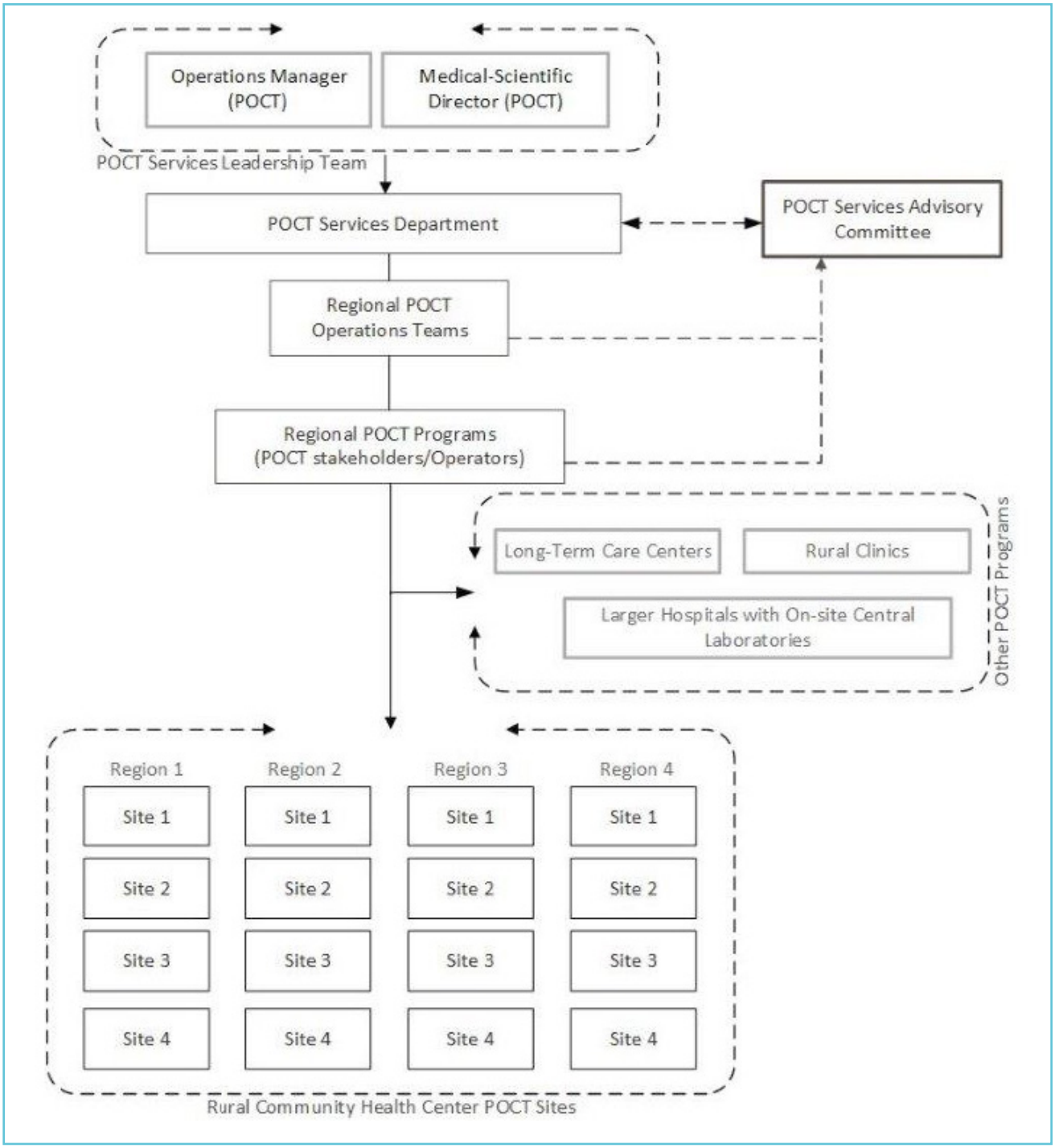
Several factors contribute to success of multisite testing networks involving POCT (31). First is having the support of administrators and decision makers across the network. This requires that the benefits of POCT are understood by all. Secondly is the support from laboratorians within the network. Thirdly is use of a horizontal collaborative approach to developing and maintaining a cooperative network. It is reasonable to expect considerable cultural differences across different health care centers providing POCT. Moreover, meeting the needs of diverse groups requires leaders that are skilled in working collaboratively with individuals from diverse backgrounds. Collaborative leaders establish relationships of mutual trust; gain committment from network participants by providing a clear rationale and communicating the benefit and vision for the network; maintain transparency in decision making; involve participants of the network, in planning and decision making for the network and thereby establishing the group identity; clearly expresses expectations up front and establishes accountabilities; and provides a clear and fair appeal mechanism for decisions such that individual participant rights are protected (31, 32).

LEADING POCT NETWORKS

A supportive governance structure is important to the success of a POCT network. It requires a leadership team taking a collaborative approach. Kremitske et al. (33) described a system to drive practice improvement and innovation through use of co-led leadership teams. These dedicated teams, led by an operational leader and doctoral director, focuses on the improvement and standardization of practices, working with each site to establish cultures of excellence and collaboration (27, 34), and discovering new ideas and emerging leaders from within the workforce, and by engaging other laboratory professionals system-wide. This best practice team approach helps support a common best practice focused culture. Clinical governance in the POCT network is provided by the doctoral/medical lead who has oversight for continuous improvement of services, improving assessability, making evidence-based clinical decisions, and through fostering local environment where service excellence flourishes and the wellbeing of the patient is protected (35). Key objectives of the leadership team include developing, implementing and promoting POCT policy, standards, training programs, and building and nurturing partnerships with clinicians and other healtcare providers at networked sites. This also includes communicating and coordinating activities across sites, establishing and monitoring outcomes for the network, maintaining multidisciplinary local groups for decision making, and maintaining a robust risk management process for the protection of POCT operators and patients (35).

A common organizational framework for support of POCT services that can be applied across remote and rural laboratory networks is made up of a POCT network leadership team, POCT coordinators, and various POCT committees. Figure 1 shows a possible operational framework. The willingness to work collaboratively with a diverse group of stakeholders is important to the quality and effectiveness of POCT programs. Horton et al. (26), identified 5 stakeholder groups to consider for large laboratory networks. This included laboratory professionals, physicians, policy makers, politicians, and the public. Not to be understated is the importance of serving the interests of the

Figure 1 POCT governance structure



The POCT Services Advisory Committee is comprised of the POCT leadership team and multidisciplinary stakeholders from different geographical regions. This is the main decision-making body. Regional POCT Operations Teams coordinate routine operation of POCT programs for sites within a region. These teams are comprised of regional POCT coordinators (for quality management oversight and local program coordination), regional laboratory leaders, and other POCT support staff. Rural community health centers are small hospitals with emergency rooms. Regional POCT programs consist of local POCT stakeholders and rural site POCT operators and are assisted by regional POCT operations teams.

patient and the public by open communication and involvement when implementing new service systems (26) and by gauging their satisfaction with the services provided. Furthermore, leaders must demonstrate cultural sensitivity when working across diverse workplace cultures and for building trust. Licher et al. (19) indicated that to improve the acceptability to healthcare workers required that POCT and its related processes be compatible and a good fit for the local setting. Arriving to this point requires collaboration with local stakeholders. Healthcare stakeholders must be trained and familiarized with the interpretation and application of test results, and with limitations of technologies that can restrict the scope for use in patients and for specific clinical indications. It is important that clear information on interpretation and limitations of POCT be presented in written documents to assure roles are established and understood. A clear set of accountabilities should be communicated to participant sites up front, and supported by monitoring to confirm that expectations are met and reported back to participants (27). Furthemore, clear statements concerning courses of action when expectations are not met. There should be regular meetings at a frequency of at least quarterly for sharing of information and group decision making that involve participation by local stakeholders (31). This collaborative interaction can be done through POCT committees (11). (Figure 1)

EVALUATION AND PROCESS IMPROVEMENT

The widely accepted Donabedian model for quality in health care involves sub-grouping under areas of structure, process, and outcomes (36). This model extends quality focus beyond process to more subtle components of the interplay between structure, process, and outcome. The Donabedian model called on the consideration of ethical dimensions of participants in quality systems, was rooted in compassion, and was determined by attitudes to the patient, the profession, and higher spiritual elements, as essential contributors to a quality systems success (37). Structural metrics address how and by whom services are delivered and is covered by certification of individuals, accreditation of organizations, and whether there was adequate supporting infrastructure like special facilities and technologies in place to support service delivery. The contribution of process to quality is rooted in the specific evidence-based activities that occur during service, and these should be linked to an outcome metric, or will otherwise risk unintentional wastage of resources and effort. Outcome is the ultimate measure of healthcare performance and has traditionally focused on mortality and care-related morbidities, but recently expanded to include counts of readmissions, improvements in functional status, degree of improved accessibility, quality of life, and patient satisfaction. Hence, the patient satisfaction survey has become a common means for assessing the outcome of a service and assessing accountability of organizations and programs to the public. However, there is little evidence of an association between high patient satisfaction scores and improved outcomes (38, 39). Patient surveys reflect patient perception about services they receive - this does not necessarily align with appropriate or evidence-based practice.

Establishing a robust system to develop, monitor and manage outcomes requires a clear statement of goals and objectives and then establishing metrics accordingly. Evaluations to support quality management and continuous improvement activities (6, 31, 34) should be system-imbeded as part of a standardized POCT quality management system applied across the testing network. When viewing the

Donabedian model through a contemporary lens at least one area seems unresolved, that is a prospective consideration of the potential for negative impacts (risks) by the system. The organization of a quality management system according to international standards including a risk management framework, carefully monitored, and continuously improving the system helps fill this gap.

CONCLUSIONS

Delivery of high quality and safe POCT programs across vast geographical areas to remote rural settings presents many challenges. Nevertheless, many jurisdictions are considering POCT as part of a more cost-effective service delivery model for servicing such populations. Establishing and maintaining multiple POCT programs in these settings is facilitated by a standardized approach but with customized consideration of each location and then by working collaboratively with local health care workers at each site. Leadership can be provided by a POCT team consisting of operational service leads and clinical doctoral leaders to provide oversight for the programs overall, and as resources for local sites participating in the POCT network. Sensitivity to local cultural norms is important to a collaborative approach by leadership, and to gaining stakeholder trust and support when establishing standardized systems for quality management and operational efficiency.

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In this issue: POCT – making the point

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Connectivity strategies in managing a POCT service

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ARTICLE

Point of Care Testing is increasingly being used for diagnosis and management of various disease states. Management of different Point of Care instruments at multiple sites can be challenging, particularly when such instruments are operated by non technical staff. Connectivity is critical for optimal management of these services which are intimately linked to operator training and competency and are important in minimising harm to the patient by reducing analytical errors. Furthermore, connectivity improves turn around time leading to faster decision making by physicians. Recent advances in technology such as 5G and artificial intelligence are likely to lead to a greater focus on personalized care as a result of big data analysis and development of algorithms.

INTRODUCTION

Point -of-care testing (POCT) is one of the fastest growing aspects of clinical laboratory testing. It is estimated to be increasing by at least 10–12 % per year, with some areas increasing 30 % per year. POCT is defined as patient sample testing at or near the site of patient care whenever medical care is needed. The purpose of POCT is to improve the patient outcomes with higher quality of care by providing immediate information to the physicians about the patient's condition (1). The clinical utilization of POCT should be evidence-based, cost-effective, and focus on improving patient outcomes (2).

WHAT IS CONNECTIVITY

It is a process that enables Point of Care instruments to connect with the Lab or Hospital Information Systems and link with the electronic medical record. An open-access data management system is a key prerequisite as it enables connection to devices from any manufacturer. Such a system automatically validates and transfers patient results obtained from POCT devices to the electronic medical record and helps to monitor and manage data, POCT devices, and operators.

ADVANTAGES AND BENEFITS OF CONNECTIVITY

Laboratorians need to convince hospital administrators that connectivity and its related costs are included when providing and implementing a Point of Care service particularly when it involves multiple sites, multiple tests and multiple instruments. A systematic review identified quality assurance, regulatory issues, and data management as recurrent, significant barriers to clinical implementation of POCT (2).

Faster TAT and error prevention

Since the greatest benefit of a POCT result is a rapid turn around time (TAT), connectivity enables timely reporting of results, with results flowing automatically to patients' electronic medical records. The diversity of point-of-care testing (POCT) locations, devices, and operators makes its management and connectivity challenging. Clinical governance implies that a QC strategy is in place such that POCT improve the clinical outcome, safety, reliability, suitability and efficiency of the POCT testing process (3-5). POCT is usually carried out by non-laboratory personnel, who sometimes may not appreciate the value of quality assurance practices and find them a burden resulting in non compliance of such procedures (6). Most errors in POCT have been reported to be analytical (7) which highlights the importance of QC procedures as well as operator training and competency and how the potential harm to a patient may be greater than laboratory based tests (8). In practice many hurdles are faced when training large numbers of operators and keeping track of their competency, particularly with staff turnover. Connectivity allows these operations to be managed seamlessly and more effectively. Current data systems have the ability to monitor several instruments from multiple manufacturers.

Quality control, instrument maintenance, operator management and competency

ISO 15189 states that "Quality Control (QC) materials shall be periodically examined with a frequency that is based on the stability of the procedure and the risk of harm to the patient from an erroneous result" (1). QC connectivity enables co-ordinators to keep central oversight of quality control (QC), device management, user database and competency management. POC connectivity enhances POC staff productivity and helps manage a growing POC program without the need to increase staff (9). It further

reduces the training burden on the POCT team by its ability to streamline IQC reviews and enable test performances review. Device management is critical to maintaining optimal performance of various Point of Care devices that might be used at different sites in the hospital. Connectivity through configuring alerts allows co-ordinators to identify non functioning instruments and resolve instrument issues before they become critical. As part of ISO requirements operator management is necessary whch entails verifying operator certification and competency. Thus, connectivity also supports the issuance of reports that document initial training, 6 monthly and yearly competencies, all of which are needed for accreditation purposes. Data systems are also essential for managing consumables for POCT devices. These tools include reports showing usage and device workload that laboratorians can use to establish the frequency and size of supply orders, potentially reducing costs by eliminating the waste of expired reagents and controls. Reagent and control lot numbers, as well as established QC ranges, can be entered into the data system and uploaded to the POCT devices. POC connectivity promotes overall improved documentation which includes pulling out QC and management reports.

Traceability, audits and data monitoring

There is a requirement for traceability for all aspects of the testing procedure in the ISO regulations. POCT results must be labelled clearly to show when and where they were generated, and by whom. Batch numbers of reagents and consumables must also be traceable. Accreditation standards require monitoring of data such as correlation testing, linearity and analytical measurement range verification, proficiency testing, calibration and patient identification. Data systems can automatically capture this data and document it for review. Though this can be entered manually it is prone to transcription errors and require laborious and time consuming processes. This also allows for audits that ensure that quality assurance procedures are being followed in a timeous manner and ensure adequate risk management and error prevention that are associated with POCT. For example giving insulin based on erroneous glucose results is a significant patient care risk (10) Another study from Canada reported the value of audits in identifying repeat discordant glucose results. (11) Furthermore, POC connectivity makes possible automated billing for all POC tests. Revenue leakage of up to 20% can be caused from tests conducted not being recorded in the Electronic Health Record (EHR).

Connectivity for regulatory compliance and inventory management

Two areas of the testing process are usually scrutinised as part of regulatory requirements. The first is the training and competency of the personnel carrying out the testing and the second is the verification of strict adherence to the procedures specified by the manufacturer. These are labour intensive and time-consuming, especially for large POCT programs that include multiple testing locations, a large number of operators, and an extensive POC test menu. The use of Data Management Systems (DMS) reduces the manual workload and improves efficiency for the POCT coordinator.

Accreditatation

Accreditation is a good way to demonstrate competence and commitment to a high standard of service, with responsibility assigned to the appropriate stakeholders within a healthcare system (12). For point-of-care tests, the use of information systems directly interfaced with the devices or connected through a middleware, serve to ensure that generated results are transmitted without manual interventions, such as transcription, as soon as they

are generated or the devices are docked. This fulfills the requirements of both accuracy and timeliness for optimizing clinical decision support, with accuracy here - meaning freedom from errors associated with manual data entry and not the analytical performance of the POCT instrument.

In the study by Mays and Mathias, 14.2% of the discrepant results (or about 1 in 100) contained risk of *patient harm* in acting on *inaccurate results* (13). Another study found that 24% of reported lab results were inaccurate in critical care patients (14). Accreditation enhances the public confidence in those test results.

THE ROLE OF STANDARDS

In the past, one drawback to POCT connectivity was that since different POCT devices have differing interface capabilities some could only be unidirectionally interfaced, while others were capable of a bi-directional interface. This was challenging and costly when it came to interfacing POC instruments with LIS, EHR or HIS. In 2000, the Connectivity Industry Consortium was formed with the goal of developing POCT connectivity standards. These standards evolved into the Clinical and Laboratory Standards Institute (CLSI) POCT1-A2 connectivity standard (15). The intent of the standard was to work toward a plug-and-play environment for POCT connectivity, where devices are easily interfaced to the LIS, EHR, and HIS. CLSI POCT1-A2, Point-of-Care Connectivity: Approved Standard—Second Edition (15) was developed for those engaged in the manufacture of point-of-care diagnostic devices. These standards have facilitated the development of POCT management systems that can connect multiple devices from various manufacturers, thereby eliminating the need for a computer for each POCT device.

STRATEGIES FOR ENHANCING CONNECTIVITY FOR POCT OPERATIONS

(a) Use of emerging technology such as intelligent connectivity to enhance POCT operations

Intelligent connectivity is the combination of 5G, artificial intelligence (AI), and internet of things (IoT) that forms what we call “intelligent connectivity.” Intelligent connectivity largely focuses on the deployment of 5G due to an increase in digital density.This functions as the percentage of connected data used in a unit of activity. This is expected to accelerate technological development from which POCT can benefit.

Artificial Intelligence (AI)

Information collected by devices such as those used for POCT, can now be easily analyzed by AI technology. This will enable personalized patient management and help in decision making. This will allow farmore effective use of data generated by POCT.

This increase of digital density due to increasing collection of data through multiple Point of Care Testing of data via IoT will generate “Big Data “ which will help create predicative algorithms by training through machine learning systems. This strategy can therefore be used in POCT to providing personalised solutions for patient management. An increase in digital density due to intelligent connectivity will also create multiple value propositions but this would need security solutions for data privacy and measures to prevent cyber-attacks.

(b) Research and networking as a key strategy to optimise connectivity solutions for POCT

Laboratories that wish to provide better POCT solutions should first research the options available. At the same time they need to contact colleagues on their experience with available data

management systems. In identifying the best option connectivity goals need to be established at the same time. Of course it is also critical to identify and consult with all stakeholders to create an environment for success and buy in. Seeking institutional approval is another ingredient that ensures financial viability and support.

Another important step is to gather key players to discuss POC connectivity goals. This early support and buy-in is an essential ingredient for success.

Use of cellular connectivity as a strategy for Point of Care Testing mangement

The use of cellular networks is also being explored in ambulances and for disaster management.

CONCLUSION

POCT results – irrespective of where they are generated or delivered – must be accurate, precise, relevant and timely to optimize clinical decision support as they have a direct impact on the medical management of patients. Quality Management of POCT in a healthcare facility must involve all stakeholders and assign responsibility appropriately. Connectivity is critical to the successful implementation of a POCT service and should be planned and costed for when such a service is desired. It will have an added benefit of fewer repeats ordered and make the service more efficient and cost effective.

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POCT in developing countries

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ARTICLE

Point of Care Technology (POCT) means acquiring clinical parameters from the place where the patient is, thus generating faster test results leading to a faster turnaround time. However, improvements in patient outcomes depend on how healthcare delivery professionals and system utilize faster turnaround times. Thus, POCT, by itself, does not lead to better clinical outcomes. Throughout the last two decades, advances in POCT have been impressive, but its impact on developing countries depends on the present healthcare infrastructure. Presently, in most developing countries, POCT is delivered in remote locations or Physicians chamber or Hospital setup of Emergency rooms, Operation Theaters, ICU. It is applied for therapeutic aid (for treatment of certain diseases like diabetes or myocardial infarction), preventive measures (for targeted screening in high-risk groups) or surveillance measures (monitoring of routine blood parameters). There are several challenges in implementing POCT

like poor patient demographics, lack of workforce, training, lacking healthcare infrastructure, reluctance in physicians to accept new technology and certain technological limits. Although it may take time, solutions to these challenges will lead to a proper implementation of POCT in the developing nations. Further, integrating it with mobile phone technology will lead to higher acceptance and application. The boom of POCT will depend on the overall improvement and capacity building in the healthcare infrastructure of developing nations.

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INTRODUCTION

Point-of-care testing (POCT) is a rapidly growing diagnostic tool that has improved delayed testing challenges in resource-limited settings worldwide, especially in areas with the unavailability of modern laboratory equipment and trained human resources [1]. The objective of POCT is to provide a rapid test result for prompt clinical decisions to improve the patient's health outcomes. It can be used in primary health care (PHC) clinics, outpatient clinics, patient wards, operating theatres, clinical departments, mobile clinics, and even small peripheral laboratories [2]. POC diagnostics are easy to use devices managed by laboratory staff and other health care professionals with basic training [3]. The World Health Organization (WHO) has provided the ASSURED (Affordable, Sensitive, Specific, User-friendly, Rapid and robust, Equipment-free and Deliverable to end-users) guideline, which forms the basis of the development of POC devices globally [4].

The POCT market is projected to reach 38 billion USD by 2022 from 23 billion USD in 2017, with a Compound Annual Growth Rate (CAGR) of 10% during the forecast period [5]. Several factors like the increasing incidence of target diseases, the high prevalence of infectious diseases, especially in developing countries, and increasing preference for healthcare from home across the globe contribute to the significant growth of POCT devices worldwide [6].

TYPES OF POCT TECHNOLOGY

In 1956, Singer and Plotz developed the lateral flow or Lateral Flow Immunoassay (LFIA) technology from the latex agglutination test [7]. This technology over the years has evolved significantly and has proven to be the most straightforward and most successful diagnostic POCT platform. Briefly, this technology uses paper, polymer, nitrocellulose or any other composite substrate membrane with the ability to separate, capture and detect the parameter(s) of interest [8]. Since the LFIA components can transport fluid (blood, serum, urine) via capillary actions, the need for using external pumps is obviated. Various formats can be used to develop an LFIA, depending on the need [9]. The immense growth of LFIA has probably been due to the vital need for preventive measures against communicable diseases, the requirement for the development of practical screening tools to manage an early diagnosis of diseases like cancer and the absence of low-cost devices with minimal mantainence requirements [10].

Although LFIA based techniques have facilitated the rapid and effortless point-of-care diagnosis of several diseases, a significant limitation in their application is due to their over-simplicity, which establishes the requirement of more complex devices capable of providing accurate diagnosis [11]. Significant advancement of microfluidic technologies and its applications have been observed in the field of laboratory diagnosis over the last 25 years [12]. This technology allows the creation of small-sized automated diagnostic devices that may complement the existing lateral flow immunoassay devices and may prove to be ideal POCT tools of the future due to their certain

advantages over LFIA [13]. These advantages include the possibility of using complex multiplexing, having different types of sequential sample pre-conditioning steps, advanced reagent storage, incorporation of simultaneous steps of addition, mixing and washing of reagents, ability to perform centrifugation at various speeds and the option to integrate various detection strategies which may eventually lead to higher sensitivity and clarity. Microfluidics has provided encouraging results in several diagnostic application like routine chemistry, immunological assays, flow cytometry and molecular diagnostics [14].

THE PAST AND PRESENT OF POCT IN DEVELOPING COUNTRIES

In the 1970s, the development of the human pregnancy test was the initial application that drove POCT platform development. Several rapid tests for detecting communicable diseases like Tuberculosis, Hepatitis-B, HIV were developed in dipstick format and were used in developing nations. Later, immunochromatographic strips were also introduced for POC based diagnosis, and the technology has witnessed several evolutions [15]. These rapid tests have become very popular in developing nations with diverse applications, including infectious diseases, cancer, and cardiac diseases.

Several study groups have evaluated the potential of microfluidics as a POCT tool, especially in developing nations' resource-limited environment. A mission named Diagnostics for All's (DFA) was initiated by George Whitesides and his team at Harvard University (2007) to expand diagnostic modalities in developing nations. The group focuses on developing cheap, easy and rapid point of care tests with minimal workforce/training requirements based on patterned paper technology. The group has reported a device for monitoring of drug-induced hepatotoxicity in individuals at risk. The device performance characters showed linear values of liver function indicators with CV <10% [16].

In South Africa, the application of a centrifugal microfluidic technique for POCT was evaluated by Hugo et al. [17]. They reported ways by which several functions employed in testing could be integrated into the centrifugal microfluidic platform for various diagnostic applications. Research groups and industries are also working on the development of a lab-on-a-chip for the diagnosis of malaria. On evaluation by a third party, a sensitivity and specificity of 96.7% and 100% respectively was reported for the prototype device. Jing et al. have reported the use of microfluidics in the diagnosis of Tuberculosis [18]. Several work is ongoing in the development of POC devices for the detection of other infectious diseases. However, most of these devices are unsuitable for developing nations as their development remains in a nascent stage without any clinical trials to validate them.

ISSUES IN POCT IMPLEMENTATION IN DEVELOPING COUNTRIES

The developing countries face several challenges and barriers in setting up appropriate infrastructures for Point of Care Testing facilities [19]. One of the significant challenges is the absence of regulatory standards for introducing POCT methods to various markets. Further, there is a shortage of qualified personnel trained in various POCT methods. In most developing countries, healthcare experts' ratio to the general population is relatively low, indicating an apparent healthcare training discrepancy. Finally, there is also an issue regarding pre-existing infrastructures, which varies across different countries and the arrangement or availability of financial resources to complete the newer diagnostic applications' purchase. It is especially relevant for the countries where the budget allocated for healthcare is considerably less in

proportion to the overall budget, making the share for diagnostics even lower. Due to the paucity of funds towards research and development of newer advanced POCT methods, there is a scarcity of POCT devices and their implementation relative to their urgent requirement in healthcare [19].

FUTURE PERSPECTIVES

It is of utmost importance that regulatory challenges are overcome while implementing new POC tools. Several microfluidic techniques have promising yet unproved potentials to aid in the POCT domain. Thus, although time-consuming in nature, regulatory processes become essential to guarantee the validity, reliability, and effectiveness of POCTs [20]. In places with the unavailability of complex laboratory instruments and personnel, the Clinical Laboratory Improvement Amendments of 1988 (CLIA) has provided the requirements needed to regulate POC devices' use. The CLIA-waiver requirements to be considered while developing and validating a new POCT device with the intent to use in developing nations have been generalized by Chin et al. [21]. The requirements are:

a. The test must be self-contained and automated, permitting the usage of unprocessed specimens
b. The test should not require technical training
c. The test should give easily interpreted results
d. The test must be robust to handle several variabilities in storage conditions, test performing timings and others.

CONCLUSION

Compared to developed nations, developing countries have many healthcare issues, making them more vulnerable to the harmful consequence of infectious and non-communicable diseases. The mortality rates from infectious diseases like Malaria, AIDS, Tuberculosis are typically higher in developing countries owing to the poor healthcare infrastructure. In the past decade, non-communicable diseases have imposed a more considerable public health burden with high morbidity and mortality in developing nations with limited resources. With such a high disease burden and strong demand, POCT devices' availability is quite limited in most developing countries. It leads to an urgent need for the research and development of newer, advanced, reliable and easy-to-implement POCT methods and devices which should also be of low cost and maintenance. Although the success of POCT in developing countries, so far, is primarily due to the contribution of lateral flow assay strips, the emerging role of microfluidics, nanotechnology and device fabrication may open up new vistas and lead to the establishment of an ideal diagnostic POCT tool of the future. Availability and implementation of such technology may quickly diminish the disease impact in these resource-limited regions and reduce the overall public health burden, especially in laboratory-free settings.

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How could POCT be a useful tool for migrant and refugee health?

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ARTICLE

Point of care testing (POCT) represents an important step forward in the clinical management of patients. POC assays are easy to use and do not require skilled personnel; therefore they are particularly useful in low resource settings where diagnostics laboratories equipped with complex instruments that require well trained technicians are not available. Samples can be processed immediately overcoming the problems related to the stability of the sample, storage and shipping to a centralized laboratory hospital based.

Furthermore, results are delivered in real-time, usually less than 1 hr; thus, a clinical decision can be taken earlier. A prompt diagnosis is crucial in the case of contagious diseases allowing a rapid isolation of the infected patient and treatment; thus, reducing the risk of transmission of the pathogen.

In this report, we address the use of POC assays in the diagnosis of infectious pathogens including hepatitis B and C viruses, human immunodeficiency virus-type 1, human papillomavirus, chlamydia trachomatis, neisseria gonorrhea, trichomonas vaginalis, mycobacterium tuberculosis and the parasite plasmodium. These pathogens are commonly detected among vulnerable people such as refugees and migrants. The described POC assays are based on nuclei acid amplification technology (NAAT) that is generally characterized by a high sensitivity and specificity.

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INTRODUCTION

In recent years, conflicts in Syria, Afghanistan, Iraq, and persecutions in South-East Asia (i.e, Rohingya in Myanmar) or sub-Saharan countries forced millions of people to leave their countries because of the economic crisis (economic migrants) or the fear of consequences if they remained in their own country (refugees). The destination is usually in neighboring countries that host the majority of refugees, but also high-income countries such as Germany, Italy, France [1]. In the last seven years, Turkey hosted the largest refugee's population with almost 4 million refugees and asylum seekers including 3.6 million Syrians and almost 330,000 people from other nations [2]. Another 1.4 million Syrians hosted in refugee camps in Jordan [3].

In Italy, during 2020, we assisted at a continuous increase in the arrivals due to the conflict in Libya [4]. International agencies, non-government organizations and governments support this vulnerable population through programs for education, healthcare, psychosocial support and other needs. The COVID-19 pandemic with its dramatic socioeconomic consequences and the impact on the health system of the affected nations, made even more critical the conditions for refugees and migrants, which already have a limited access to healthcare. Living in camps facilitates the spread of transmissible agents such as mycobacterium tuberculosis or SARS-CoV-2 with an increase in morbidity and mortality. Regarding SARS-COV-2, it has been reported that the transmission rate is high in the shelters [5], and this in turn exposes the local community to a higher risk of COVID-19. Monitoring of the health conditions of refugees and migrants within the camps is not an easy task because of the lack of clinics and hospitals. Point-of-care testing (POCT) could be a valid alternative to laboratory hospital-based testing. Furthermore, POCT does not require highly skilled and trained personnel, and overcomes the problems related to specimen stability and quality of the analytical results. Samples can be processed immediately and results delivered in real-time providing a reliable solution to the errors that may occur in the pre-analytical phase.

Here, we describe the most updated point-of-care (POC) assays using the nucleic acid amplification technology (NAAT) for the diagnosis of some common infectious diseases including viral hepatitis B and C, human immunodeficiency virus type 1 (HIV-1), sexually transmitted diseases, tuberculosis, COVID-19, and malaria.

POC ASSAYS FOR THE DIAGNOSIS OF VIRAL HEPATITIS B AND C AND HIV-1

Infection by hepatitis viruses B (HBV) and C (HCV) can be detected in serum or plasma samples by quantitative real-time PCR. The majority of the available assays are designed for batch testing of multiple specimens within a run (6-9). The Xpert® HBV Viral Load test and the The Xpert® HCV Viral Load test (Cepheid, Sunnyvale, CA, USA), on the contrary, may be run on-demand and deliver results in 90 and 105 min, respectively. The systems require a single use disposable GeneXpert cartridge, which contains

all reagents needed for sample preparation, nucleic acid extraction and quantification of PCR product. The Xpert® HBV Viral Load test has a dynamic range of quantification of 10^1 to 1×10^9 IU/mL (1.0 to 9.0 Log IU/mL), with a limit of detection (LOD) of 3.20 IU/mL for plasma and 5.99 IU/mL for serum according to the manufacturer's product package. The viral genome region targeted by the primers and probe set is the preC-C (Pre-Core-Core) gene. The assay detects the HBV genotypes A to H. Comparative studies showed the good performance of the Xpert® HBV Viral Load test when compared to other validated assays used for monitoring chronic HBV patients [10-14].

The Xpert® HCV Viral Load test quantifies HCV RNA within a range of 10 to 100,000,000 IU/mL and is validated to detect HCV genotypes 1 to 6. LOD is 4.0 IU/ml for EDTA plasma and 6.1 IU/ml for serum. It performed equally well when compared to the Abbott RealTime HCV viral load similarly to the Xpert HCV Viral Load Finger-Stick POCassay [15].

The Xpert® HIV-1 viral load assay allows the measurement of HIV-1 RNA in plasma in 91 min using a single cartridge for RNA extraction, purification, reverse transcription and cDNA real time quantitation. Test can be run on demand. Considering the very high number of infected individuals in the sub-Sahara African region, this molecular tool may be useful for monitoring infected individuals on therapy and whenever is required an urgent testing [16, 17]. The linear range of quantification of the assay is comprised between 40 to 10, 000, 000 copies/ml, and detects HIV-1 groups M (subtypes A, B, C, D, AE, F, G, H, AB, AG, J, K), N and O.

Instead, Xpert® HIV-1 Qual is designed to detect acute infection in high-risk population or vulnerable subjects. The test can be run on dry blood spot (18) or whole blood and delivers result in 93 min. There is a high correlation with widely used validated molecular assays [16-18] (Table 1).

POC ASSAYS FOR THE DIAGNOSIS OF SEXUALLY TRANSMITTED INFECTIONS

Sexually transmitted infections are still a significant global health problem, especially in developing countries where infections by human papillomavirus (HPV), chlamydia, gonorrhea, syphilis and trichomonas vaginalis are widespread [19]. POC testing can be a useful approach to identify quickly infected people. There are several HPV point-of-care testing platforms in the market such as the *care*HPV test (Qiagen, Hilden, Germany), but only the Xpert® HPV has been validated for the rapid detection of 14 high-risk HPV types [20] reported as HPV16, HPV18/45 or other high-risk HPVs (31, 33, 35, 52, 58; 51, 59; 39, 56, 66, 68). Time to result is 60 min. On the same platform can be run rapid tests for chlamydia trachomatis (CT), neisseria gonorrhoeae (NG) and *trichomonas vaginalis* (TV), which provide result in 90 and 40 min, respectively.

Other POC assays for CT/NG include the io CT/NG Assay (binx health, Inc) that uses a specific single use cartridge where the sample is directly loaded. Time to result is 30 min and the amplified product is detected by hybridization of the labeled probe and cleavage of the label [21]. Trichomonas vaginalis can be detected also by AmpliVue assay, Aptima, and Solana POC assays [22]. AmpliVue assay uses isothermal helicase-dependent amplification (HAD) and targets a conserved repeat DNA sequence of TV. The amplified product is visualized by lateral-flow strip-based colorimetric detection in a disposable device. The turnaround time is about 45 min. The assay showed a sensitivity of 100% and a specificity of 97.9%–98.3% when compared to microscopy or culture methods [22]. Compared to reference standard Aptima TV NAAT assay,

Table 1 Validated POC assays for the detection of HBV, HCV, HIV-1

Molecular assay	Specimen type	Target gene	Limit of detection (LOD)	Linear range	Time to result	Company
Xpert® HBV Viral Load test	Plasma EDTA or serum	Pre-Core-Core	3.20 IU/mL in plasma and 5.99 IU/mL for serum	10 to 1 × 10^9 IU/mL	< 60 min	Cepheid, Sunnyvale, CA, USA
Xpert® HCV Viral Load test	Plasma EDTA or serum	5'Untranslated region (UTR)	4.0 IU/mL in plasma and 6.1 IU/mL in serum	10 to 1 X 10^8 IU/mL	105	Cepheid, Sunnyvale, CA, USA
Xpert® HCV Viral Load Finger-Stick test	Whole blood	5'Untranslated region (UTR)	22 IU/mL genotype 1a, 35 IU/mL genotype 6e	100 to 100^8 IU/mL	< 60 min	Cepheid, Sunnyvale, CA, USA
Genedrive® HCV ID Kit	Plasma EDTA	5'Untranslated region (UTR)	Sensitivity at the detection threshold of 12-16 IU/ml	NA*	90 min	Genedrive Diagnostics Ltd, Manchester, UK
Xpert® HIV-1 viral load test	Plasma EDTA	ND*	18.3 cp/ml (WHO reference material); 15.3 cp/ml (VQA reference material)	40 to 10 6 copies/ml	91 min	Cepheid, Sunnyvale, CA, USA

**NA: Not applicable; ND: Not declared.*

the sensitivity of the AmpliVue was 90.7%, and the percent of agreement was 97.8% (Cohen's kappa=90.7) [23]. Solana TV assay is a qualitative PCR, which targets a conserved repeat DNA sequence of the microorganism using the HAD technology. The assay showed a high sensitivity and specificity in detecting TV in swabs and urine of both symptomatic and asymptomatic women when compared to FDA reference standards. Compared to the Aptima TV assay the sensitivity/specificity performance was 89.7%/99.0% for swabs and 100%/98.9% for urines [22]. Finally, Xpert TV showed a high sensitivity and specificity when testing vaginal swabs (96.4%/99.6%), endocervical swabs (98.9%/98.9%) and urine (98.4%/99.7%) [22] (Table 2).

Table 2 POC assays for sexually transmitted diseases

Molecular assay	Specimen type	Target gene	Time to result	Company
Xpert® HPV	Cervical cells	E6/E7	60 min	Cepheid, Sunnyvale, CA, USA
Xpert® CT/NG	Cervical, vaginal, rectal, and pharyngeal swabs; urine	gDNA (one)/ gDNA (two independent)	90 min	Cepheid, Sunnyvale, CA, USA
Xpert® TV	Vaginal and endocervical swabs; urine	*gDNA*	40 min	Cepheid, Sunnyvale, CA, USA
io CT/NG Assay	Vaginal swab; urine	gDNA (one)/ gDNA (two independent)	30 min	binx health, Inc, MA, USA
AmpliVue Trichomonas assay	Vaginal swab	Conserved repeat DNA sequence	45 min	Quidel, CA, USA
Solana TV assay	Vaginal swab; urine	conserved repeat DNA sequence	< 40 min	Quidel, CA, USA

POC ASSAY FOR THE DIAGNOSIS OF TUBERCULOSIS

Early detection of mycobacterium tuberculosis (MTB) is of paramount importance for improving patients' management and to reduce the risk of infection transmission. A POC assay endorsed by the WHO (http://www.euro.who.int/__data/assets/pdf_file/0006/333960/ELI-Algorithm.pdf) that responds to this need is the Xpert® MTB/RIF Ultra (Cepheid, Sunnyvale, CA, USA). The assay detects MTB and rifampicin resistance simultaneously in less than 80 min, and can resolve quickly those cases with a negative smear at microscopy [24]. The system is easy to use and is highly sensitive (11.8 cfu/ml) and the probes target the *rpoB* gene (Cepheid | MTB/RIF Molecular Test - Xpert MTB/RIF Ultra).

POC ASSAYS FOR THE DIAGNOSIS OF SARS-COV-2

Nowadays, emergency department are overcrowded by patients who present at admission with respiratory symptoms suggestive of coronavirus disease 2019 (COVID-19) caused by the recently uncovered severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). These patients are confined into dedicated areas in order to limit the risk of viral transmission to negative patients until the result of the PCR becomes available. With the currently available platforms, results are not available before 4-5 hr from the arrival of the sample in the laboratory. In order to speed up the diagnostic process, to reduce the risk of transmission within the hospital, and to start treatment earlier, POC assays may represent a valid diagnostic alternative. Actually, POC assay on average deliver results in less than 1 hr [25], and have a high sensitivity and specificity [26]. We have recently demonstrated an excellent level of agreement between the Allplex™ SARS-CoV-2 assay and the POC VitaPCR™ SARS-CoV-2 assay [26], confirming the utility of POCT testing in the screening of suspected COVID-19 patients [27]. A list of some POC assays currently available on the market is reported in Table 3.

POC ASSAYS FOR THE DIAGNOSIS OF MALARIA

Malaria is a global health problem and its eradication is one of the major goals of the WHO. Five plasmodium species are known to infect humans: P. falciparum, P. vivax, P. ovale, P. malariae, and P. knowlesi [28]. Severity of the disease may vary in relation to the plasmodium species; therefore, a correct identification is important for the best therapeutic approach as well as an high sensitivity. A sensitive assay is important for the identification of asymptomatic carriers that are potential infectious reservoir for the plasmodium spread [29]. Although validated assays are not available yet, efforts have been made to construct portable PCR machines that could be used near the patient [30-33]. A promising platform consists of a disposable plastic chip and a portable real-time PCR machine. The chip contains a desiccated hydrogel with the reagents needed for the identification of plasmodium by PCR. The chip can be stored at room temperature and rehydrated on demand with unprocessed blood [33].

CONCLUSIONS

POC diagnostics is becoming increasingly important within health service systems either in developing and advanced countries. The short turnaround time, the high specificity and sensitivity, the possibility to use unprocessed samples and the easy-to-use improved patients' management reducing the time of diagnosis and accelerating treatment. In the hospital settings, this translates in a more rapid transfer of the patient from the emergency department to the most appropriate clinical area. In the case of shelters where are hosted refugees or immigrants, POCT allows screening of numerous people in real-time without the need of shipping the samples to centralized hospital-based laboratories. The availability of test results in real-time allows to take immediate clinical decisions without delays with positive effects on the individual health. Vulnerable people that live in remote areas or hosted in camps or shelters will be those who benefit most from this new technology. The assays described allow for testing one or multiple infectious agents. Decision to test for one or multiple infectious agents is made based on the triage questionnaire administered to the patient.

A limitation of this new technology is represented by the cost of the assay, which is usually higher of a standard laboratory assay. A politics aiming at lowering the price of such reagents would facilitate their use in low resource settings with benefits for the local population.

Table 3 A short list of POC assays validated for the detection of SARS-CoV-2 RNA in respiratory samples

Molecular assay	Specimen type	Gene target	Limit of detection (LOD)	Time to results	Company
Xpert Xpress SARS-CoV-2	nasopharyngeal, nasal, mid-turbinate swab	E, N2	250 copies/ml	45 min	Cepheid, Sunnyvale, CA, USA
QIAstat-Dx Respiratory SARS-CoV-2 Panel	Nasopharyngeal swab	E, ORF1b, RdRp	500 copies/ml	60 min	Qiagen, Hilden, Germany
BIOFIRE® Respiratory panel 2.1	Nasopharyngeal swab	S, M	160 copies/ml	45 min	bioMérieux, Marcy l'Etoile, France
Simplexa™ COVID-19 Direct kit	nasal swab, nasopharyngeal swab, nasal wash/aspirate, and bronchoalveolar lavage	ORF1ab, S	500 copies/ml(NPS, NW/A) 242 copies/ml(NS): 1208 copies/ml (BAL)	> 60 min	DiaSorin Molecular LLC, Cypress, CA, USA
VitaPCR™ SARS-CoV-2 Assay	Nasopharyngeal swab, oropharyngeal swab	N	2.73 copies/µl	20 min	Menarini Diagnostics, Florence, Italy
ID NOW COVID-19 assay	Nasopharyngeal swab, throat swab	RdRp	125 genome equivalents/ml	13 min	Abbott Diagnostics, IL, USA

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In this issue: POCT – making the point

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Direct to consumer laboratory testing (DTCT) – opportunities and concerns

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ARTICLE

Direct to consumer laboratory testing has the potential for self-empowerment of patients. However, the Direct to consumer laboratory testing (DTCT) uses loopholes which are related to the particular situation of healthcare: While advertisements and claims for medical usefulness are very high regulated in healthcare, essentially no regulations safeguard the consumers in DTCT. The same is true for the quality of testing services since quality regulations are only mandatory in healthcare. Another problem is the lack of medical interpretation of test results. Besides being very risky for the consumers, healthcare professionals relying on test results obtained by DTCT must be aware about the risks of these data.

INTRODUCTION

With the advent of point of care testing as well as with the self-empowerment of patients ("P4-medicine") [1] and the availability of some disruptive technologies, there is no need to send all patients' specimen to a medical laboratory for testing and result reporting. One argument for increased Direct to consumer (DTC) access has come from the so-called "quantitative self-movement" which argues that increased data collection and subsequent analysis may fundamentally improve the ability for individual patients to understand and predict the state of their health [2]. Some Direct to consumer laboratory testing (DTCT) data can be analyzed by swarm intelligence or by big data analysis which allows new observations not possible with previous methods of healthcare. However, the focus on patient autonomy allows the selection of data and will introduce a significant bias to the conclusions. E.g., when DTCT is used for infectious disease testing and the positive results are excluded from the database because of fear of discrimination, analysis of these data will grossly underestimate the disease prevalence.

These new technical possibilities challenge the definition of healthcare and the legal regulations which are necessary to protect patients' wellbeing. These definitions – despite being universal – are rather complex and even differ between countries. Internet technologies will make country borders become invisible. Related to the "world-wide marketplace of laboratory tests" are attempts to blur the difference between laboratory testing for healthcare and for lifestyle purposes. The first being highly limited and regulated, the latter with very little regulation to allow free trade and the rules of the marketplace. In particular in genetic testing, in some countries such as Austria, Switzerland and Germany very strict laws protect the patient and the relatives [3]. The background of these legislations is the idea of genetic data exceptionalism and regulates in particular inaccurate promises, the discrimination of persons according to their genotype and an elaborate data protection for the results of genetic analyses [4]. If samples are sent to other countries and particular if treated as lifestyle tests, the impetus of these laws can be easily circumvented.

A challenge in laboratory testing (in vitro testing) is the impossibility of the patient to judge the quality of the Clinical Pathology service obtained: the direct contact will occur in exceptional situations only and the patient must rely on the intrinsic hurdles such as self-declaration, legal regulation and supervision by the authorities and often marketing buzz. Legal regulations in particular for in in vitro diagnostic differ substantially between health systems: E.g., in the US the FDA approves test kits for use in healthcare and CLIA approves medical laboratories individually on a regular basis. In Germany, the focus is on structural quality of medical laboratories and on performance quality (internal quality control and external quality assessment) which is regulated by the RiliBÄK (Guidelines of the National Physicians Chamber) [5]. Test kits are regulated by EU legislation similar to FDA approval (called "CE-marking"). However, for laboratory testing outside of healthcare (such as for lifestyle testing or for DTC), there are essential no quality qualifications or formal approval to be met. For lay persons, it will be nearly impossible to detect fraud by counterfeited FDA or CE markings on reagents.

Particular targets of novel testing formats are healthy subjects, obviously to access new markets and generate profits. Laboratory testing is offered to these persons "to guide their lifestyle". Numerical values such as those obtained in Clinical Pathology as well as by wearable computers ("wearables") are used to assist these persons [6]. Mostly, it remains unclear whether the purpose of this laboratory

testing is only lifestyle coaching with automatic "canned comments" (=lifestyle) or whether in fact this testing should better be regarded as regular healthcare with individual diagnoses and recommendations. The situation gets even more complex in genetic testing, not only due to ease of deducing the genotype of a person from genetic test results performed in relatives. In the US, strict regulations are in place for medical genetic tests, however, the FDA allows genetic lifestyle tests in general. It is obvious, that – rather unpredictable – some "innocent" genetic markers used for lifestyle purpose to a later point in time might become strong genetic markers with severe health implications for the patient and even his relatives. Examples are the ε3 and ε4 genotypes of APOE, which have only very little effects on lipoprotein metabolism [7] but became one of the most important markers for Alzheimer's disease [8]. Genetic counseling starts before testing with the "right of not-knowing". This right is non existing when in DTCT testing can be performed without genetic counseling. In fact, actionable action will occur based on the genetic test results even only by the interpretation of the patient himself, by using internet resources, or by medical counseling [9].

LABORATORY SETTING

Laboratory testing can be performed in different settings: The conventional testing is performed in medical laboratories; some testing is performed as POCT (point of care testing). This testing is also part of healthcare and the testing is mostly performed by medical professionals. Another type of testing is DTC (direct to consumer testing). In DTC, medical professionals are often not involved at all. The consumer (the term patient is avoided intentionally) buys either the testing device or submits his sample to a (nonmedical) laboratory and is the direct recipient of the test result [6]. Typical examples are home urine pregnancy testing, lactate testing for fitness purposes or the submission of body fluids by the consumer himself for quantitative testing or for genetic testing via mail. A recent application is self-testing for SARS-CoV-2 Antigen testing from oral fluids [10]. New techniques challenge the clear separation in particular with another layer of differentiation: in healthcare, only tests with a proven medical use may be used (evidence-based medicine). In dealing with consumers, these restrictions are not in place and the rule of marketplace allows offering tests without proven use and even with potential harm to the consumer. When different testing scenarios are listed, some tests might even fall within all of these categories. For example, the continuous glucose monitoring in patients with insulin-dependent diabetes mellitus is a medical evidence-based method [11]. However, it is performed at the point of care setting or even at home. Only some medical supervision is needed so that in most of the time the patient is the direct recipient of the testing results and will adjust insulin dosages directly from the reading of the meter. Other tests such as food stuff related IgG4 are offered by sending capillary blood drawn by the patient by mail to a central laboratory. In this case, this will be named DTC despite the testing is performed in a laboratory: there is no medical evidence for this kind of testing and the testing is only performed to satisfy the patients' curiosity (and to generate revenue for the provider of these tests). Other tests such as borrelia testing in ticks are tests neither related to healthcare nor to DTC: in this case, only non-human samples (=ticks) are analyzed. Again, there is complete lack of any medical use for this kind of commercial testing. SARS-CoV-2 Antigen testing as DTCT will erode the restriction for testing certain contagious diseases by physicians only (as defined in the Medical Act and the Quacksalver Act such as the "Heilpraktiker Gesetz" in Germany) and

will also cease the notification of public healthcare bodies since this notification is mandatory for physicians only.

CHANCES AND CHALLENGES OF DTC

One challenge is to define the purpose of laboratory testing in apparently healthy subjects: in essentially all situations, the customer (patient) is not interested in the numeric results of a test but wants an answer to possible personal consequences of testing, the medical interpretation of the testing results. It is challenging to give this individual answer to the patient when the testing may be performed only beyond healthcare* (**In essentially all countries there is a restriction of healthcare to physicians. Healthcare encompasses the diagnoses of illnesses, the prescription of diagnostic examinations, the use of invasive and/or risky diagnostic techniques, the determination of medical treatment, the prescription of medications, the clinical monitoring of patients, giving pregnancy care and deliveries and decision about isolation measures in contagious diseases*). Therefore, it is not unexpected, that the providers of DTC use rather confusing and contradictory descriptions of the services delivered. In short, in their advertisements they offer individually tailored comments and personal recommendation to the testing results but in the fine print they stress that the services offered are for wellness purposes only and may not substitute medical treatment.

Another challenge is the clear definition of medical use of tests performed in Clinical Pathology. Only very few – if any -- tests offered are clearly without any medical use. Especially many esoteric tests can be beneficial in highly selected patients and it could not be justified to ban these tests because of their limited use. However, medical knowledge is essential to restrict these tests to patients who might benefit from them. If the selection of these tests has to be done by the consumer himself, chances are very high that tests are not used to increase the consumer's / patient's benefit. There is even a very high chance that the tests produce only medical, psychological and economic harm to the users of the tests and even on society as a whole [12]. In the concept of medical commons, the resources of healthcare are limited and therefore it is the responsibility of the healthcare professionals to respect the needs of society as a whole and to use the resources in healthcare with caution [13]. If unnecessary laboratory tests are ordered, chances are very high that even under state-of-the-art conditions numerous abnormal (=out of the reference range limits) test results will occur just by chance. If medical tests with little medical meaning or / and even insufficient performance of the testing procedure are used, even a remarkably high percentage of all test results will be abnormal and will confuse the customer. A similar situation is present for genetic tests when – driven by curiosity – testing is performed in the absence of a medical questions and the high number of genetic variants (many of them with unknown meaning) or of testing errors will lead to extensive follow-up procedures. In most case, the costs for the follow-up medical procedures (such as additional laboratory testing, invasive procedures, psychological support) has to be covered by the society (such as public health insurance) even when the impetus of testing was the sole curiosity of the customers [12]. Given the concept of reference ranges with 5% of the results being "abnormal" and the long list of tests available on the background of the current health illiteracy of the population, the contralateral damage of DTC is of extremely high impact. When the real performance of DTC is monitored, the rate of abnormals is even much higher (about four times higher than regular laboratory tests) [14]. In average, a testing panel of only 5 tests will result in one false abnormal result!

Another challenge is DTC testing performed at the interface between lifestyle testing and healthcare. This occurs if data from DTC are presented to the attending physician to guide medical therapy. This is of particular concern since DTC testing has not to be performed under the same quality standards (e.g. in Germany, quality standards are only given for testing in healthcare and not for lifestyle purposes [5]) and in the US, huge DTC companies either claimed to be exempt from FDA approval since the tests allegedly were developed and used only within the organization (under the exemptions valid for laboratory developed tests) or they failed to reach minimum performance goals over extended periods of time for critical tests such as in coagulation testing [15]. If a physician relies on the (incorrect) data presented from DTC, the liability will be with the physician primarily. It will be difficult or even impossible to charge the health-illiterate patient, the unqualified non-medical laboratory or the administrator of the hospital or the health plan who recommended the DTC laboratory since the physician is regarded to be the only one in the whole process who could judge medically the (insufficient) quality of the DTC services. A comparable situation is present when the patient himself performs the testing and the physician relies on this self-testing data only [9]. In these cases, the integrity of the data presented to the physician is another point of concern since unlike to the protected and elaborate ways of data collection in health, consumer health data are often collected by apps which can be easily manipulated by the patient or by others.

Another challenge by DTC is the concept of obtaining evidence in medicine: In DTC, the restrictions of healthcare are not valid. The medical claim of a certain test or of a panel of tests have to be judged in studies and the conclusion of these studies have been scrutinized by structured processes by peers and institutions such as in health technology assessment [16]. In DTC, often blogs and social media are used to advertise the products. Typically, the "experiences" of consumers (i.e. bloggers paid and supported by the vendor of the tests) are presented who claim improved vitality after getting the individual recommendations of DTC. These, false, claims would be illegal in health care. However, if a possible customer of a certain DTC test will do a search in the internet, essentially all comments on these tests will only be the biased recommendations of the test and scientifically-proven negative comments appear at the end of the search list only. This shows that social media and online comments offer an easy way to inject biased, incorrect, or misleading information. It is a continuing challenge of the medical and scientific community to respond to these online comments to build up a counterpart. This can be particularly challenging since the business plan of DTC companies can be severely challenged by evidence-based clarifications and the DTC companies will try to eliminate such clarification by the whole armamentarium of legal allegations [17] and 'trolls' (online harassers) [18].

Other challenges of DTC is the intense use of IT services [19]. Medical data is regarded as overly sensitive data and numerous restrictions for storage and access must be obeyed by healthcare professionals. Additional regulations prohibit the exclusive use of telemedicine in some countries such as in Germany. Critical is the intense use of external IT service providers because of the risks such as data theft, right of possession of medical data, integrity of medical data, legal issues of cloud storage and numerous other issues. If IT services become essential for the medical process, another obstacle is the general relation between a patient and his physician who becomes invisible behind the IT interface: Unlike a commercial firm, physicians may not extend their services by unlimited hiring employees or even

outsourcing medical services. E.g. in Germany, there is the obligation in medicine to render qualified services and in person (Common service law §613 (1) "BGB", Physician law: §19 (1), for patients under public insurance §32 (1) "Zulassungsverordnung für Vertragsärzte" and §15 (1) „Bundesmantelvertrag-Ärzte"). Other professions such as biomedical specialists can be employed in the Clinical Pathology laboratory, but the whole laboratory must be guided and managed by the Clinical Pathologists and may not be a huge commercial testing facility only.

CONCLUSION

DTCT bears severe risks to patients and customers relying on the results of these tests. Of particular concern is in many cases the absence of claims of medical usefulness. In addition, despite being an in vitro method, there is a very high chance of substantial medical harm as well as of severe economic impact on the users of DTC testing (psychic harm, follow up procedures) and on the society as a whole with huge negative impact on medical commons.

In addition, the negative news of large-scale wrong-doing in DTC and the replacement of evidence-based medicine by advertisements in the social media jeopardize the privileged situation of healthcare and of real laboratory testing in Clinical Pathology laboratories. Outside the laboratory, there are extremely high personal liability risks for healthcare professionals relying on DTCT data. Finally, the essential and medically-sound regulations of genetic data protection laws as well as of infection control are often leveraged by DTCT.

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Clinical assessment of the DiaSorin LIAISON SARS-CoV-2 Ag chemiluminescence immunoassay

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ABSTRACT

Background

Due to the large volume of tests needed in a relatively short time for screening and diagnosing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, antigen immunoassays may provide a potential supplement to molecular testing. This study was aimed to assess the clinical preference of DiaSorin LIAISON SARS-CoV-2 Ag chemiluminescence immunoassay.

Methods

An upper respiratory specimen was collected in a series of patients referred to the Laboratory Medicine service of Pederzoli Hospital (Peschiera del Garda, Verona, Italy) for screening or diagnosis of SARS-CoV-2

infection. Nasopharyngeal samples were assayed with DiaSorin LIAISON SARS-CoV-2 Ag test and Altona Diagnostics RealStar® SARS-CoV-2 RT-PCR Kit.

Results

The final study population consisted of 421 patients (median age, 48 years; 227 women), 301 (71.5%) with positive result of molecular testing, and 126 (29.9%) with cycle threshold (Ct) values of both *E* and *S* genes <29.5, thus reflecting higher infectivity. The area under the curve of DiaSorin LIAISON SARS-CoV-2 Ag test 0.82 (95% CI, 0.79-0.86) for sample positivity and 0.98 for higher sample infectivity (95% CI, 0.97 to 0.99). The optimal cut-off for sample positivity was 82 $TCID_{50}$/mL (0.78 sensitivity, 0.73 specificity and 77% diagnostic accuracy), whilst that for identifying samples associated with a high infective risk was 106 $TCID_{50}$/mL (0.94 sensitivity, 0.96 specificity and 95% diagnostic accuracy).

Conclusion

The performance of this chemiluminescence immunoassay would not permit it to replace molecular testing for diagnosing SARS-CoV-2, but may enable rapid and efficient detection of subjects with high SARS-CoV-2 viral load, who are responsible for the largest proportion of infectious clusters.

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INTRODUCTION

Irrespective of the need for timely identification, isolation and/or treatment patients with active severe acute respiratory coronavirus 2 (SARS-CoV-2) infection, targeted population screening may represent a valuable resource for purposes of preventing or containing COVID-19 outbreaks [1,2]. Recent guidance provided by both the World Health Organization (WHO) [3] and the Task Force on COVID-19 (coronavirus disease 2019) of the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) [4] has endorsed the potential usage of antigen immunoassays, which are specifically designed to detect various SARS-CoV-2 antigens (especially those of the nucleocapsid protein) in biological materials, mostly nasopharyngeal samples and saliva.

The more clinically valuable and safe applications of SARS-CoV-2 antigen immunoassays encompass the screening of subjects with highly suggestive signs or symptoms of infection, those entering high risk workplaces or other crowded settings (e.g., long term care homes, healthcare facilities, schools, airports and stations, factories, offices and theatres, among others), as well as subjects with known exposure to SARS-CoV-2 infected individuals. In all these cases, a positive result of a SARS-CoV-2 antigen immunoassay is associated with a higher probability of active SARS-CoV-2 infection, whilst a negative test result cannot straightforwardly rule out the possibility of an ongoing infection characterized by low nasopharyngeal and/or saliva viral load [3-5]. This aspect has hence persuaded both the WHO and the IFCC Task Force on COVID-19 to emphasize the importance of the diagnostic performance characteristics in assay selection, thus recommending the use of SARS-CoV-2 antigen immunoassays with high specificity (i.e., preferably ≥0.97) and acceptable sensitivity (i.e., advisably ≥0.80).

Besides the vast array of the so-called antigen rapid detection tests (Ag-RDTs) currently available on the diagnostic market, as recently reviewed by the Cochrane COVID-19 Diagnostic Test Accuracy Group [6], some immunoassays fully suited for central laboratory automation are becoming increasingly available by the in vitro diagnostic industry. There are many potential advantages to these tests compared to Ag-RDTs, thus including higher analytical sensitivity, generation of quantitative results, larger

throughput and possibility of full interface with the laboratory information system (LIS), thus enabling to permanently store test results for longitudinal patient monitoring and/or for guiding clinical decision making, since higher viral loads have been convincingly associated with enhanced risk of clinical deterioration and/or development of severe/critical illness in patient with COVID-19 [7]. Therefore, this study was aimed to assess the clinical performance of the novel DiaSorin LIAISON SARS-CoV-2 Ag chemiluminescence immunoassay.

MATERIALS AND METHODS

Study population

The study population included a series of patients referred to the Laboratory Medicine service of the Pederzoli Hospital (Peschiera del Garda, Verona, Italy) between March 29 and April 18, 2021, for diagnosis or screening of SARS-CoV-2 infection. An upper respiratory specimen (Virus swab UTM™, Copan, Brescia, Italy) was collected upon hospital admission from each patient by a skilled healthcare operator and was then used for both SARS-CoV-2 antigen and molecular testing. All specimens were analyzed within 1 hour from collection.

DiaSorin LIAISON SARS-CoV-2 Ag

The novel DiaSorin LIAISON SARS-CoV-2 Ag (DiaSorin, Saluggia, Italy) is a fully-automated chemiluminescence immunoassay developed for quantitative assessment of SARS-CoV-2 nucleocapsid (N) antigen protein in nasal or nasopharyngeal swabs eluted in universal transport medium (UTM) or viral transport media (VTM). According to the manufacturer, the target usage of the assay should be when reference molecular tests are unavailable, when the long turnaround time of molecular testing may preclude timely patient management, as well as for permitting to analyze large volumes of specimens during outbreaks and/or for screening asymptomatic people with the purpose of identifying potential SARS-CoV-2 (super)spreaders.

Briefly, anti-SARS-CoV-2 nucleocapsid rabbit polyclonal antibodies are coated onto magnetic particles linked with an isoluminol derivative. During a first incubation step, the nucleocapsid antigen eventually present in the test sample binds to the conjugate. After a subsequent incubation, the solid phase reacts with viral antigens bound to the conjugate, and the unbound material is then removed by washing. The starter reagents are then added, triggering a flash chemiluminescence reaction, whose light signal is proportional to the concentration of SARS-CoV-2 nucleocapsid antigen present in the test sample.

According to the manufacturer's declaration, the time to first test result performed on the fully automated chemiluminescence analyzer LIAISON® XL (DiaSorin, Saluggia, Italy) is 42 min, the throughput is 136 tests/hour, the analytical sensitivity is 22 $TCID_{50}$/mL, the upper limit of quantitation is 100,000 TCID50/mL, whilst the total imprecision ranges between 2.9% to 18.4%. The values of the local total imprecision, calculated on daily performance of quality controls, were almost overlapping.

Altona Diagnostics SARS-CoV-2 molecular testing

Altona Diagnostics RealStar® SARS-CoV-2 RT-PCR Kit (Altona Diagnostics GmbH, Hamburg, Germany) is a real-time reverse transcription polymerase chain reaction (rRT-PCR) assay for detecting SARS-CoV-2 RNA in a vast array of clinical specimens, including nasopharyngeal swabs. This technique entails two separate amplification and detection steps of SARS-CoV-2 genes, the first targeting the *E* gene sequence and the second the *S* gene. The test also uses a set of probes and primers for amplifying an

internal control, aimed at sorting out possible rRT-PCR inhibition. The assay was perfumed using a Bio-Rad CFX96™ Deep Well Dx Real-Time PCR Detection System (Bio-Rad Laboratories, Hercules, CA, USA). Test results were reported both as quantitative and qualitative measures. In the former case, results were provided as cycle threshold (Ct) value of both *E* and *S* genes, whilst qualitative data were reported as positive/negative at test cut-off (i.e., Ct <45 or ≥45) or at the infectivity threshold defined Gniazdowski et al. (i.e., Ct <29.5 or ≥29.5) [8]. The assay has a total run time of around 2-3 hours.

Statistical analysis

The diagnostic efficiency of DiaSorin LIAISON SARS-CoV-2 Ag was assessed by comparing test results with those obtained with molecular testing, using Spearman's correlation, by constructing receiver operating characteristic (ROC) curves, and calculating the diagnostic accuracy, sensitivity and specificity at the two diagnostic thresholds of rRT-PCR positivity (i.e., Ct value <45) and association with potential infectivity (i.e., Ct value <29.5).

Statistical analysis was performed with Analyse-it software (Analyse-it Software Ltd, Leeds, UK). Quantitative data were reported as median mean and interquartile range (IQR).

The investigation was performed as part of routine clinical laboratory operations, using pre-existing specimens collected for systematic SARS-CoV-2 diagnostic screening and testing at the local facility, and thereby patient informed consent and Ethical Committee approval were unnecessary.

All test results were anonymized prior to statistical analysis. The study was conducted in accordance with the Declaration of Helsinki, under the terms of relevant local legislation.

RESULTS

The final study population consisted of 421 patients (median age, 48 years and IQR, 31-59 years; 227 women, 53.9%), 301 (71.5%) with positive result of rRT-PCR (i.e., Ct values of both *E* and *S* genes <45), and 126 (29.9%) with Ct values of both *E* and *S* genes <29.5, thus reflecting potential association with higher infectivity according to Gniazdowski et al. [8]. In the 301 rRT-PCR positive samples, the Spearman's correlation between antigen concentration and Ct values of the *E* and *S* gene was r = -0.85 (95% CI, -0.88 to -0.82; p<0.001) and r = -0.84 (95% CI, -0.87 and -0.81; p<0.001), respectively.

The distribution of DiaSorin LIAISON SARS-CoV-2 Ag values in nasopharyngeal samples with Ct values above or below the diagnostic thresholds of rRT-PCR positivity or association with higher infectivity is shown in figure 1. The median values in rRT-PCR positive samples was 94.8 (IQR, 82.9-1466.9) $TCID_{50}$/mL compared to 78.2 (IQR, 75.2-84.2) $TCID_{50}$/mL in those testing negative (i.e., Ct values >45; p<0.001), whilst that in samples associated with high infectivity risk was 3819.1 (IQR, 198.6-28061.3) $TCID_{50}$/mL compared to 82.0 (IQR, 76.7-88.4) $TCID_{50}$/mL in those with lower infectivity risk (i.e., Ct values >29.5; p<0.001).

The diagnostic performance of the DiaSorin LIAISON SARS-CoV-2 Ag immunoassay versus molecular testing is shown in figure 2. Briefly, the area under the ROC curve (AUC) for rRT-PCR positivity and association with potential infectivity was 0.82 (95% CI, 0.79-0.86; p<0.001) and 0.98 (95% CI, 0.97 to 0.99; p<0.001), respectively. The optimal cut-off for identifying rRT-PCR positivity was 82 $TCID_{50}$/mL, which was associated with 0.78 sensitivity (95% CI, 0.73 to 0.83), 0.73 specificity (95% CI; 0.64 to 0.80) and 77% diagnostic accuracy (95% CI, 73 to 81%). For comparison, the 200 $TCID_{50}$/mL cut-off suggested by the manufacturer was associated

with 0.31 sensitivity (95% CI, 0.25 to 0.36), 1.00 specificity (95% CI; 0.97 to 1.00) and 50% diagnostic accuracy (95% CI, 45 to 55%), whilst the 100 $TCID_{50}$/mL cut-off suggested by Häuser et al [9] was associated with 0.45 sensitivity (95% CI, 0.39-0.51), 0.99 specificity (95% CI, 0.95-1.00) and 61% accuracy (95% CI, 56 to 65%). The optimal cut-off for identifying samples with higher risk of infectivity, which may hence characterize the so-called super-spreaders, was 106 $TCID_{50}$/mL, which was associated with 0.94 sensitivity (95% CI, 0.88 to 0.98), 0.96 specificity (95% CI; 0.93 to 0.98) and 95% diagnostic accuracy (95% CI, 93 to 97%).

DISCUSSION

The impact of SARS-CoV-2 diagnostics on laboratory medicine, requiring the expedient implementation of rapid and accurate diagnostic techniques for decision making regarding patient diagnosis, isolation, and/or treatment, has been so dramatic that it has been defined more or less as an "Armageddon" in the pages of this journal [10]. In fact, it is unquestionable

Figure 1 **Test results (median and interquartile range) of DiaSorin LIAISON SARS-CoV-2 Ag chemiluminescence immunoassay in nasopharyngeal samples positive at molecular testing (i.e., cycle threshold values of both SARS-CoV-2 *S* and *E* genes <45), and in nasopharyngeal specimens associated with higher infectious risk (i.e., cycle threshold values of both SARS-CoV-2 *S* and *E* genes <29.5).**

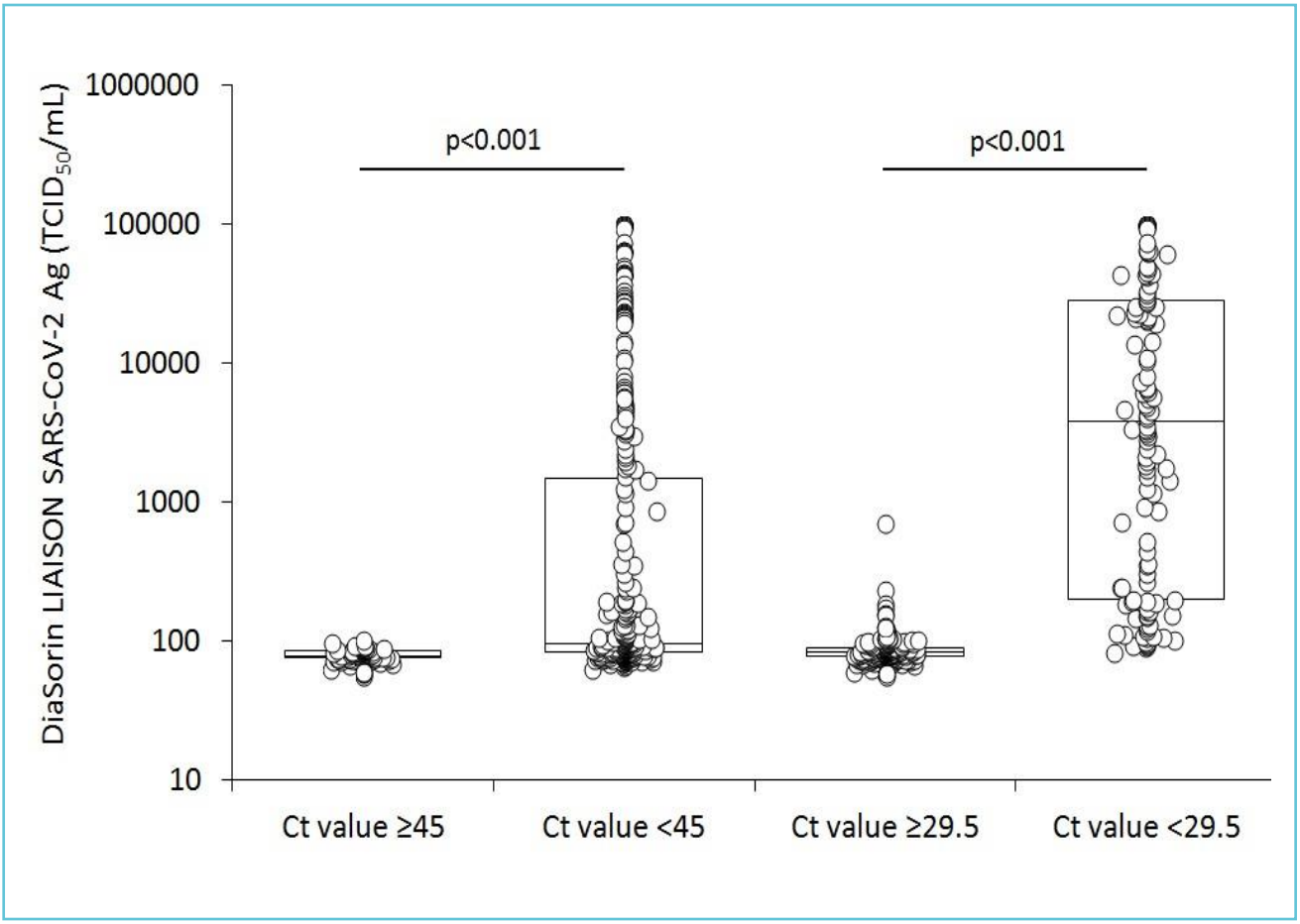
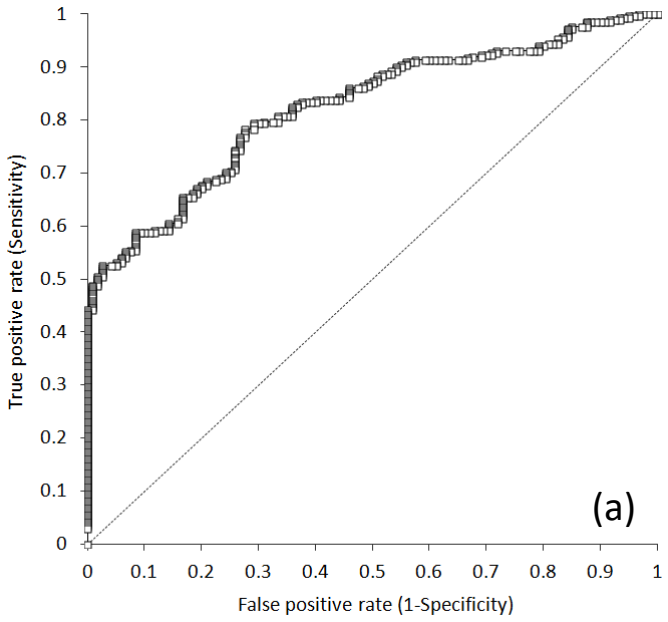
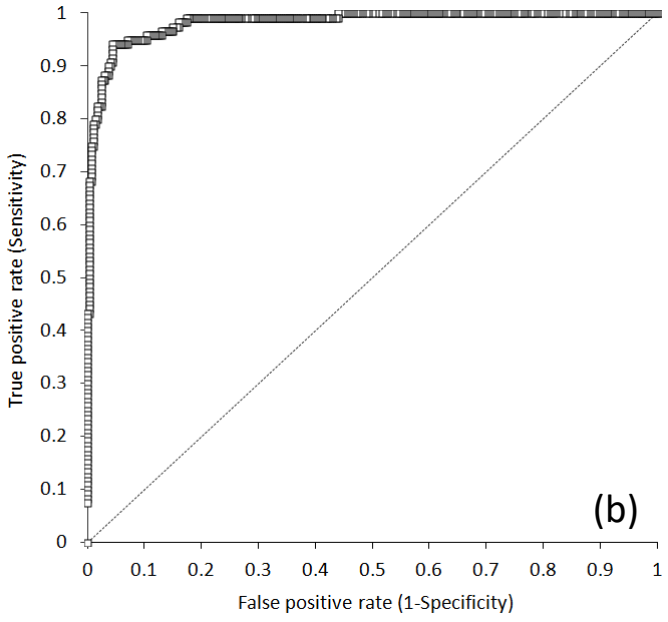


Figure 2 Receiver operating characteristic (ROC) curve of DiaSorin LIAISON SARS-CoV-2 Ag chemiluminescence immunoassay for:
(a) identifying positive nasopharyngeal samples at molecular testing (i.e., cycle threshold values of both SARS-CoV-2 *S* and *E* genes <45); or
(b) discriminating nasopharyngeal specimens associated with higher infectious risk (i.e., cycle threshold values of both SARS-CoV-2 *S* and *E* genes <29.5).





that many diagnostic facilities have virtually collapsed, and many others are still struggling with ongoing shortages of human and analytical resources, as recently underpinned by the results of a global survey promoted by the American Association of Clinical Chemistry [11]. In this rapidly evolving situation, the availability of high throughput and accurate techniques for screening and/or diagnosing SARS-CoV-2 infections, especially for identifying the so-called super-spreaders, a limited number of persons but among which nearly 90% of the viral particles circulating in the community are carried [12], should be regarded as a top priority. The use of rapid and high throughput SARS-CoV-2 antigen immunoassays has been proposed as a potential solution to this urgent matter, provided that their clinical performance are validated in real-life scenarios.

The results of our clinical assessment of the novel DiaSorin LIAISON SARS-CoV-2 Ag chemiluminescence immunoassay suggest that this technique has excellent performance for detecting nasopharyngeal samples with high viral load (i.e., Ct values <29.5), though its cumulative sensitivity appears considerably lower when all specimens are considered. These results are well-aligned with those recently presented by Häuser and colleagues [9]. Briefly, these authors also found that when applying the manufacturer-recommended cut-off of 200 $TCID_{50}$/mL, the specificity was 1.00, as in our cohort, however, the diagnostic sensitivity was only 0.40, which is very similar to the 0.31 sensitivity that we found in our study. When the cut-off was lowered to 100 $TCID_{50}$/mL, Häuser et al. found the sensitivity increased to 0.50 while only marginally decreasing the specificity to 0.98. Interestingly, these values are very similar to those found in our study using that same diagnostic threshold (i.e., 0.45 sensitivity and 0.99 specificity, respectively). Nonetheless, in our cohort, the optimal cut-off for identifying sample positivity was even lower, 82 $TCID_{50}$/mL, which yielded 0.78 sensitivity, 0.73 specificity and 77% diagnostic accuracy.

In a separate investigation, Lefever et al. also evaluated the diagnostic performance of DiaSorin LIAISON SARS-CoV-2 Ag immunoassay versus a reference NAAT [13], reporting 0.68 sensitivity and 1.00 specificity at the 200 $TCID_{50}$/mL manufacturer's cut-off. Regardless of which cut-off is used, both our data and previously reported data [9,13] would hence suggest that the diagnostic accuracy of this chemiluminescence immunoassay appears still insufficient to completely replace NAAT as the reference technique for diagnosing SARS-CoV-2 infection, since neither in our cohort or in previous studies, the minimum required sensitivity recommended by the WHO and the IFCC Task Force on COVID-19 (i.e., ≥0.80) could be reached.

That said, the diagnostic performance of DiaSorin LIAISON SARS-CoV-2 Ag for identifying samples associated with higher infectivity (i.e., with Ct values <29.5) was excellent, exhibiting an AUC of 0.98, and displaying 0.94 sensitivity, 0.96 specificity and 95% diagnostic accuracy at the 106 $TCID_{50}$/mL cut-off. These values are aligned to, or even better than the minimum performance requirements currently recommended by both the WHO and the IFCC Task Force on COVID-19 [3,4].

Importantly, the data published by Lefever and colleagues are consistent with our findings, since they also found 0.83 sensitivity in nasopharyngeal specimens with a high and potentially infective SARS-CoV-2 viral load (i.e., Ct values of *N* gene <30) [13]. This would imply that this fully-automated chemiluminescence antigen immunoassay could be especially suited, and thereby reliably used, for rapidly and efficiently detecting subjects bearing high SARS-CoV-2 viral load (i.e., the so-called super-spreaders), who are responsible for the vast majority of infectious clusters [14,15].

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Conflicts of interest

The authors declared that there is no competing interest.

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Lessons learned from the COVID-19 pandemic: emphasizing the emerging role and perspectives from artificial intelligence, mobile health, and digital laboratory medicine

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ABSTRACT

SARS-CoV-2, the new coronavirus causing COVID-19, is one of the most contagious disease of past decades. COVID-19 is different only in that everyone is encountering it for the first time during this pandemic. The world has gone from complete ignorance to a blitz of details in a matter of months. The foremost challenge that the scientific community faces is to understand the growth and transmission capability of the virus. As the world grapples with the global pandemic, people are spending more time than ever before living and working in the digital milieu,

and the adoption of Artificial Intelligence (AI) is propelled to an unprecedented level especially as AI has already proven to play an important role in counteracting COVID-19. AI and Data Science are rapidly becoming important tools in clinical research, precision medicine, biomedical discovery and medical diagnostics. Machine learning (ML) and their subsets, such as deep learning, are also referred to as cognitive computing due to their foundational basis and relationship to cognition. To date, AI based techniques are helping epidemiologists in projecting the spread of virus, contact tracing, early detection, monitoring, social distancing, compiling data and training of healthcare workers. Beside AI, the use of telemedicine, mobile health or mHealth and the Internet of Things (IOT) is also emerging. These techniques have proven to be powerful tools in fighting against the pandemic because they provide strong support in pandemic prevention and control. The present study highlights applications and evaluations of these technologies, practices, and health delivery services as well as regulatory and ethical challenges regarding AI/ML-based medical products.

1. INTRODUCTION

The first report of a respiratory infection classified as "pneumonia of unknown etiology" was provided to the WHO Country office on December 31st 2019 in Wuhan, a metropolis located in China's Hubei province [1,2]. This has led to an intensive outbreak investigation program and to the identification of a novel virus belonging to the Coronaviridae (CoV) family as the cause of this illness. Coronaviruses, of which there are 7 strains, are large RNA spherical viruses with a helical capsid and a lipid envelope that can directly multiply in host cells due to presence of RNA polymerase. They are common in human beings as well as animals (camels, cattle, cats, and bats). The virus that causes COVID-19 is designated as Severe Acute Respiratory Syndrome corona virus 2 (SARS-CoV-2); previously referred to as 2019-nCoV, "CO" standing for corona, "VI" for virus, and "D" for disease [3].

Since the onset of this pandemic, medical and laboratory professionals have completely modified the organization of their work and their relation with clinicians and patients. People are spending more time than ever living and working in the digital milieu propelling AI to an unprecedented level. The second surge of cases worldwide seems more difficult to understand and explain than the first wave. The resurgence of the virus is a huge setback for the countries that had largely succeeded in bringing infection rates down to manageable levels over the summer, after implementing drastic lockdowns. The upside of the present situation is that more tests are available, and people who are hospitalized with the virus are less likely to die. At the same time, the virus's long-term complications, ranging from respiratory disability to cognitive decline, now seem more ominous (the "long Covid"). Our understanding of the mode of transmission is currently incomplete and is constantly modified by various scientific resources on a time-to-time basis. As reported by the WHO, COVID-19 is primarily transmitted between people through respiratory droplets and contact routes [4]. As droplets containing the virus may remain in suspension for several hours as aerosols, and thus increase airborne contamination, proper ventilation and use of disinfectants contribute to the restriction of the spread of the virus. Moreover, recent studies [5,6] suggest that COVID-19 can cause myocarditis, even in people who initially exhibited mild symptoms, or had recovered. These observations are concerning even if rare and still debatable.

Respiratory infections could be transmitted through droplets of different sizes: when the

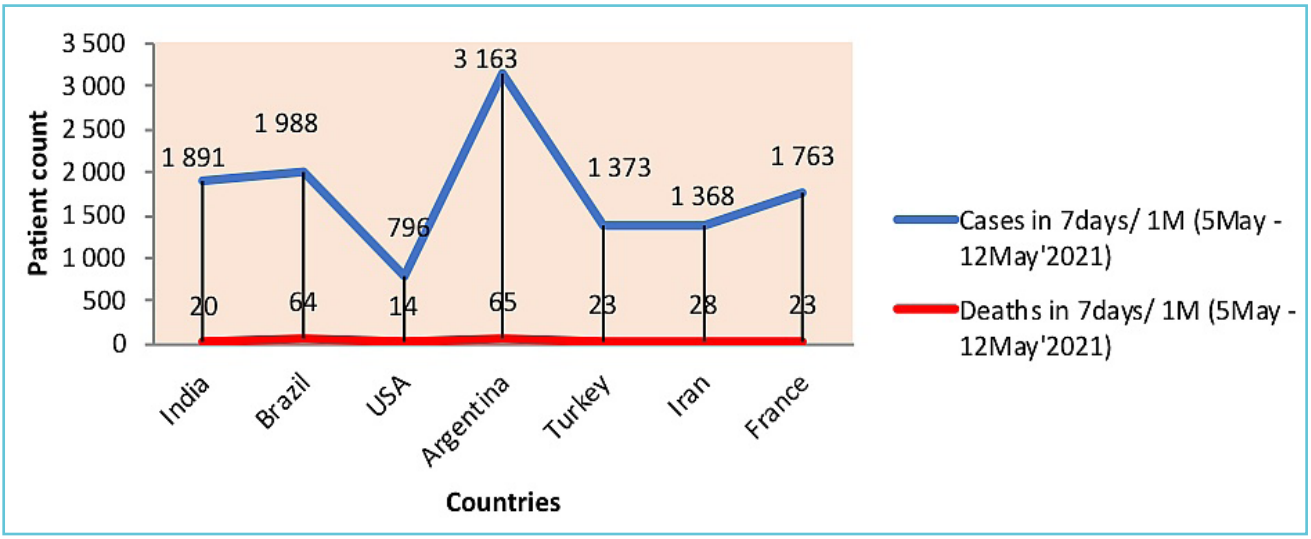
droplet particles are >5-10 µm in diameter they are referred to as respiratory droplets, and when are <5µm in diameter, they are referred to as droplet nuclei. These are respiratory secretions from coughing or sneezing landing on the exposed persons' mucosal surfaces, such as through nose, mouth and eyes [7]. Droplets typically do not travel more than six feet (about two meters) and do not linger in the air, while patients are thought to be most contagious when they are symptomatic. Severe cases may lead to difficulty in breathing or shortness of breath with persistent pain chest and confusion [8].

Worldometer is a resource run by an international team of developers, researchers, and volunteers with the goal of making world statistics available in a time relevant format. Worldometer was voted as one of the best free reference websites by the American Library Association (ALA) and it is a provider of global COVID-19 statistics for a global audience. As per weekly data accessed from 5th-12th May 2021, the total confirmed cases in the world were 5,246,979 whereas total confirmed deaths were 89,174 (Figure 1).

Several strategies, such as medical aid, notification, infection control, testing and radio imaging have been developed to monitor and control the spread of COVID-19. However, emerging technologies with the adequate utilization of Artificial Intelligence (AI) and Mobile Health devices offer new perspectives to face COVID-19 and other viral outbreaks. The adoption of AI and big data is expected to make significant contributions towards facilitating simulations for contact tracing for a better early detection and prevention, online training of healthcare workers, cooperation among regions, and to develop drugs and vaccines [9,10,11].

Looking at Laboratory Medicine, even if implementing new techniques is always exciting, Clinical Laboratory professionals have to adhere to all relevant best practices and regulations. In particular considering that AI and Machine learning already surround us, the first questions are how AI works, what its value is in healthcare and how to initiate an AI project? [11,12].

Figure 1 **Seven day average of confirmed COVID-19 cases and deaths per million population in India, Brazil, USA, Argentina, Turkey, Iran, France, in the period 5-12 May 2021**



Source: https://www.worldometers.info/coronavirus/weekly-trends/#weekly_table.

Moreover, the complexity of human physiology as well as requirements to validate a deep learning system for clinical implementation might be challenging towards machine learning techniques practical applications. Although great promise has been shown with deep learning algorithms in a variety of tasks across precision medicine, these systems are currently far from perfect. In particular, obtaining high-quality annotated datasets is still a challenge for deep learning training. Additionally, it is necessary to introduce definitions and key concepts and how the performance of these new tools can be validated and monitored.

This review focuses primarily on some key technologies such as Mobile Health (mHealth), the internet of things (IoT), telehealth, and artificial intelligence (AI) for COVID-19 modeling and simulation to prevent the rapid spread of coronavirus disease and to maximize safety during the pandemic.

2. ARTIFICIAL INTELLIGENCE (AI) AT A GLANCE

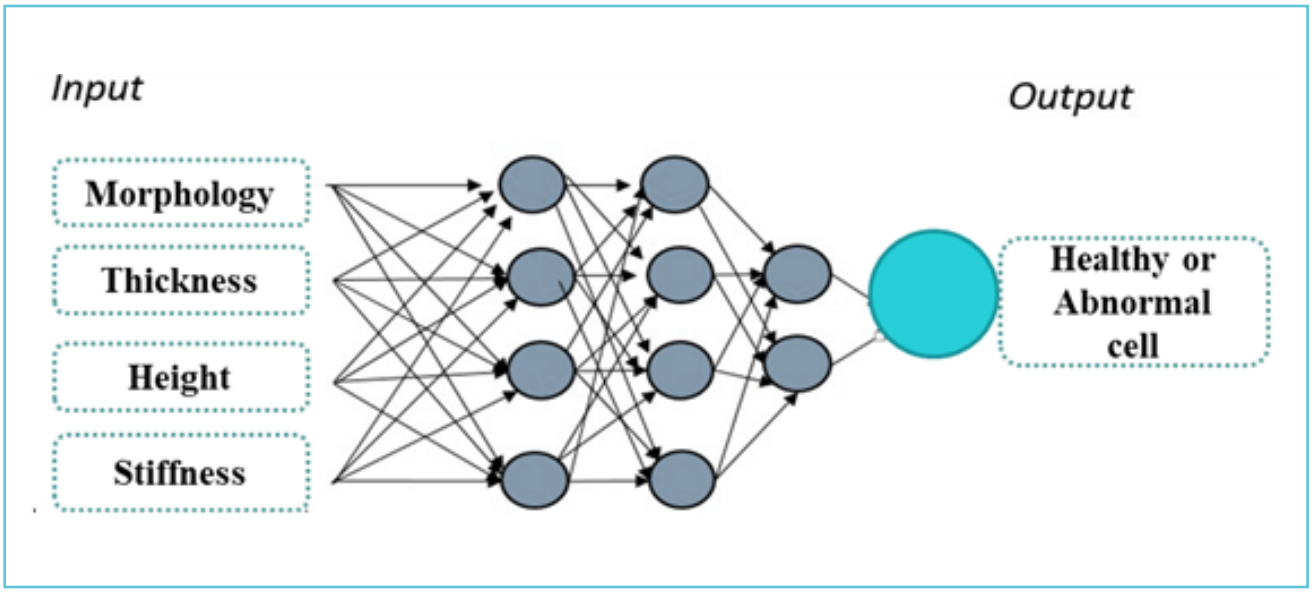
The process for the development of Artificial Intelligence (AI) systems must include basic terminology and definitions, risk evaluation and management, bias as well as assessment of the trustworthiness and robustness of neural networks and machine learning systems. Importantly, ethical and social concerns have also to be addressed. Fundamentally, AI refers to a program with ambitious objectives to understand and reproduce human cognition, creating cognitive processes comparable to those found in human beings. This has been linked to the recent success of Machine Learning (ML) which is a branch of Artificial Intelligence (AI) and computer science that focuses on the use of data and algorithms to imitate the way humans learn, gradually improving its accuracy. AI uses machine learning to analyze data in real time at a speed and volume that no human being ever could. Various applications of ML have been developed in translation, in health to identify diseases and diagnosis. IBM Watson Genomics is a prime example of how integrating cognitive computing with genome-based tumor sequencing can help in making a fast diagnosis. Biopharma companies are leveraging AI to develop therapeutic treatments in areas such as oncology. Medical imaging diagnosis is an advanced application which works on image diagnostic tools for image analysis. Personalized treatments can be more effective by pairing individual health with predictive analytics. More devices and biosensors with sophisticated health measurement capabilities hit the market, allowing more data to become readily available for such cutting-edge Machine Learning (ML)-based healthcare technologies [13].

There are two broad categories of AI: Narrow AI which carries out specific tasks and is what we are used today and General AI which aims to create capabilities and likely won't exist in our lifetime. Artificial intelligence describes a range of techniques for decision analysis and prediction that allow computers to perform tasks typically thought to require human reasoning and problem-solving skills with the help of predetermined rules and search algorithms, or using pattern recognizing machine learning models [14]. Thus, Internet of Things (IoT) involves processing large amounts of data and recognizing patterns in the data. Early AI research in the 1950s explored topics like problem solving and symbolic methods. In the 1960s, the US Department of Defense began training computers to mimic basic human reasoning whereas Defense Advanced Research Projects Agency (DARPA) completed street mapping projects in the 1970s. Over time it allowed connections to data with the help of powerful computers and large enough data sets and processing

information with advanced technologies in the field of life sciences e.g, processing of large datasets generated in different fields of omics such as genomics, proteomics, metabolomics, metagenomics and transcriptomics. The intersection of Machine Learning (ML) with genomics and imaging technologies is an important tool in cancer diagnosis and its prognostication. In one study, an integrative model combining 'omics data with histopathology images generated better prognostic predictions in lung adenocarcinoma patients compared to predictions with image or 'omics analysis alone. However several constraining factors need to be addressed such as the ability to train and validate these algorithms in a clinical setting. Another is the standardisation and aggregation of data (imaging and 'omics) across different research or medical centres before being utilized for patient care. [15].

Artificial Neural Networks are a common type of machine learning inspired by the way the brain works. It consists of a multi-layered network of interconnected units (like neurons) that process information by responding to external inputs. Thus, relaying of information between units requires multiple transfers of data to find connections and derive meaningful data by a mathematical-computational model. It came with promising outcomes in modern healthcare system and empowered diagnostics. [16]. This technique can be helpful for analyzing various pathologies, such as identifying cancer cells or abnormal cells, where the model relates with the input of different features such as cell morphology, height, stiffness and thickness and motility too with the help of powerful advanced automated microscopes that uses advanced tools of image processing based on ML algorithms. In figure 2, the first, second and third hidden layer of neurons for passing information is in Dark BLUE color (fig 2). The prediction with final outcome is depicted in Light BLUE color. The arrows connecting the different circles schematize how the human neural network works and connects to transfer the information from one layer to another one to provide the final output through the output layer [17, 18].

Figure 2 **Artificial intelligence and neural network in analyzing different morphological features such as cell morphology, height, stiffness and thickness to identify healthy or abnormal cancerous cells**



3. AI MATTERS IN THE MODERN WORLD

Over the recent times, there have been huge technological developments in the field of machine learning and especially with artificial neural networks. AI is becoming a ubiquitous technology with endless applications; AI algorithms are designed to make decisions, often using real-time data bringing information from a variety of different sources e.g., sensors, digital data or remote inputs. AI is a game changer capable of doing very fast precise things (and jobs); robotics is one of the most exciting areas for AI development. The same technology has been integrated into a variety of sectors, such as finance, national security, health care, and transportation sectors. Prominent examples being used popularly are Google Maps, AI autopilots in commercial airlines and Social Networking-Facebook [19].

Nevertheless, the developers who are using AI tools, need to engage more with society to provide transparency and standards to address system robustness, data quality and boundaries will increase trust and the ability to interact with a variety of data repositories. Future trends and benefits for AI will see more hands-free applications (e.g., smart glasses). Plagiarism detection for regular text (e.g. essays, books, etc.) relies on a having a massive database of reference materials to compare to the student text. In Plagiarism Checkers, Machine Learning can help detecting the plagiarizing of sources that are not located within the database, such as sources in foreign languages or older sources that have not been digitized. In simple terms, by using techniques like machine learning, big data and analytics. AI systems provide insights into the applications that would not be attainable otherwise. These insights are at the core of AI intelligence [19, 20].

As the pandemic progresses, we are also likely to see the emergence of more applications able to link datasets that we used to train an algorithm to understand how to apply concepts such as neural networks, to learn and produce desirable results. In this context there are many implications for privacy, indeed the linking of datasets may increase the likelihood of patients identification, the profiling of sensitive data, and let data to be available to a broader set of users or data managers. It has been recognized that the reuse of unidentifiable data could potentially serve future public health responses and research. It should be considered that the nature, the accessibility and the utilization of data necessitate transparency and a clear governance processes that should be in place from the outset ensuring that data privacy is protected to the greatest possible degree [21].

4. DOES AI ACT AS A DRIVER OF THE EVOLUTION OF TECHNOLOGY AND BIOMARKERS?

AI has the potential to aid progress in everything from the medical sphere to saving the planet, yet as the technology becoming more complex, questions of trust arise. AI is a fast-changing field full of innovators and disruptors, thus development of norms and standards is becoming a big task and interoperability is vital. AI technologies are developing so quickly that international standards are also needed for transparency and common language. AI has led to the significant paradigm shift in the medical knowledge due to its ability to support decision-making and to improve both diagnostic and prognostic performance for better patient care and outcome. Besides mundane medical tasks, AI in the form of a smart patient assistant is capable of facilitating protracted and mutually beneficial relationships with patients, especially those with chronic diseases that require long remote care [19, 22].

Input data is large and can be varied ranging from socio-environmental, clinical-laboratory to omics-data. The buzz around AI in medical imaging has turned into a boom. There are a large number of startups and health companies working on a wide variety of solutions for example, startups are developing blood testing systems that use computer vision algorithms for the analysis of blood samples. Such tests are used for the diagnosis of a range of disorders including infection, anemia, and certain cancers. The US-based startup Athelas utilizes computer vision technology to help oncology patients track their white blood count and neutrophils. Athelas blood-testing device performs analysis within minutes and requires only a fingerprick of blood [23], the device is FDA cleared for use in point-of-care settings. Merantix® is a German company that applies deep learning to medical issues. It has an application in medical imaging that "detects lymph nodes in the human body based on CT scan images." Thus, it became revolutionary and helpful in identifying small lesions or growths that could be problematic [24]. Cardiovascular diseases are the leading cause of death today and innovations in early diagnostics and treatment of these diseases are relevant. One example of such innovations is an image analytics platform that processes MRI data with AI algorithms in order to evaluate arterial functions. In France, Imageens develops a range of web-based platforms for the early detection and diagnosis of cardiovascular diseases. The company's products process MRI images with AI algorithms in order to create a morphological and functional analysis of the arteries, as well as an evaluation of the left ventricular diastolic function. The latter application is of great value considering that congestive heart failure in the United States afflicts 10 percent of senior citizens and estimatedly costs $35 billion each year.

Millions of people die from stroke every year, and millions become disabled for the rest of their life. Quick and accurate stroke diagnostics based on brain images is crucial for timely and effective treatment. Startups are developing computer vision and artificial intelligence solutions in order to support clinicians in the challenging task of brain image evaluation. Netherlands-based Nico.lab developed StrokeViewer®, an AI-powered cloud-based clinical decision support system that makes a complete assessment of relevant imaging biomarkers within three minutes. The system also enables a rapid image exchange between hospitals and personal devices for the timely triaging of stroke victims.

In these scenarios, AI tools are helpful to predict potential challenges in advance. It further helps to allocate resources for patient education, sensing, and proactive interventions even at home care while maintaining social distancing as an important measure. Several applications have been successfully performed and have helped to improve significantly in both diagnostic and therapeutic applications in relation to personalized care. This is a pivotal time to be involved in AI related technologies to fostering innovation and to help by collective work to propel the wide scale adoption of AI and big data systems. The healthcare investments in AI are increasing, creating or accentuating disparities in the adoption of innovation in healthcare. The implications of introducing and scaling AI in healthcare and its full potential of AI is still being discussed, questions have to be raised about its potential impact on health care professionals and certain specialties, while issues around ethics, use of personal data, and AI-related risks must also be debated in ensuring that citizens fully reap the benefits of AI.

Data is a powerful tool than ever in a pandemic where rightful information can be helpful in predicting the nature of spread of disease and its extent, whereas on the other side it is also helpful in planning and utilizing existing resources to fight the battle against the same. Information

about virus spreads, about how the health and care systems will respond and where they experience hard strain, is needed. Lives can be lost if there are inconsistencies in data, so finding a centralized, fast and efficient way of storing and extracting data is crucial. The so called Data Curation becomes more necessary to resolve four main challenging issues: data integration, electronic dissemination, data sustainability, and metadata. [23,24,25].

5. TELEHEALTH

Telehealth has become an important communication and treatment tool during COVID-19. It is a gateway to how healthcare will be delivered in the future and has enabled the transition to consumer-centric care paradigms. Because of the need to create social distancing in a safe environment and the introduction of reimbursement for virtual visits, telehealth has become an important communication and treatment tool during the COVID-19 pandemic [26].

Telehealth involves the use of communication systems and networks to enable either a synchronous or asynchronous session between the patient and the provider. A virtual care solution usually involves a much broader scope of clinical and work-flow processes, remote monitoring, and several providers over time. Although there is no universal agreement, telemedicine generally refers to the remote delivery of medical or clinical services, while telehealth is a larger platform that includes telemedicine along with remote non-clinical services, such as provider training, administrative meetings, and continuing medical education, in addition to clinical services. Virtual care extends the options to manage the patient well beyond a specific event. High-quality patient treatment is vital, and e-technologies enable healthcare and Lab medicine staffs to collaborate and provide the best possible care for them. Knowledge can be shared in real-time and patient information is consistent because data is being shared digitally, providing the best care possible. Understanding the benefits of telehealth and the delivery of useable, safe and efficient healthcare during the pandemic is paramount [27].

6. MOBILE HEALTH (mHEALTH) TRENDS

Advances within the connected, mobile health sectors and mobile wireless networks globally have led to a series of innovations technologies that address global health-related challenges. mHealth in short for mobile health is the practice of medicine and health care over mobile devices, tablets, personal device assistants (PDAs) and tablet computers. mHealth applications include the use of mobile devices in collecting community and clinical health data, delivery of healthcare information to practitioners, researchers and also for real-time monitoring of patients' vital signs [23]. It has shown to have a positive effect on patient care outcomes, as evidenced by a reduction in adverse events and hospital length of stay. Mobile devices and apps have provided many benefits for HealthCare Practitioners (HCPs), allowing them to make more rapid decisions with a lower error rate, increasing the quality of data management and accessibility, and improving practice efficiency and knowledge [28]. However, HCPs should be aware of the need to use mHealth devices that have been certified for use according to FDA and CE IVD regulations and specialists in laboratory medicine can provide support in addressing ISO and notified bodies requirements.

Global mobile apps market 2020-2024

In news article published by "Business Wire" London [29], it is estimated that the global mobile apps market size is expected to grow by USD 497.09 billion during 2020-2024. As per the report, the COVID19 market impact can be expected to be significant in the first quarter but

gradually lessen in subsequent quarters with a limited impact on the full-year economic growth, according to the latest market research report by Technavio. The development of hybrid mobile apps and growing technology of smartphones will have a positive impact on the market and contribute to its growth significantly over the forecast period (Fig 3) [23, 29].

7. WHAT IS REMOTE PATIENT MONITORING?

Connected health devices run the gamut from wearable monitors, and Bluetooth-enabled scales, to monitor weight and tension, and facilitate continuing health monitoring. They provide health measures of patients and transmit them back to providers to track vitals, to analyze data in real-time manner and facilitate healthcare decisions from a remote distance. Thus, Remote Patient Monitoring (RPM) is a type of ambulatory healthcare helping patients and doctors to use mobile medical devices. RPM technology usually includes monitoring devices such as heart or blood pressure trackers for patients receiving care in the hospital. The recorded or live data is then sent to a physician by using a cloud-connected system with the help of an application on the doctor's phone where they advise and notify staff accordingly. Data transfer should be performed according to data standards and regulation with the example of the European Global Data Protection Regulation (GDPR) and with devices qualified and validated for their technical and medical performances. Considerable additional effort is required to ensure appropriate multi-stakeholder involvement in the development, evaluation and best use of mobile devices and applications for remote monitoring. Remote patient monitoring technologies are akin to telemedicine technologies, since they automatically observe and report on patients, often with chronic illnesses, so caregivers can remotely keep tabs on patient. Emerging technologies are key elements for implementation of reliable RPM, where Sensors and Bluetooth technology are some of its technology driven key components [30, 31].

Figure 3 Technavio market research report showing growing penetration of smartphones to boost market growth

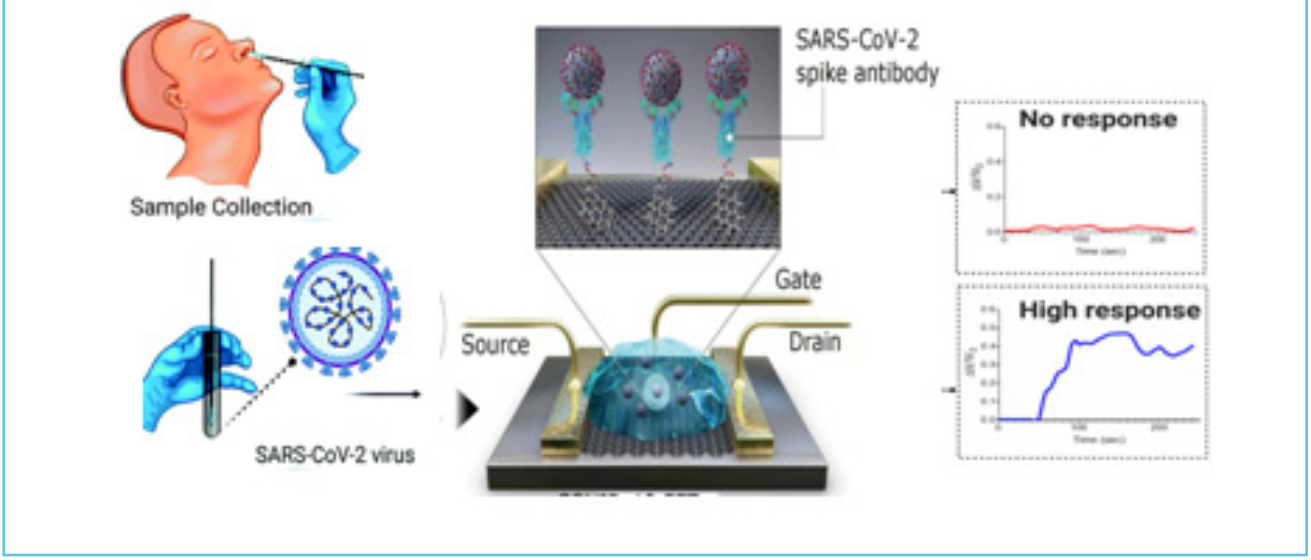
Source of information: Business Wire, Global Mobile Apps Market 2020-2024.

7.1. Biosensors

Wireless sensor networks are being produced to enable IOT technology and are helpful in bridging the physical and digital worlds. In the structured information flow, input data is collected by the sensor devices and sent to the data control center for further feedback through several data channels in parallel. The IOT devices and edge network remains important to keep large set of data records in a structured manner. Under the biological limits, the Biosensors technology can help in detection of specific biological analytes and monitoring of their specific functions. Though the technology and advancement in medical knowledge has grown tremendously, but it always has given associated challenges to overcome. It always necessitates the need based noninvasive, small-sized, portable, and cost-effective sensors for medical application to develop. AI enhanced microfluidics and compact small interactive POCT labs are also set to alter the way diagnostics is carried out. The biosensors applications have shown important role in various fields, such as cancer diagnosis, cardiovascular disease, and wound healing whereas regenerative medicine have also shown a growing interest in biosensors technology ranging from biomanufacturing (such as mass culture cells for organ fabrication or to produce chemicals), organ-on-a-chip technologies and indicators of therapeutic efficacy [32]. Organ-on-a-chip technologies are utilizing microfluidic equipment and small cell clusters of a particular tissue type to replicate behaviour of normal tissue and cells and assessing the response to drugs and other external stimuli. The technology has advanced vastly by using biosensors for real-time monitoring of the behavior of microtissues and organoids. In one more futuristic approach, nanotechnology will be incorporated into biosensors that monitors stem cell differentiation status prior to their transplantation for therapeutic purposes [33].

Further, during the COVID-19 pandemic, there is a surge in demand for promptly testing of mass population with the faster and direct detection of viral pathogen. The modern biosensor-based methods for the detection of the SARS-CoV-2

Figure 4 Modern biosensor-based methods for the detection of the SARS-CoV-2 virus

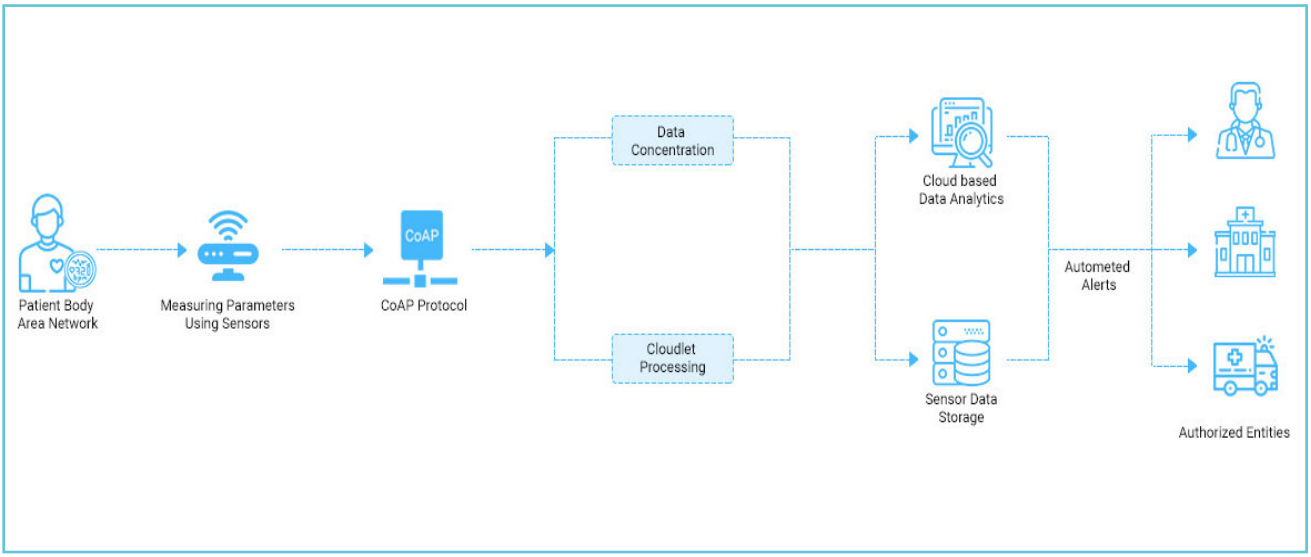


virus are mostly based on detecting virus surface proteins and internal genetic material (Figure 4). In the near future, emerging new technologies such as rapid cum portable RNA extraction preps, CRISPR-Cas based paper strips, nucleic acid hybridization, DhITACT-TR chip-based, graphene-FET, Au/Ag nanoparticles based electrochemical biosensor could pave the efficient ways of rapid, highly sensitive and more promising biosensing cum diagnostic devices for viral pandemics. Thus, a surge in technology and its appropriate usage can help to personalize the medical approach with tailored specific treatments. Biosensing technologies will enable early detection to facilitate reducing healthcare costs, given that prevention is always much less expensive than treatment [34, 35].

7.2. Bluetooth technology

Over the last several years, wireless technologies have made significant progress, and they are now being integrated into many mainstream applications. In particular, Bluetooth is now seeing increased use in a variety of medical applications ranging from home-healthcare devices to operating room equipment. Bluetooth is particularly well suited for cable replacement, allowing for mobile connectivity. It also provides excellent security and reliability and coexists well with other wireless technologies (Fig. 5) and, it is a relatively low-cost technology to implement. They use virtually no power and, because they don't travel far, are theoretically more secure than wireless networks. The first mobile device that incorporated both communication and computing features was the Blackberry, which was introduced in 2002. Subsequently, Apple and then smartphones that run the Google Android operating system were introduced for better functioning and desired outcome. Developers, solution providers, facilities managers and government agencies are turning to Bluetooth technology to implement innovative solutions that help managing the spread, accelerate reopening efforts, and enable safer treatment of patients during the COVID-19 pandemic and disease outbreaks. Bluetooth enabled proximity warnings remind employees and visitors to maintain safe distances to reduce the risk of viral transmission. Thus, flexibility of Bluetooth technology and easy availability in our phones and devices is helping us to minimize the spread and enable safe reopening. [36].

Figure 5 Remote patient monitoring and sensors technology



Personalizing Healthcare with Remote Patient Monitoring at the doorstep is possible with the help of a number of technologies driven healthcare innovations and integrative technologies. It is made efficient by low power wireless technologies like BLE/BT4.0, embedded biometric sensors, wearable monitoring devices, portable telehealth devices, powerful smart phones and Cloud Technology for Electronic Health Record storage and data analytics, e.g., blood pressure cuffs, glucometers, and pulse oximetry. The system can transmit and store the data in secure format systems accessible to clinicians or care givers. It can monitor and flag abnormal readings, as well as produce alert signals where the situation can be responded while reviewing the data and take appropriate actions. Thus, it is also enhancing quality care with reducing medical care cost [36, 37]. Few successful examples are: Aetna, ITriage

This patient-facing mobile app allows patients to directly find information on their health conditions and gives them step-by-step guidance to treat conditions in the most effective way possible. ITriage gives patients directions on whether their conditions require a visit to the emergency room.

Digital Sound Systems Inc. (DSS Inc.)

It gives providers a suite of Emergency Health R-based mobile features that enhance care coordination, patient care and safety. It provides both clinical and administrative tools that range from emergency room and home health mobile care management to automatic billing systems and scheduling tools.

Epic Systems, MyChart Mobile

Its viewable data includes test results, immunizations, medication and health conditions indicated by a provider. MyChart also allows a patient to confirm appointments, pay their healthcare bills, and upload patient-generated data such as fitness metrics from a wearable health device.

MEDITECH, Ambulatory EHR

It allows providers to access complete web charts, giving them instant access to patient records across healthcare organizations on a single mobile device. Providers can tap on a patient's record to view test results, order prescriptions and note the progress of health conditions. It also helps to identify at-risk patients.

8. HOW COULD AI AND mHEALTH BE USED IN FIGHTING COVID-19 AND OTHER PANDEMICS?

8.1 AI and smartphone-based COVID-19 testing

With the need to limit physical contact and trace COVID-positive individuals rapidly, public health authorities worldwide are finding rapid, point-of-care (POC) tests for the novel coronavirus increasingly attractive. Whether it is for testing antibodies or antigens, regulatory authorities are issuing approvals for such kits so as to boost testing capacities. Approvals are limited to kits for use by healthcare workers for now; but several companies are working on at-home rapid tests and could soon follow suit in gaining approvals. From accuracy issues to uncertainties about the virus itself, rapid coronavirus tests have evolved these last months to offer more reliable testing methods. Some rapid COVID tests come in kits that detect antibodies faster through specialized, portable detection devices like the Abbott ID NOW. Rapid tests can be a game changer; in particular when there are a lot of cases and little access to equipped testing facilities. At the beginning of April, India tested only some 150 000 people; one of the lowest testing rates per capita worldwide. Fast-forward a few months to August and the country ran over a million coronavirus tests in a single day.

This boost in testing capacity was possible since Indian authorities adopted antigen assays. And since they help identify individuals most likely to spread the infection, appropriate measures to isolate them can be taken in a timely fashion. These developments can be helpful to enable smartphones to be capable of conducting a coronavirus disease (COVID-19) testing [38].

SANOFI - "at-home test for COVID-19"

"Sanofi" (the French healthcare company) has teamed up with the Californian company "Luminostics" to build an at-home test for COVID-19. They use a glow-in-the-dark nanoparticle that can be picked up by a smartphone's camera to deliver results in 30 minutes without needing a medical professional. Users take a swab up their nose to gather bacteria, and then insert it into a device containing a chemical that includes nanoparticles. If the patient has been infected, the nanoparticles glow and emit a signal that is captured by the smartphone camera and processed using artificial intelligence. People would be given their results through an app which could also connect them to a doctor via video call to discuss a diagnosis. This diagnostic platform will compose of an iOS/Android app with instructions to run the test, capture and process data to display test results, and then to connect users with a telehealth service based on the results. Thus, with this over-the-counter (OTC) solution for COVID-19 testing will be easy to use and with reducing contamination by lowering infection risk [39].

MDBio COVID-19 test kit

It is laboratory-grade diagnostics and couples with smartphone for an automated testing in easy to follow 7 steps. It is an FDA preapproved kit for emergency use. It allows for high capacity testing, and rapid sharing of testing information anytime, anywhere [40].

Apps to determine COVID-19 disease severity

As per "New York University Dentistry (NYU) College of Dentistry", it is stated that it will be "Identifying and monitoring those at risk for severe cases could help hospitals prioritize care and allocate resources like ICU beds and ventilators. Also, these patients can be safely managed at home". The researchers validated the model using data from more than 1,000 New York City COVID-19 patients. The app has been retrospectively evaluated in the Family Health Centers at NYU Langone in Brooklyn, which serve more than 102,000 patients. To make the tool available and convenient for clinicians, they developed a mobile app that can be used at point-of-care to quickly calculate a patient's severity score coupled with a clinical decision support system [41].

AI Tool-Chest X-ray

The "American College of Radiology (ACR)" noted that CT decontamination is required after scanning COVID-19 patients may disrupt radiological service availability and suggests that portable chest radiography may be considered to minimize the risk of cross-infection. Additionally, Chest X-Ray utilization for early disease detection with "ground glass opacities" may also play a vital role in areas around the world with limited access to reliable real-time reverse transcription polymerase chain reaction (RT-PCR) COVID testing [42]. Recently, AI based -Handheld X-ray Camera being developed by HandMed as reported in "JLK inspection". It has an AI based abnormality score and with heatmap visualization of abnormal lesion. This technique is based on the Convolutional Neural Network, which is a class of deep neural networks, most commonly applied to analyzing visual imagery. As per the report, this system has been trained using over 1.1 million chest X-ray data, and it will analyze result report with

integrated telemedicine for earliest response and further action [43].

8.2 Monitoring of pandemics and clusters – tracing

GPS receiver communicates with satellites that orbit the Earth through radio waves. There are currently 32 GPS satellites in orbit – 27 are in primary use while the other serves as backup in case another satellite fails. To determine location, a GPS receiver has to use trilateration to determine your exact location. It means GPS receiver has to follow three simple steps: 1) The locations of at least three satellites above you. 2) Where you are in relation to those satellites. 3) The receiver then uses trilateration to determine your exact location [44]. Smartphones have a GPS chip which uses satellite data to calculate one's exact position. It can ascertain your outdoor position reasonably accurate. When a GPS signal is unavailable, geolocation apps can use information from cell towers to triangulate your approximate position. To be ethical, a contact-tracing app must abide by four principles: it must be necessary, proportional, scientifically valid and time-bound [45].

Apps to curb the spread of COVID-19

COVID-19 outbreak led countries to adopt different strategies to deal with the outbreak. The implementation of mobile software applications in order to monitor people and carry out contact tracing has been a trend adapted on a global scale. EENA -European Emergency Number Association has done comprehensive analysis of 108 COVID-19 apps that are implemented or under consideration in 73 different countries worldwide [46]. They categorized them into five clusters for a common understanding:

- Informational apps - At a time where there is a lot of misinformation/disinformation about COVID-19, these apps provide users with information regarding the disease outbreak (e.g., latest news, fact sheets, guidelines etc.) e.g., Bolivia – Bolivia Segura
- Self-assessment/Medicalreportingapps- It helps to reduce the burden on health-care facilities and ensure that those most in need are getting the right treatment, e.g., India – ArogyaSetu App
- Contact tracing apps - The aim is to prevent quarantine breaches and consequently mitigate the spread of COVID-19. Contact tracing apps are also being used to track infected people e.g., USA – How we feel
- Multi-purpose apps - It combines at least two of the previous clusters i.e., informational apps, self-assessment/medical reporting apps and contract tracing e.g., Ivory Coast - Anticoro
- Other apps related to COVID-19 - It helps in resource management (e.g., masks) and to fight against disinformation e.g., Taiwan - NHI App
- WHO Academy's mobile learning app - It provides critical, evidence-based information and tools to health workers. It is designed to enable them to expand their life-saving skills to fight COVID-19. It serves COVID-19 knowledge resources developed by WHO, including up-to-the-minute guidance, tools, training, and virtual workshops. Importantly, the content is available in seven languages.

The shift in paradigm of internet and technologies has led to the rise of new surveillance technologies, especially drones, cameras, smart phones and robots that are responsible for keeping individuals in the public space in order. At the same time, with the deployment of surveillance technologies, the ethics of privacy protection are now rightly on the agenda. Many

countries in Asia, Europe and other global regions are implementing these applications for monitoring the social interactions via the digital tracking of individuals. Several technologies are in use to achieve desired objectives such as telephone tracking, GPS applications, Bluetooth applications, bank card and transport card systems or even video surveillance and facial recognition; there are many technical means for different purposes. The use of digital tools for tracking individuals raises the risk of harming individual and collective freedoms, in particular respect for privacy and protection of personal data, as well as the risk of discrimination. Digital tools make it possible to quantify, geolocate, map, control and sometimes inform. In a time of health crisis, tracking may be used for three purposes. Firstly, observing collective mobility and confinement practices to reconstruct population movements during confinement period. Secondly, tracking could permit identifying contacts and detecting people who were potentially exposed to the virus. Finally, tracking can create control of individual confinements by observing an individual patient for quarantine and confinement measures [46, 47].

Globally, countries are using the legal and technical means at their disposal to legitimize these systems. The real value of tracking applications comes from their interoperability and their ability to share data with central and local health IT systems which can help statistical analysis, outbreak mapping, capacity management and early clinical intervention for high-risk groups. Furthermore, there has been a huge increase in cyberattacks since the start of the pandemic and especially in healthcare, with ransomware attacks targeting hospitals, government agencies and research centers, among others. This means that these e-platforms and telehealth resources are attractive targets for attackers who wish to spread malware through a health system and causing damage that really disrupts clinical care on a large scale. This poses an immediate threat to patient safety. Thus, the deployment of such devices must be supervised such as GDPR and the e-privacy directive by Europe. They authorize the processing of geolocation data via electronic communication means, provided that they have previously obtained either the express consent of the individuals or have anonymized the data collected. A number of considerations must be taken into account to guarantee that personal data is legally processed and, in any case, it should be remembered that any measure taken in this context must respect general legal principles and must not be irreversible, a condition that can legitimize restrictions on freedoms provided that these restrictions are proportionate and limited to the period of emergency [47, 48].

8.3 Empowerment and prevention of mental health disorders

As per the WHO experts and scientific data available, it is predicted that this pandemic is expected to remain, until it reaches its declining phase. At the same time, social distancing is also an important precautionary measure to prevent pandemic spread. At a time when social distancing has forced individuals to stay within the premises, the mobile applications have helped to supply essentials. Apps are making sure that the lockdown doesn't cut people off basic necessities like groceries, etc. beyond that it can engage, educate, encourage and entertain to help everyone cope during this crisis period. This is where; Telemedicine or Tele Mental Health Services has proved to be promising option for patient care and treatment. Each and every class of society from students to teachers, workers to business got affected with restrictions for lockdown, online teaching, work at home and others [49]. Furthermore, with rising pressure on falling economy with extra financial burdens have opened fearsome

stress related to job, security, future, finances, health, etc. Health issues may include stress, anxiety, fearsome loneliness, and depression which are worsening and raising demands for psychological treatments and counselling sessions. Similar initiatives were considered important and started by different nations e.g., The Australian Government extended previous telemedicine programs and provided additional funding services through Medicare Benefits Schedule dealing with range of mental disorders such as depression, anxiety, stress, anger, grief, etc. during the COVID 19 period. One such service is Betterhelp (betterhelp.com), which adopts texting, video conferencing, telephonic chat, etc. and reduces risk of exposure with remote monitoring and assurance [50, 51].

9. WHAT ARE THE CHALLENGES TO OVERCOME AND HOW INTERNATIONAL SCIENTIFIC SOCIETIES COULD HELP?

While the majority of HCPs have adopted the use of mobile devices, the use of these tools in clinical care has been debated since their introduction, with opinions ranging from overwhelming support to strong opposition. Important concerns were expressed as,

- **Reliability** for making clinical decisions
- Protection of patient data with respect to **privacy**
- Impact on the **doctor–patient relationship**
- Lack of oversight with respect to standards
- Content **accuracy**, e.g., patient management
- **Medico legal** and ethical implications for practitioners
- To be evaluated with regard to **utility** in clinical practice and claimed outcome
- **Lack of data** that support or identify the best approach
- **FDA**-Policy for Device Software Functions and Mobile Medical Applications Guidance. First issued in 2013 and then updated in 2015 and 2019. FDA issued this guidance document to clarify the subset of software functions to which the FDA intends to apply its authority.
- eHealth - The European Commission published a Staff Working Document and a Communication on Digital Transformation of Health and Care, empowering citizens and building a healthier society. These policy documents will give direction to EU activities in this field in the coming years.

These ranges of potential effects of AI on the fundamental human rights are related to social security, data gathering, unintentional bias and discrimination amongst society, lack of public awareness and limited understanding about the consequences. It may lead to unknown ill-informed consequences and subsequent harm later. Thus, ethical concerns in relation to complex nature of artificial intelligence ranges from issues such as job losses from automation, degradation of the environment and furthering inequalities, to issues which may affect our privacy, judgement ability, and even personal relationships. In the view of this rapidly developing technology, all countries approach together and make efforts for preparing robust principle is important. Many independent ethical initiatives for AI have been identified, such as Germany's Institute for Ethics in AI, funded by Facebook, and the private donor-funded Future of Life Institute in the US. Numerous other countries are working for AI ethics councils, including Germany, UK, India, Singapore, Mexico and the UAE [52, 53, 54].

Under the future economic policies framework, it will be required to support workers those were displaced by AI technology due to reduced manpower requirements. Successful AI development requires substantial investment in view of automation and machines, so as to drive government processes with equal knowledge share for all but not to devoid lower income countries. Such example of data sharing and collaborative approaches has been shown by India where they promise to share its AI solutions with other developing countries, and efforts to make it as a fundamental part of education which is available to all. Thus, it will be of prime importance to address these issues in view of futuristic multifaceted challenges associated with AI [53, 55, 56].

10. CONCLUSION

In the face of the 2020 health crisis, it has never been more important for medical labs to remain agile around emerging technologies initiatives. We operate in a world where change is constant. Successful innovation requires not just an understanding of today's needs, but also the ability to project ourselves in the future. Innovators in the field of AI and big data may come from sectors which are not always familiar with medical ethics and research regulation. Issues around patient safety are important to be addressed. The fact is machines are better at numbers than humans, but you will always need a human warrantee to validate and support the process.

As a point of argument and in terms of safety, machines are much better at recognizing things like rare diseases, simply because they are working from a bigger dataset. Algorithms could standardize assessment and treatment according to up-to-date guidelines, raising minimum standards and reducing unwarranted variation.

Emerging technologies can empower patients to manage their condition and can help reducing preventable readmissions. It can improve prescription adherence and allow uninterrupted doctor patient relationship. It is important to remember the potential of emerging technologies to help solve some of our biggest challenges, in particular when they relate to human safety. Several challenges are paving the way of emerging technologies ensuring that aspects such as accountability, responsibility, trust, traceability and human values are handled equally so they can gain wide acceptance. International standards could help to create an ethical foundation for building of a novel health and laboratory ecosystem based on emerging technologies.

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Catering for the point-of-care testing explosion

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ABSTRACT

The ease of performing a laboratory test near to the patient, at the point-of-care, has resulted in the integration of point-of-care tests into healthcare treatment algorithms. However, their importance in patient care necessitates regular oversight and enforcement of best laboratory practices. This review discusses why this oversight is needed, it's importance in ensuring quality results and processes that can be placed to ensure point-of-care tests are chosen carefully so that both oversight can be maintained and patient care is improved. Furthermore, it highlights the importance of delivering focused webinars and continuing education in a variety of formats.

INTRODUCTION

Point-of-care diagnostics has grown at an unprecedented rate. The convenience of being able to test yourself or a patient by a small, portable point-of-care device, that is easy to use, requires very little trouble shooting and provides results within a matter of seconds to minutes has fueled the explosion in point-of-care testing instruments world-wide, enabling them to find a key role in managing patient health. Furthermore, the current COVID-19 pandemic has illustrated, more so to the general public at large, the importance of having a process in place for efficient diagnosis and triaging of patients for disease management [1]. However good POC technologies are, there is a need for governments with help from national societies to develop strategies for effective implementation [2].

A recent survey conducted by the International Federation of Clinical Chemistry and Laboratory Medicine Committee on Point-of-Care Testing (IFCC C-POCT) (Figure 1) showed that 62% of member societies did not have an official point-of-care testing committee (Figure 2A) and in 55% of member countries, point-of-care testing was performed without any formal regulation (Figure 2B). This data show that whilst point-of-care testing has become an important part of patient testing and diagnostic algorithms, it is still being performed in a significant number of countries without official hospital and regulatory oversight. This does not necessarily mean that it is being done incorrectly, however being performed in a non-standardized way, without official oversight does open up that possibility. This is important because having a POC testing committee and standardized POC testing guidelines mandated nationally leads to accountability in the management of POC testing. Moreover, these numbers gathered by the IFCC C-POCT, are actually an underestimation since only a very small number of countries represented South America, Africa, Asia and the Middle East (Figure 1).

Figure 1 World map showing the IFCC member countries that responded to the point-of-care testing survey

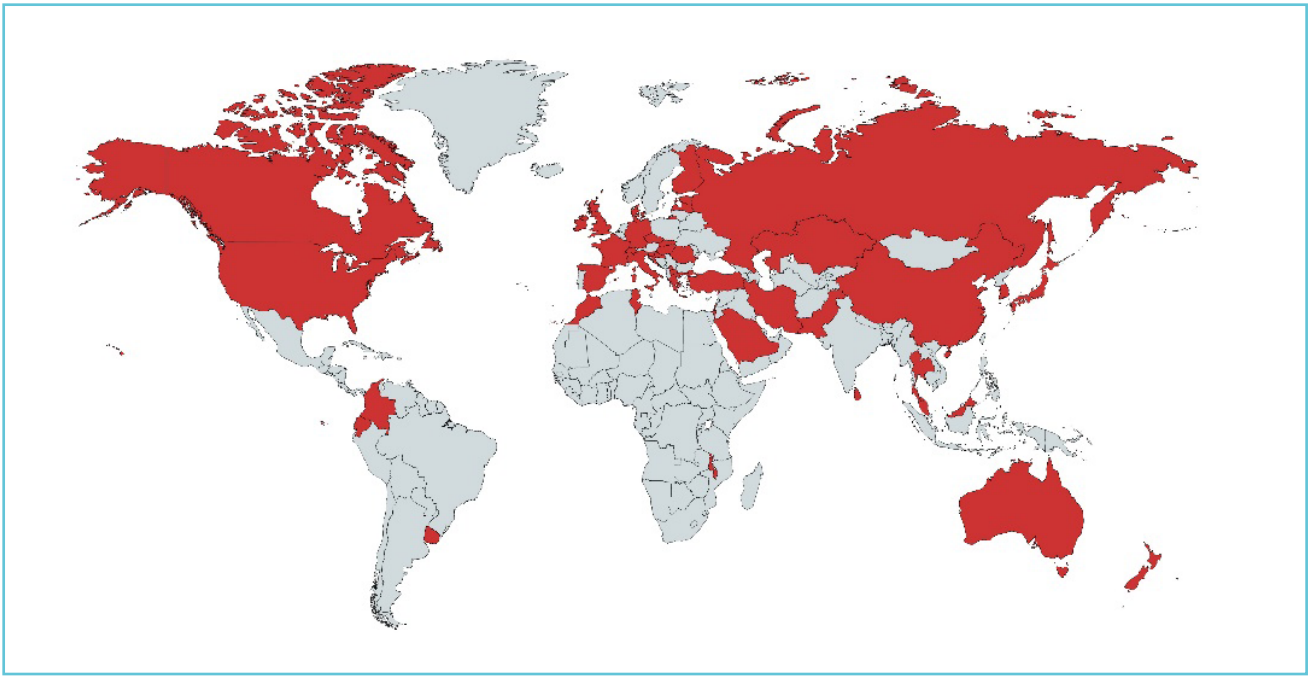


Figure 2A A. Does your society have a point-of-care testing committee?

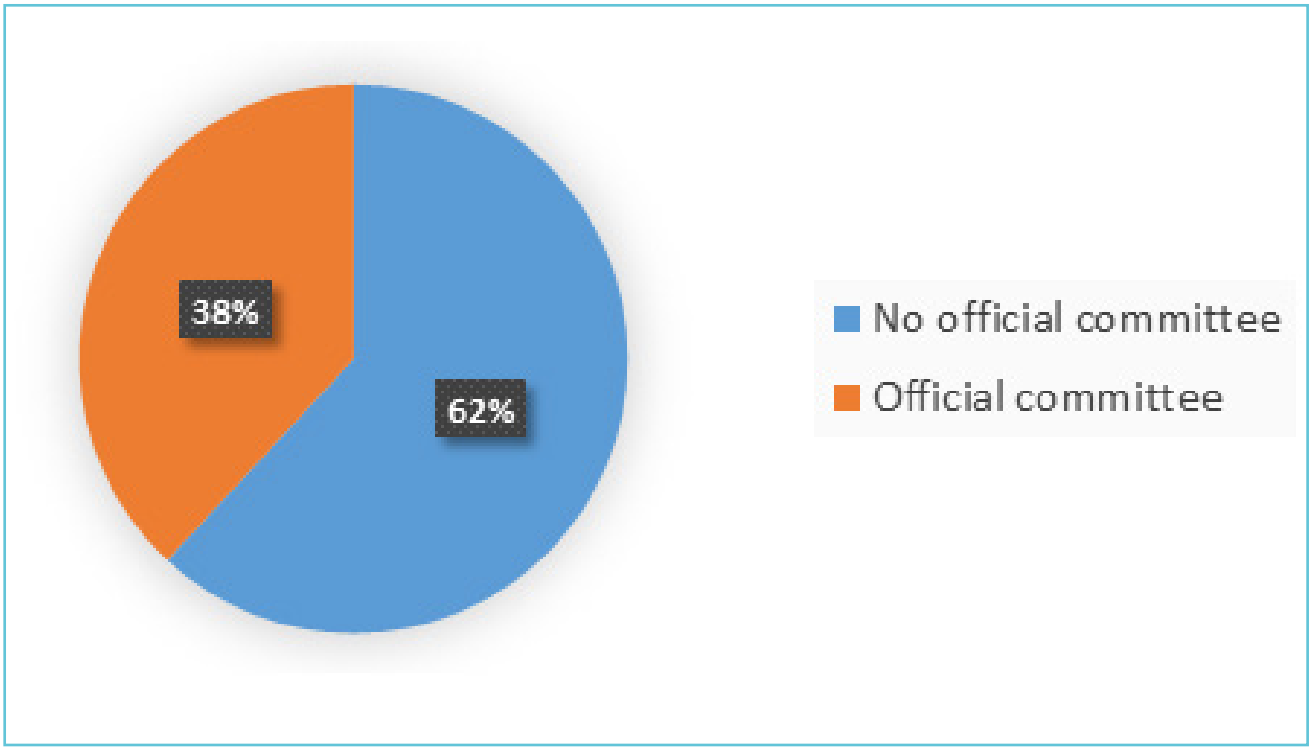


Figure 2B Is point-of-care testing regulated in your country?

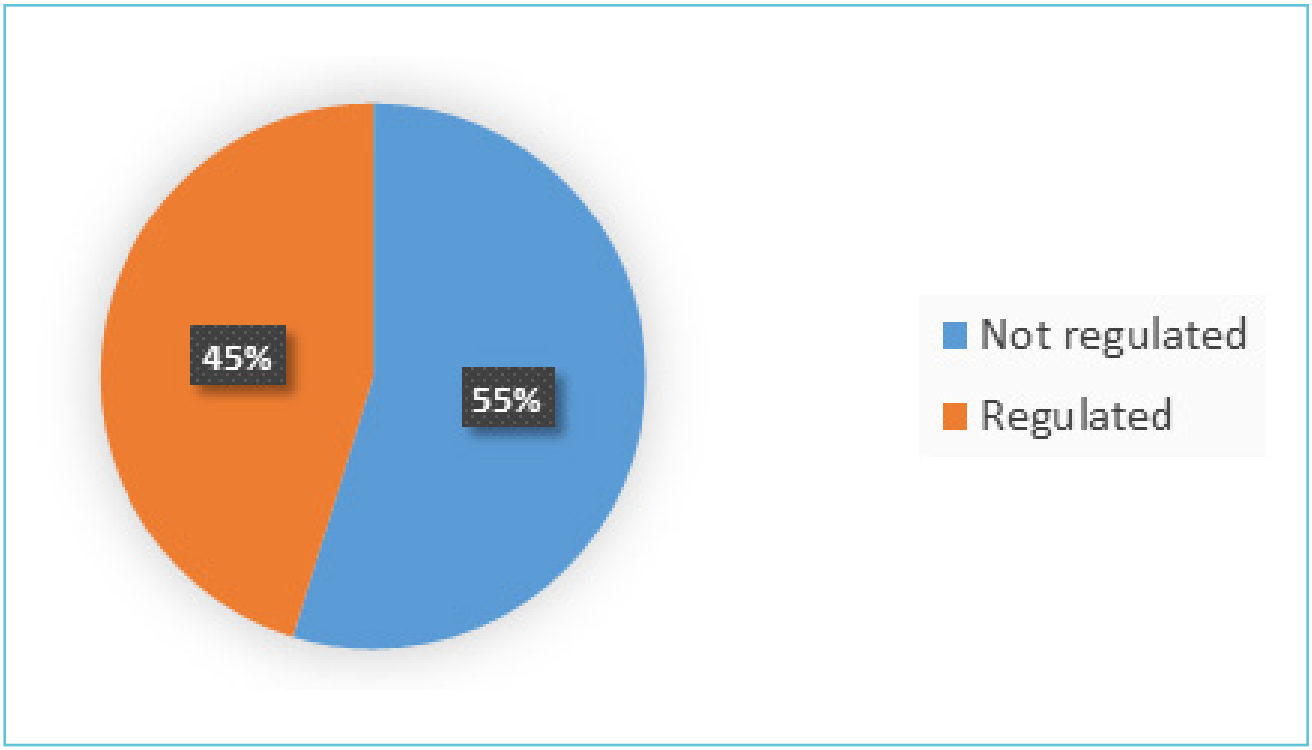
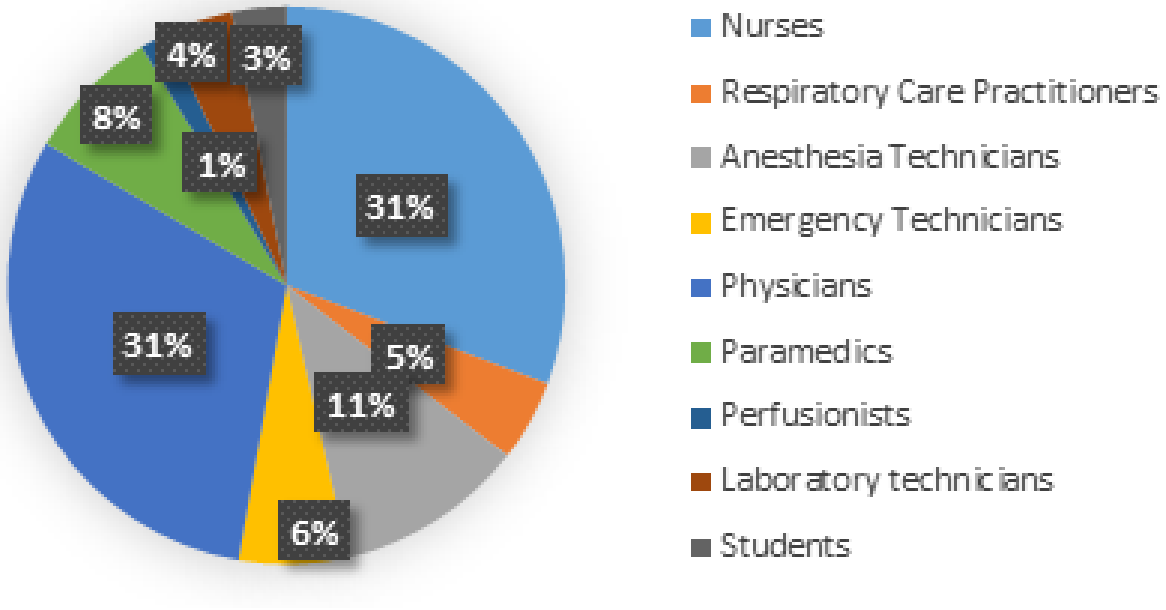


Figure 3 Point-of-care testing by job category



Performing POC testing in a non-standardized manner, without any official quality assurance program that includes performance improvement indicators, and regular audits, makes the POC testing program vulnerable to potential errors in the pre-analytical, analytical and post analytical stages and thus hinders potential benefits it can provide in patient management through the system. Simply following the manufacturer's instructions is not always sufficient to ensure quality results. Employing regulatory guidelines that have been developed through collaboration amongst experts within the field with a "best laboratory practices" mindset, using clinical and industry quality benchmarks, in addition to manufacturer recommendations is important.

For example, in 2016, a hospital in the United States found two patients with hepatitis C infections due to unsafe practices in a hemodialysis unit. Further investigation showed that there was a lack of compliance to infection control processes such as failure to change gloves when staff moved between equipment or using ungloved hands without proper hand hygiene. Lack of cleaning and disinfection of environmental surfaces (visible bloodstains on dialysis machine, on dialysis station televisions, and on patient chairs) [3].

The instruments being used for PT/INR patients are also potential sources of infection. In another United States study [4], nurse staff demonstrated a lack of infection control and best practices, despite training and competency in the use of the instruments. The staff were also not educated on the type of disinfectant to use, and the contact time for the disinfectant to remain wet on the surface of the prothrombin monitoring device [4].

Depending on the manufacturer, the package insert does not always fully address good laboratory practices. For example, when using glucose meters, the vendor may not always mention in their package inserts that glucose meters

needs to be disinfected when used between different patients. In a multicenter study of glucose meter usage in 12 hospitals in the United States, that were classified as urban, suburban, or rural, 30.2% ± 17.5% of the glucose meters studied had blood contamination, and the incidence was 2 times higher in the intensive care units. The number of operators per unit also correlated with higher incidences of blood contamination [5, 6], and another U.S. study found that hepatitis B infection outbreaks were increased in long-term care facilities [7, 8]. These examples highlight the importance of education associated with POC testing that goes beyond the package insert and regulation in the form of standardized policies that addresses the three phases of testing, in addition to regular audits and most importantly accountability corrective actions for deficiencies.

An important feature of POC testing that sets it apart from other healthcare disciplines is that the users can come from a wide variety of backgrounds, including, nurses, nurse aids, respiratory care practitioners, perfusionists, physicians, paramedics and other healthcare workers (Figure 3). As a result, training has to be geared to address the different educational backgrounds, often with no previous laboratory experience and a lack of familiarity with concepts such as quality control, quality assurance and root cause analysis [9].

Consequently, there is a requirement to have a robust POC testing program headed at a minimum by a director or equivalent to initiate institutional change and a POC coordinator that can implement the change [9]. The POC coordinator is the key to any successful POC testing program and is often a clinical laboratory professionals since they have both laboratory experience and knowledge. People-skills are equally important because they are constantly communicating to POC test users and involved in their training and education [10].

In the United States, the Clinical Laboratory Improvements Amendments of 1988 (CLIA'88) regulate laboratory testing through three federal agencies: the Food and Drug Administration (FDA), Center for Medicaid Services (CMS) and the Center for Disease Control (CDC). Each agency has a unique role in assuring quality in laboratory testing (See Table 1.)

The FDA categorizes tests according to their level of complexity [11]. There are three categories: waived, moderate complexity, and high complexity. A test that is classified as "waived" is simple to use, and will not cause harm to the patient if done incorrectly. Generally, over-the-counter and at-home use tests are given this category. The next classification, moderate and high complexity tests (also known as non-waived testing) is determined by the FDA committee, after reviewing the package insert and making the assessment based on 7 categories, with each being given a score of 1, 2, or 3. The lowest level of complexity is given a score of "1" and "3" to the highest level of complexity. When the 7 scores are added together if the sum is 12 or below it is a moderate complexity test and if above 12, a high complexity test. See Table 2, showing how FDA determines whether a test is categorized as moderate or high complexity and grades it accordingly by giving it a score of 1-3 [11].

In the United States, point-of-care tests used in hospitals usually belong to either waived or moderately complex category. This categorization can be effective in limiting the adoption of a POC tests in a hospital because each category is associated with different regulations, in terms of quality assurance practices, such as frequency of quality control, linearity, calibration, instrument correlations. For waived tests, manufacturer's instructions need to be followed, however, moderately complex tests in addition require linearities to be performed if applicable, instrument correlations, enrollment

into proficiency testing or external quality assessment programs and individual quality control plan (IQCP). In the absence of an IQCP, two levels of external quality control (QC) must be performed daily or if the manufacturer recommends, at the change of each shift for non-waived POC tests. If an IQCP is implemented, daily QC can be limited to the internal QC, (if this is available) and performance of external QC at the manufacturer frequency, with new lot/shipments of reagents, and at least monthly, whichever is more frequent. An IQCP is developed based upon guidelines published by the Clinical Standards Institute (CLSI) EP23-A, Laboratory Quality Control Based on Risk Management [12].

Table 1 In the U.S. three federal agencies have been designated to regulate different aspects of CLIA'88

Clinical Laboratory Improvements Amendments, 1988 (CLIA'88)		
Food and Drug Administration (FDA)	**Center for Medicaid Services (CMS)**	**Center for Disease Control (CDC)**
Categorizes tests based on complexity	Issues laboratory certificates	Provides analysis, research, and technical assistance
Reviews requests for Waiver by Application	Collects user fees	Develops technical standards and laboratory practice guidelines, including standards and guidelines for cytology
Develops rules/guidance for CLIA complexity categorization	Conducts inspections and enforces regulatory compliance	Conducts laboratory quality improvement studies
	Approves private accreditation organizations for performing inspections, and approves state exemptions	Monitors proficiency testing practices
	Monitors laboratory performance on Proficiency Testing (PT) and approves PT programs	Develops and distributes professional information and educational resources
	Publishes CLIA rules and regulations	Manages the Clinical Laboratory Improvement Advisory Committee (CLIAC)

Table 2 Showing how FDA determines whether a test is categorized as moderate or high complexity test and grades it accordingly by giving a score of 1-3)* (adapted from reference 11)

Categorization criteria
1 – Knowledge
• Score 1. (A) Minimal scientific and technical knowledge is required to perform the test; and (B) Knowledge required to perform the test may be obtained through on-the-job instruction.
• Score 3. Specialized scientific and technical knowledge is essential to perform pre-analytic, analytic or post-analytic phases of the testing.
2 - Training and experience
• Score 1. (A) Minimal training is required for pre-analytic, analytic and post-analytic phases of the testing process; and (B) Limited experience is required to perform the test.
• Score 3. (A) Specialized training is essential to perform the pre-analytic, analytic or post-analytic testing process; or Substantial experience may be necessary for analytic test performance.
3 - Reagents and materials preparation
• Score 1. (A) Reagents and materials are generally stable and reliable; and (B) Reagents and materials are prepackaged, or premeasured, or require no special handling, precautions or storage conditions.
• Score 3. (A) Reagents and materials may be labile and may require special handling to assure reliability; or (B) Reagents and materials preparation may include manual steps such as gravimetric or volumetric measurements.
4 - Characteristics of operational steps
• Score 1. Operational steps are either automatically executed (such as pipetting, temperature monitoring, or timing of steps), or are easily controlled.
• Score 3. Operational steps in the testing process require close monitoring or control, and may require special specimen preparation, precise temperature control or timing of procedural steps, accurate pipetting, or extensive calculations.
5 - Calibration, quality control, and proficiency testing materials
• Score 1. (A) Calibration materials are stable and readily available; (B) Quality control materials are stable and readily available; and (C) External proficiency testing materials, when available, are stable.

- Score 3. (A) Calibration materials, if available, may be labile; (B) Quality control materials may be labile, or not available; or (C) External proficiency testing materials, if available, may be labile.

6 - Test system troubleshooting and equipment maintenance

- Score 1. (A) Test system troubleshooting is automatic or self-correcting, or clearly described or requires minimal judgment; and (B) Equipment maintenance is provided by the manufacturer, is seldom needed, or can easily be performed.
- Score 3. (A) Troubleshooting is not automatic and requires decision-making and direct intervention to resolve most problems; or (B) Maintenance requires special knowledge, skills, and abilities.

7 - Interpretation and judgment

- Score 1. (A) Minimal interpretation and judgment are required to perform pre-analytic, analytic and post-analytic processes; and (B) Resolution of problems requires limited independent interpretation and judgment.
- Score 3. (A) Extensive independent interpretation and judgment are required to perform the pre-analytic, analytic or post-analytic processes; and (B) Resolution of problems requires extensive interpretation and judgment.

** Note: A score of 2 is assigned to a criteria heading when the characteristics for a particular test are intermediate between the descriptions listed for scores of 1 and 3.*

There are three sections of an IQCP [13]:

(1) Risk assessment:

The purpose is to map the testing process so to identify procedural weaknesses. At a minimum it is made up of 5 components:

i. Specimen
ii. Test system
iii. Reagent
iv. Environment
v. Testing personnel

(2) Quality Control Plan (QCP)

The Quality Control Plan describes the processes that the point-of-care testing program has implemented to mitigate the procedural weaknesses identified in the risk assessment. The following is an example of what it may include:

i. Electronic controls
ii. Internal controls
iii. Proficiency testing (PT)
iv. Calibration Maintenance
v. Training and competency assessment

(3) Quality Assessment (QA)

This monitors the quality control plan to determine of the processes that have been put in place to reduce the weaknesses in the testing processes are effective and evaluates, but is not limited to the following:

i. QC reviews
ii. PT performance reviews
iii. Chart reviews

iv. Specimen rejection logs

v. Turnaround time reports

vi. Complaint reports

Webinars form an essential communication tool that has been increasingly used due to the social restrictions imposed by the COVID-19 pandemic. Their effectiveness can be seen in figure 5A-C which breaks down some of the data gathered from a recent Asia Pacific Point-of-Care Webinar on "The Role of Blood Gas in Overall Management of COVID-19 Patients."

CONCLUSION

Point-of-care testing will become increasingly intertwined with how healthcare systems manage acute and chronic diseases. Furthermore, a lack of reliance on healthcare infrastructure in resource limited settings makes POCT devices an attractive alternative to centralized laboratory testing [14]. Best laboratory practices are essential for meaningful results as is their appropriate use. However, the point-of-care diagnostics explosion outpaces global regulatory oversight that is needed in this sector and confirms the need to meet this demand with focused webinars, educational and practical workshops to ensure best laboratory practices are followed.

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Figure 5A Registrants – by countries (640 registrants)

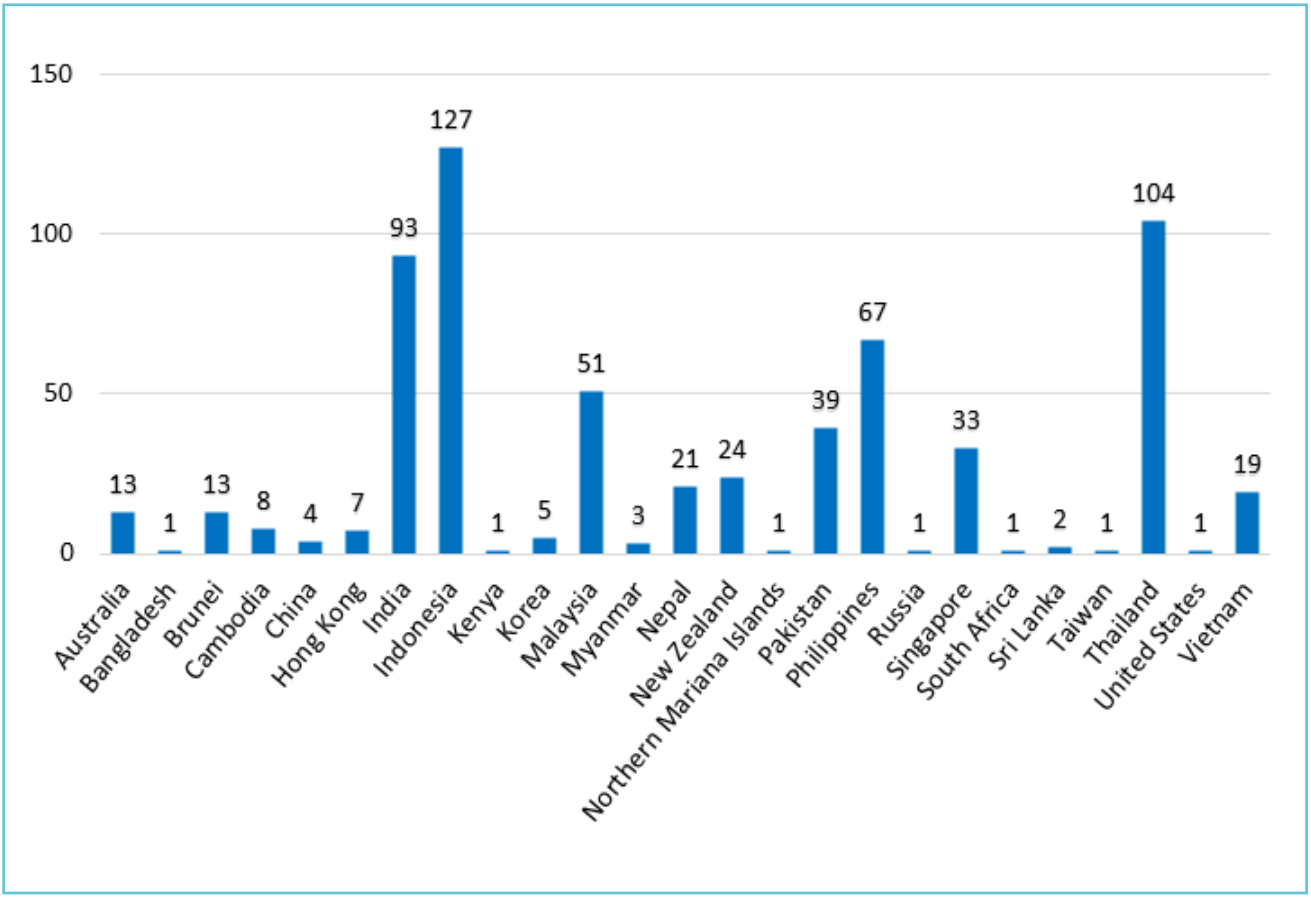


Figure 5B Live attendance by countries (219 registrants)

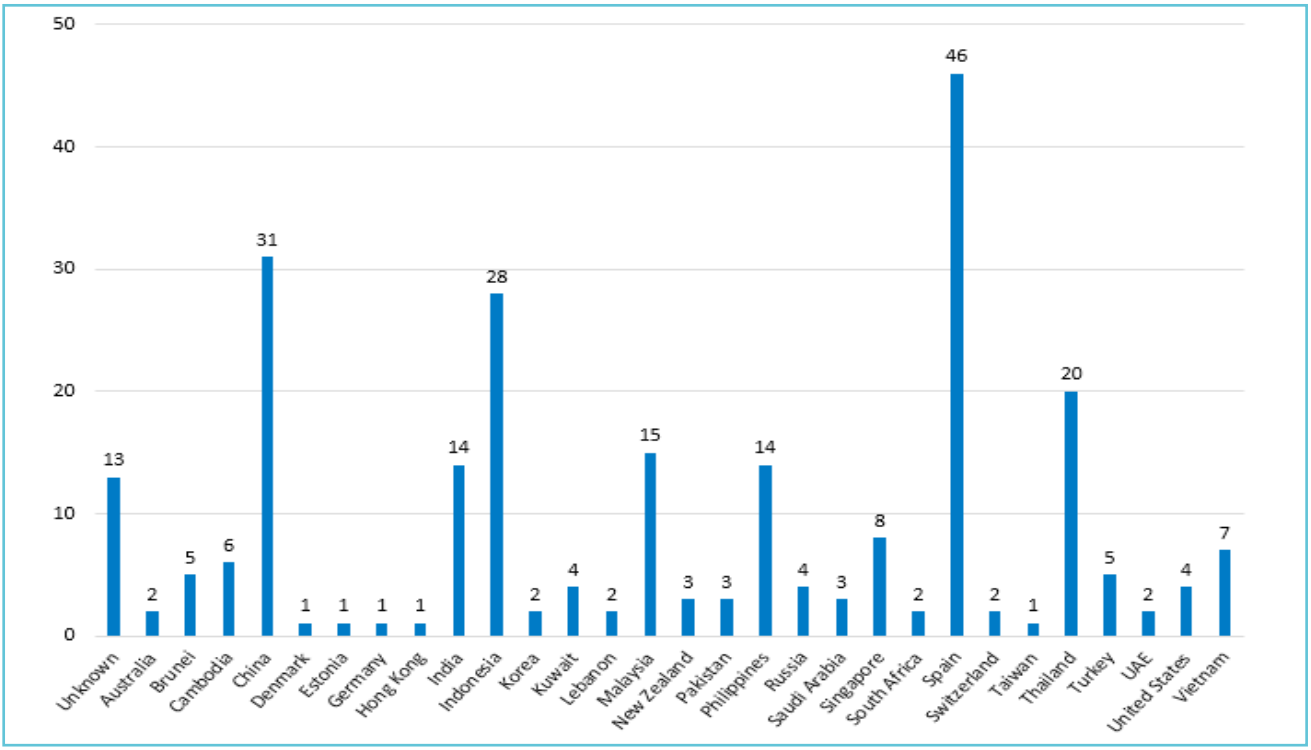
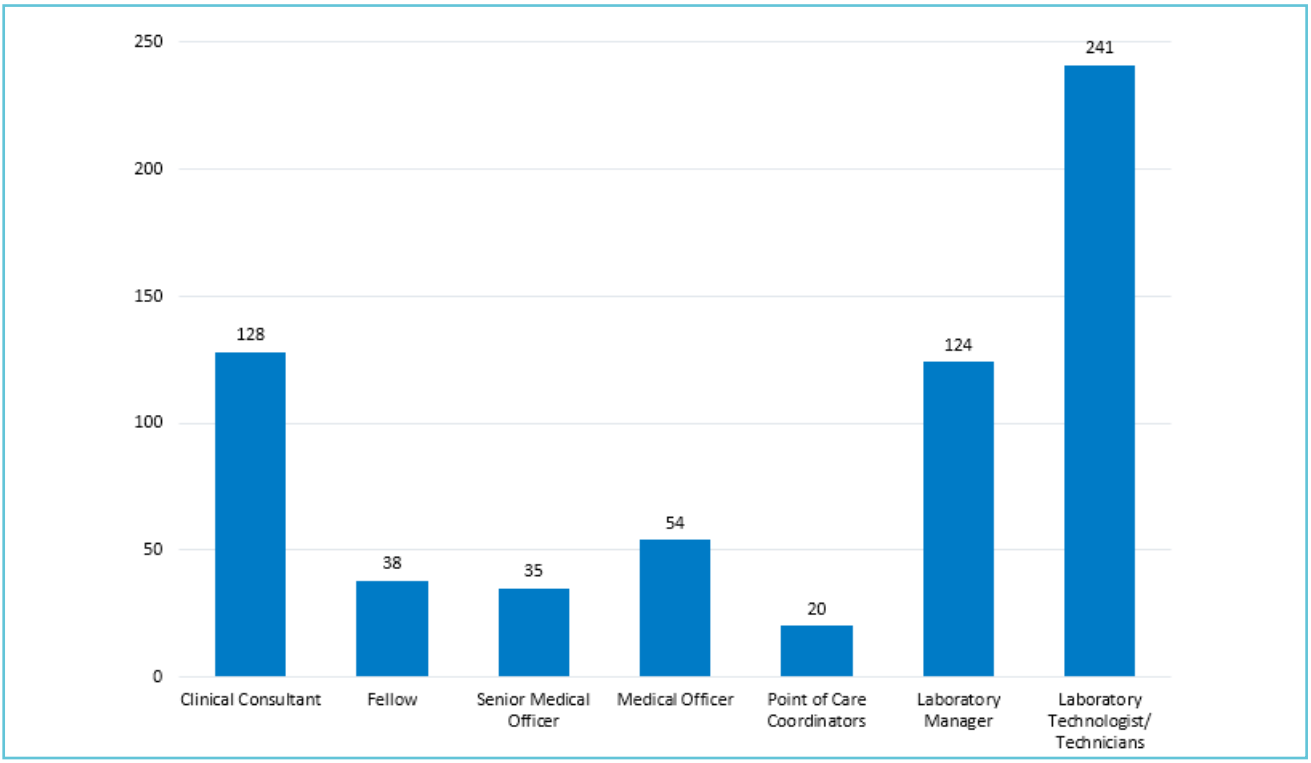


Figure 5C Registrants by job titles



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Predictive model of severity in SARS CoV-2 patients at hospital admission using blood-related parameters

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Key words:
SARS CoV-2, COVID-19, prediction, severity, blood parameters

ABSTRACT

Introduction

Blood test alterations are crucial in SARS CoV-2 (COVID-19) patients. Blood parameters, such as lymphocytes, C reactive protein (CRP), creatinine, lactate dehydrogenase, or D-dimer, are associated with severity and prognosis of SARS CoV-2 patients. This study aims to identify blood-related predictors of severe hospitalization in patients diagnosed with SARS CoV-2.

Methods

Observational retrospective study of all rt-PCR and blood-test positive (at 48 hours of hospitalization) SARS CoV-2 diagnosed inpatients between March-May 2020. Deceased and/or ICU inpatients were considered as severe cases, whereas those patients after hospital discharge were considered as non-severe. Multivariate logistic regression was used to identify predictors of severity, based on bivariate contrast between severe and mild inpatients.

Results

The overall sample comprised 540 patients, with 374 mild cases (69.26%), and 166 severe cases (30.75%). The multivariate logistic regression model for predicting SARS CoV-2 severity included lymphocytes, C reactive protein (CRP), creatinine, total protein levels, glucose and aspartate aminotransferase as predictors, showing an area under the curve (AUC) of 0.895 at a threshold of 0.29, with 81.5% of sensitivity and 81% of specificity.

Discussion

Our results suggest that our predictive model allows identifying and stratifying SARS CoV-2 patients in risk of developing severe medical complications based on blood-test parameters easily measured at hospital admission, improving health-care resources management and distribution.

❖❖❖❖❖

INTRODUCTION

The new SARS CoV-2 (COVID-19) emerged in Spain in March 2020, reaching the pandemic peak in the second half of that month, posing a serious challenge to health-care professionals.

The clinical picture features fever, asthenia, and respiratory symptoms such as dyspnea, cough, or more severe complications like pneumonia or adult respiratory distress syndrome. The remarkable activation of coagulation, inflammation, and endothelial session and hypoxia present a key role in the patients' severity, with an 8% of ICU hospitalizations due to ventilatory support demand (1). Mortality estimates of hospitalized patients are around 21% (1).

Clinical laboratory has played a crucial role in this disease, due to blood-test alterations presented by SARS CoV-2 patients: lymphopenia, lactate dehydrogenase (LDH) elevations, D-dimer (DD) or C-reactive protein (CRP) are characteristics of the disease (2,3,4,5), as well as increased ferritin and interleukin-6 (IL6), both inflammatory markers that sound alarm of a more critic prognosis (1,3).

Several studies have shown that blood-test parameters are associated with SARS CoV-2 mortality, such as CRP (5,6,7), presenting a higher sensitivity than other parameters like age, neutrophils and platelets. DD is also associated with an elevated risk of mortality (8), and other mortality predictive models include LDH, lymphocytes, transaminases, or hyperglycemia (9,10,11).

Other blood parameters were less studied at the beginning of the pandemic, but gained relevance over time, such as creatinine. Recent studies showed strong associations between elevated creatinine and a higher mortality risk in SARS CoV-2 patients. Other blood parameters present even more important prognostic capacity, as they proved to be useful to identify those patients who will require more resources and that might be candidates of ICU admission. In a recent meta-analysis, Brando et al. (3) highlighted the importance of hematological alterations in severe patients, with the ferritin being the most relevant biochemical marker of disease progression. In the studies published by Huang (4) and Liu (14) at the beginning of the pandemic, the predictors of ICU admission were leukocytosis, neutrophilia, lymphopenia, DD, LDH, total bilirubin and alanine aminotransferase (ALT). There are studies that established predictive models with different results, but they all highlight the relevance of CRP, LDH (15,16,17,18), lymphocytes, platelets (17,19), IL-6 and DD (20). In the meta-analysis published by Timotius (21), procalcitonin, albumin, CRP, DD, and LDH were identified as relevant predictors of disease severity. However, they also highlight that thresholds for each parameter are not clearly

defined yet, and that more research should be conducted on that regard.

Thus, the main objective of this study is: to establish a predictive model of disease severity based on blood-test clinical parameters in COVID-19 patients diagnosed at first hospitalization. As a secondary objective we also aim at analyzing clinical and blood-test alterations of those patients.

MATERIAL AND METHODS

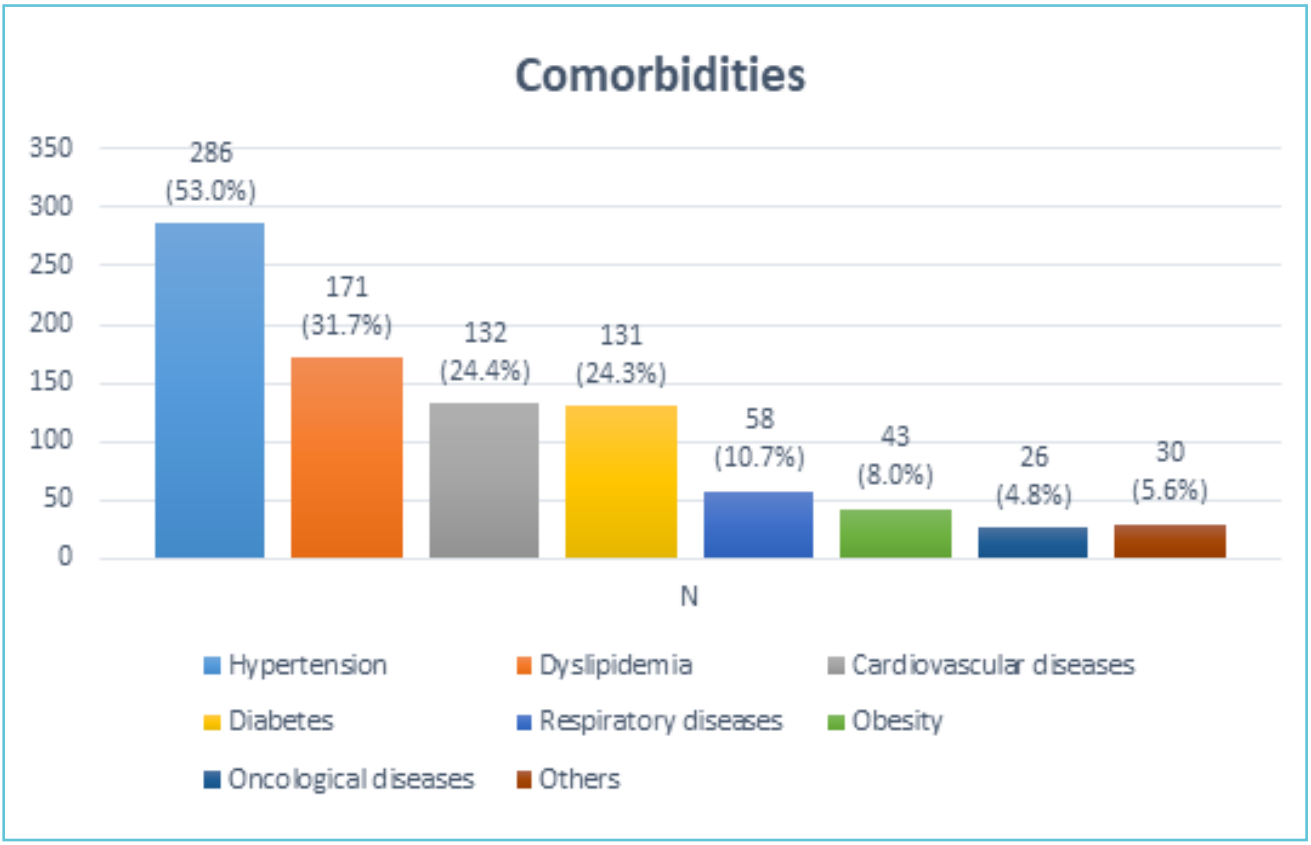
Sample selection

Observational retrospective study. SARS CoV-2 positive patients through rRT-PCR, hospitalized between March 9 and May 9, 2020. Deceased or admitted to ICU patients were considered as severe, and those discharged after hospitalization (not ICU) were considered as non-severe patients. The demographic characteristics collected were: sex, age and comorbidities such as hypertension (HT), diabetes, obesity, dyslipidemia, respiratory, oncological and cardiovascular diseases.

The first blood test of the patient was collected upon admission, always within the first 48 hours after admission.

Hematological variables: leukocytes (x10^3/ µL), lymphocytes (x10^3/ µL), neutrophils (x10^3/ µL), platelets (x10^3/ µL), D-dimer (µg/ mL) and fibrinogen (mg/ dL). Biochemicals: creatinine (mg/ dL), ALT (U/ L), aspartate aminotransferase (AST) (U/ L), creatinine kinase (CK) (U/ L), ferritin (ng/ mL), LDH (U/ L), CRP (mg / L), total proteins (g/ dL), Troponin T (pg/ mL) and total bilirubin (mg/ dL). Hematological parameters were analyzed on an Advia2120 (Siemens®), fibrinogen and D-Dimer on STA-R-Max (Stago®)

Figure 1 Frequency and type of comorbidities in the sample (n and %)



and biochemical parameters on a Cobas 8000 (Roche diagnostics®).

We utilize the most commonly used measurement units in clinical laboratories.

Exclusion criteria:

- Patients without blood-test analysis 48 hours.
- Transfer to another hospital or medical hotel.
- Patients with hematological conditions (due to alteration of the blood count data).
- Patients with hemolyzed samples that could interfere with the results.

Statistical analyses

Statistical analyses were conducted using STATA version 15. The median and interquartile range (IQI), with the method of the weighted average, were used to describe quantitative data. The association between disease severity and comorbidities was assessed using the prevalence ratio.

To test differences between severe and non-severe SARS CoV-2 patients, comparisons were based on the medians, estimating 95% confidence intervals and *p*-values using the Bonett-Price estimation (Bonett and Price, 2002). In the case of troponin T, a comparison of proportions was conducted.

To build the predictive logistic regression model, we first randomly divided the total sample (540 patients) into two parts: 2/3 (360 patients) as a training sample to estimate the model and 1/3 (180 patients) as a validation sample that is subsequently used to assess the reliability of the model. To select the variables to include in the model, a previous screening of the insignificant variables was carried out, based on the results of univariate logistic regressions with a single independent variable. Thus, variables with p values < 0.20 on the univariate regression models were included in the multivariate logistic regression model. We selected the best model from all possible equations, reducing the number of parameters to be included in the equation in order to obtain a more stable model and also facilitate its handling in clinical practice without losing predictive power. To avoid including strongly correlated terms in the model, that might potentially cause stability problems in the estimation algorithm, we discarded parameters that are physiologically and/or pathophysiologically related to each other and provide similar information, keeping only one of them in the equation when it is significant. This is the case of hematological parameters, liver function, kidney function and inflammation/infection. We verify that the final model selected does not violate the assumptions of the logistic regression model. For this, the lineal relationship between the logit and each of the predictors, the absence of collinearity and the absence of distant values and influencing values were evaluated. Outliers were excluded from the analyses, that is, cases with distant values in the predictor variables and cases poorly predicted by the model, detected by residual analysis, and cases with high influence values, detected by three diagnostic indices: DBeta influence index (Hosmer, Taber and Lemeshow, 1991) and the DX2 and DDev indices (Hosmer, Lemeshow and Sturdivant, 2013). Finally, we evaluated its predictive ability by calculating the prediction loss with the validation sample.

RESULTS

The sample comprised a total of 540 patients hospitalized during the first epidemic wave of the SARS-CoV-2 virus during the months of March-April. The age range was from 22 to 99 years and the median age was 68 years with no significant difference between the number

of men (n = 314, 58.15%) and women (n = 226, 41.85%) (p = 0.526).

Regarding disease severity, 374 patients (69.26%) presented mild disease development and a median age of 65 years; and 166 patients (30.74%) presented severe disease with a median age of 75 years. In this last group 155 patients died, which represents a mortality of 28.7% in the overall sample of admitted patients.

Regarding sex, the prevalence of severity in men is 1.21 times higher than in women (95% CI 0.927 to 1.571) (p = 0.158). 78.52% of the patients presented some type of comorbidity. The prevalence of comorbidity is presented below (graph 1).

The probability of greater severity in patients with comorbidities is 33.25%, while the probability of greater severity in patients without comorbidities is 21.55%. The prevalence of greater severity in patients with comorbidities is 1.54 times higher than in patients without comorbidities (95% CI 1.063 to 2.239) (p <0.05).

Table 1 displays descriptive statistics of the blood-test variables and age in both groups studied, median and interquartile range. Table 2 shows the comparison of medians between the two groups: severe vs non-severe, along with its statistically significance.

To build the predictive model of disease severity, we followed the procedure described in the materials and methods section, with the parameters finally estimated (Table 3).

The estimated model equation that predicts the value of the log-odds (logit) of developing severe disease in patients with SARS CoV-2 according to age and laboratory parameters: lymphocyte count, creatinine, total protein, glucose, AST and PCR, is:

Ln O_{severe} = (-9.215265) + 0.1087873 x **Age** (years) - 0.8933988 x **Lymphocytes** (x10^3/ µL) + 0.5728488 x **Creatinine** (mg/ dL) - 0.2791245 x **Total proteins** (g/ dL) + 0.0076588 x **Glucose** (mg/ dL) + 0.01179 x **AST** (U/ L) + 0.0092949 x **CRP** (mg/ L)

To select the optimal cut-off point, we chose the cut-off point p = 0.2859 that maximizes efficiency and corresponds to a sensitivity of 81.5% (95% CI: 70.4 to 89.1) and a specificity of 81.0% (95% CI: 74.6 to 86.2). For the observed prevalence in our sample (27.2%), the positive predictive value is 61.6% and the negative predictive value is 92.2%.

We assessed the significance of the estimated model using the likelihood ratio test. We obtained a result (χ^2 = 111.69; df = 7; p <0.001) that indicates that the estimated model is significant, that is, the set of terms included in the model predicts disease severity in a statistically significant way.

We used the area under the ROC curve (AUC) to assess the predictive ability of the model (AUC = 0.895; exact 95% CI: 0.849 to 0.931), with a prediction loss of less than 5% in the validation sample.

DISCUSSION

Early identification of COVID-19 patients at risk of progressing to severe disease will lead to a better management and more efficient use of medical resources. In this article, we established a predictive model of severity through clinical and blood-test parameters that include age, lymphocytes, creatinine, total proteins, glucose, AST and CRP in the first 48 hours upon admission and that correlate with an increased risk of severe COVID -19 disease.

Regarding the demographic data, a large percentage of patients presented some type of comorbidity (78.5%), but there were no significant differences in disease severity in this regard. Consistent with the SEMI study (1), we observed a large number of patients (52.9%)

Table 1 Descriptive statistics of blood-test parameters and age (n, median, and interquartile range)

	Non-severe disease			Severe disease		
Parameter	**n**	**Median**	**IQI**	**n**	**Median**	**IQI**
Age (years)	374	65	[55; 72]	166	75	[67; 86]
Leukocytes (x10^3 / µL)	374	5.68	[4.608; 7.575]	166	6.765	[4.973; 10.635]
Neutrophils (x10^3 / µL)	374	4.08	[3.048; 5.823]	166	5.3	[3.758; 9.288]
Lymphocytes (x10^3 / µL)	374	1.01	[0.74; 1.34]	166	0.735	[0.498; 1.06]
Neutrophil / lymphocyte ratio	374	4.06	[2.64; 6.25]	166	6.98	[4.57; 13.52]
Platelets (x10^3 / µL)	374	205	[158.5; 257.7]	166	191.5	[153.75; 264.25]
Fibrinogen (mg / dL)	192	590.5	[483; 659.5]	67	663	[469; 741]
D-dimer (µg / mL)	331	0.69	[0.45; 1.17]	137	1.14	[0.72; 2.235]
Glucose (mg / dL)	374	111.5	[101; 134]	166	139	[118; 177]
Creatinine (mg / dL)	374	0.9	[0.8; 1.1]	165	1.2	[0.9; 1.5]
Total bilirubin (mg / dL)	186	0.485	[0.4; 0.51]	77	0.4	[0.4; 0.6]
Aspartate aminotransferase (AST) (IU / L)	187	29	[21; 43]	75	38	[25; 58]
Alanine aminotransferase (ALT) (IU / L)	336	27	[18; 43]	150	26	[17; 44.25]
Lactate dehydrogenase (LDH) (IU / L)	354	280	[226; 347.25]	158	356.5	[274; 501.5]
Creatine kinase (CK) (IU / L)	197	76	[49.5; 127]	68	124.5	[68.5; 321]
Total proteins (g / dL)	185	6.5	[6.2; 6.85]	75	6.3	[5.8; 6.6]
C-reactive protein (CRP) (mg / L)	365	47.8	[21.05; 91.6]	163	115.2	[59.2; 239.4]
Ferritin (ng / mL = µg / L)	213	563	[266; 1212.5]	87	880	[400; 1699]
Troponin T (pg/mL): < 14 ≥ 14	196	138 (70.41%) 58 (29.59%)		65	20 (30.77%) 45 (69.23%)	

Table 2 Median comparison between severe and non-severe patients and statistical significance

Parameter	N	Difference between medians	Confidence interval 95%	*p*-value
Age (years)	540	10	7.199 a 12.801	<0.001
Leukocytes (x10^3 / µL)	540	1.085	0.436 a 1.734	0.0011
Neutrophils (x10^3 / µL)	540	1.22	0.388 a 2.052	0.0041
Lymphocytes (x10^3 / µL)	540	-0.275	-0.368 a -0.182	<0.001
Neutrophil / lymphocyte ratio	540	2.923	1.500 a 4.346	<0.001
Platelets (x10^3 / µL)	540	-13.5	-32.747 a 5.747	0.169
Fibrinogen (mg / dL)	259	72.5	15.655 a 129.345	0.0124
D-dimer (µg / mL)	468	0.45	0.226 a 0.674	<0.001
Glucose (mg / dL)	540	27.5	18.921 a 36.079	<0.001
Creatinine (mg / dL)	539	0.3	0.203 a 0.397	<0.001
Total bilirubin (mg / dL)	263	-0.085	-0.154 a -0.0164	0.0152
Aspartate aminotransferase (AST) (IU / L)	262	9	0.665 a 17.335	0.0343
Alanine aminotransferase (ALT) (IU / L)	486	-1	-5.537 a 3.537	0.666
Lactate dehydrogenase (LDH) (IU / L)	512	76.5	42.185 a 110.815	<0.001
Creatine kinase (CK) (IU / L)	265	48.5	2.337 a 94.663	0.0395
Total proteins (g / dL)	260	-0.2	-0.370 a -0.0300	0.0211
C-reactive protein (CRP) (mg / L)	528	67.4	43.384 a 91.416	<0.001
Ferritin (ng / mL= µg / L)	300	317	-5.264 a 639.264	0.0539

Disease severity	Troponin T (pg/mL)		Total	Proportion	IC 95% (Wilson)	*p*-value
	< 14	≥ 14				
Non-severe	138	58	196	0.296	0.236 a 0.363	<0.001
Severe	20	45	65	0.692	0.572 a 0.791	

Table 3 Parameter estimates from the multivariate logistic regression model to predict disease severity

Severity	Odds Ratio (OR)	CI 95%
Age (years)	1.114925	1.069048 a 1.162772
Lymphocytes (x10^3/ µL)	0.4092624	0.1648353 a 1.01614
Creatinine (mg/ dL)	1.773312	0.8017985 a 3.921976
Total proteins (g/ dL)	0.7564457	0.3590133 a 1.593841
Glucose (mg/ dL)	1.007688	1.000588 a 1.014839
Aspartate aminotransferase (U/ L)	1.01186	0.995918 a 1.028057
C-reactive protein (mg/ L)	1.009338	1.004526 a 1.014174
Intercept	0.0000995	0.000000124 a 0.0798615

presenting hypertension, followed by dyslipidemia (31.7%). On the contrary, our sample had a higher prevalence of diabetes mellitus (24.7% vs 18.7% in the SEMI study) and less obesity (7.9% versus 21.2%).

The proportion of male patients presenting severe illness was higher than the women's (62.6% and 37.36%, respectively), but the differences were not statistically significant. It is worth highlighting the role of age, with a statistically significant difference of 10 years between the patients presenting severe (median 75) and non-severe (median 65) disease. These results are consistent with different studies evidencing positive associations between age and disease severity (5,22), with some of them suggesting the age of 60 years as the cut-off point of severity (22, 7).

Regarding the blood-test parameters, we found significant differences between severe and non-severe patients in leukocytes, neutrophils and lymphocytes, RNL, fibrinogen, d-dimer, glucose, creatinine, total bilirubin, AST, LDH, CK, total proteins and CRP. Similarly, troponin T presents a proportion of values equal to or greater than 14 versus negative troponins, significatively higher in the group with greater severity.

Age and 6 basic biochemical and hematological parameters easily available in any hospital center were included in our final predictive model of disease severity: lymphocytes, CRP, AST, creatinine, glucose, and total proteins. The associations between lymphopenia, elevated CRP and disease severity are widely supported in the literature (15, 16, 17 19, 23). On the other hand, our results show an association with severity in parameters not that studied, such as elevated AST (10) and glucose (11), along with decreased total proteins (24). On the contrary, it is worth noting that other well-studied parameters as ferritin, LDH and D-dimer do not predict severity in our study. In our hospital, a thromboprophylaxis protocol with weight-adjusted low-molecular-weight heparin was quickly implemented

as soon as the patient was admitted, which might be reflected in the D-dimer results.

It should be noted that kidney failure presented an important role as a predictor in the final predictive model, with creatinine showing an Odds ratio of 1,773, data consistent with the studies published by Liang (17) and Torres (23), which show predictive scores of severity and mortality respectively.

The area under the curve of our multivariate logistic regression model, close to 1, indicates that our predictive model allows classifying patients in mild or severe severity based on their age and the above mentioned laboratory analytical parameters. Loss of prediction, less than 5%, indicates that our model is reliable and predicts satisfactorily. At a cut-off point of 0.2859, our model presented a good sensitivity (81.5%) and specificity (81.0%), showing a high negative predictive value of 92.2% for the prevalence of severity in our sample.

To make our results even more sensitive and more specific, we proposed generating a gray area, so that patients with a result < 0.3 would have a high negative predictive value (92.2%), patients with > 0.7 would show a high positive predictive value (86.5%) with a specificity of 97.13%. Patients in the range of (0.3 - 0.7) would be in an intermediate gray zone. If we apply this to our study sample, 20% of the patients would remain in the gray area and giving high sensitivity and specificity to the cut-off points of 0.3 and 0.7. To use this predictive model in other populations or laboratories, we recommend recalculating and adapting these cut-off points to the specific target population.

Our study has several strengths. First, we provide a practical quantitative prediction tool based on just 7 variables, which are inexpensive and easily obtained from routine blood tests. This prediction is conducted at the time of admission, that is, in the first 48 hours after the patient's arrival at the hospital and marks the difference with other predictive studies that do not specify when the analytical variables are collected, which may bias the results. Second, the sample size: we included 540 patients of which 166 present severe disease, thus guaranteeing the robustness of the equation and its validation.

Regarding the limitations, firstly, it is a retrospective study that included all patients at admission, without discriminating whether they were severe or mild at the beginning, secondly, the epidemiological context of the period when the study was conducted may bias the time of analysis when admitting patients with advanced disease and therefore not all patients have the data at the same time of the disease, which can alter our results.

In summary, our data suggest that our predictive model allows in identifying and stratifying COVID-19 patients at risk of severe disease through easily accessible analytical parameters at admission, improving the management and distribution of healthcare resources.

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Clinicians' Probability Calculator to convert pre-test to post-test probability of SARS-CoV-2 infection based on method validation from each laboratory

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ABSTRACT

Background

Despite best efforts, false positive and false negative test results for SARS-CoV-2 are unavoidable. Likelihood ratios convert a clinical opinion of pre-test probability to post-test probability, independently of prevalence of disease in the test population.

Methods

The authors examined results of PPA (Positive Percent Agreement, sensitivity) and NPA (Negative Percent Agreement, specificity) from 73 laboratory experiments for molecular tests for SARS-CoV-2 as reported to the FIND database, and for two manufacturers' claims in FDA EUA submissions.

PPA and NPA were converted to likelihood ratios to calculate post-test probability of disease based on clinical opinion of pre-test probability. Confidence

intervals were based on the number of samples tested. An online calculator was created to help clinicians identify false-positive, or false-negative SARS-CoV-2 test results for COVID-19 disease.

Results

Laboratory results from the same test methods did not mirror each other or the manufacturer. Laboratory studies showed PPA from 17% to 100% and NPA from 70.4% to 100%. The number of known samples varied 8 to 675 known patient samples, which greatly impacted confidence intervals.

Conclusion

Post-test probability of the presence of disease (true-positive or false-negative tests) varies with clinical pre-test probability, likelihood ratios and confidence intervals.

The Clinician's Probability Calculator creates reports to help clinicians estimate post-test probability of COVID-19 based on the testing laboratory's verified PPA and NPA.

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Key points

1. Asymptomatic patients, unavoidable false-positive results, and low disease prevalence make it difficult for clinicians to interpret SARS-CoV-2 test results.
2. The same SARS-CoV-2 test result from different laboratories conveys a different post-test probability of disease.
3. Clinicians can convert a patient's clinical pre-test probability of COVID-19 disease to a range of possibilities of post-test probability with reports from the online Clinicians' Probability Calculator.

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Abbreviations

PPA: *positive percent agreement (sensitivity)*
NPA: *negative percent agreement (specificity)*
LR+: *Positive likelihood ratio*
LR-: *Negative likelihood ratio*
EUA: *emergency use authorization*

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INTRODUCTION

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a novel coronavirus that has caused a worldwide pandemic of the human respiratory illness COVID-19.[1] During the COVID-19 outbreak, accurate testing has been a unique and constant challenge for the scientific community. Despite best efforts, false positive and false negative test results are unavoidable[2,3]. At no time in history has the medical community embarked on a diagnostic testing campaign that is not being pursued for clinical reasons, but instead for epidemiological reasons unrelated to the medical aspects of the illness. There are three different types of testing available, molecular testing, antigen and antibody testing.[4] The gold standard at present for diagnosing suspected cases of COVID-19 is molecular testing by real-time reverse transcription polymerase chain reaction (RT-PCR), which is a nucleic acid amplification test that detects unique sequences of SARS-CoV-2 virus.[5] With an increasing number of asymptomatic patients, understanding of the probability of true and false results has never been so critical. Likelihood ratios convert a clinical opinion of pre-test probability to post-test probability, independently of prevalence of disease in the test population.[6,7] This article explores a modified application of likelihood ratios to provide practical guidance to the relative probability of true and false test results.

SIGNIFICANCE OF PRE-TEST AND POST-TEST PROBABILITY OF COVID-19 INFECTION

Pre-test probability and post-test probability are the probabilities of the presence of COVID-19 before (pre) and after (post) a diagnostic test.[8] During the COVID-19 pandemic detecting pre-symptomatic or asymptomatic patients has been of paramount importance. However, tests are often performed with low pre-test probability missing such patients. Although sometimes confused with simple prevalence of disease, the clinical pre-test probability of disease can be more precisely estimated with clinical information on each patient. The probability of infection based on patient symptoms roughly increase with loss of appetite, loss of smell and/or taste, myalgia or fatigue, a strong feeling of weariness, fever, cough, shortness of breath and clinical symptoms of pneumonia[9,10,11,12]. Post-test probability of disease is calculated from the clinical opinion of pre-test probability based on increasing patient symptoms and the quality of the testing process as reflected by PPA, PNA and likelihood ratios.

PPA, NPA, LIKELIHOOD RATIO AND CONFIDENCE INTERVAL

Positive percent agreement (PPA) is the proportion of comparative/reference method positive results in which the test method result is positive. Negative percent agreement (NPA) is the proportion of comparative/reference method negative results in which the test method result is negative.[13] To evaluate the test methods, PPA (sensitivity) and NPA (specificity) are the most common metrics utilized.

The likelihood ratio uses PPA and NPA to create a ratio of the probability that a test result is correct to the probability that it is not. A likelihood ratio is the percentage of ill people with a given test result divided by the percentage of well individuals with the same result (true result: false result). When combined with an accurate clinical diagnosis, likelihood ratios improve diagnostic accuracy in a synergistic manner[6,7,8].

- Likelihood ratios are calculated from PPA and NPA:
- Positive LR = (PPA / (100 – NPA) (True Positives / False Positives)
- Negative LR = (100 – PPA) / NPA (False Negatives/True Negatives)

Likelihood ratios are calculated to determine 2 things: (i) how useful a diagnostic test is; and (ii) how likely it is that a patient has a disease[7]. Likelihood ratios range from zero to infinity (9999.9). The higher the value, the more likely the test will indicate that the patient has the condition.

Confidence interval gives an estimated range of values which is likely to include an unknown population parameter[14]. Confidence intervals provide a range of possible results: minimum, probable and maximum. They tell the end-user how much faith they can have in the value reported.

The likelihood ratio, and thus post-test probability is driven by test PPA and NPA. Reported values of PPA and NPA vary between laboratories using the same method, and the values reported by that manufacturer to FDA for EUA evaluation. Clinical samples may be sent to different testing laboratories, and laboratories may change methods.

The process is described here and available in the online "Clinician's Probability Calculator" can create a report to assist clinicians project post-test probability of disease based on their clinical estimate of pre-test probability and the quality of the testing process used to create the result.

METHODOLOGY

1. The authors used the calculations and definitions in Table 1 to examine results of individual laboratory experiments for molecular tests for SARS-CoV-2 as reported to the FIND database[15], and for selected methods in FDA EUA submissions[16,17].
2. We created an Excel spreadsheet and then designed an online application to graph confidence intervals of post-test probability of infection on with a positive or negative test result (on the y-axis) against the clinician's estimate of pre-test probability (on the x-axis.) Confidence intervals for the graph and each of the following indicators are driven by PPA and PNA reported, plus the number of samples tested[14]:
   a. Post-test probability of SARS-CoV-2 infection with positive and negative test result.
   b. Number of true positive and negative tests in every ten positive or negative results seen.
   c. Number of false positive and negative tests in every 10 positive or negative results seen
   d. One in 'x' positive tests is true, and one in 'x' negative tests is True.

Table 1 Common definitions and key calculations

PPA: Drives the True-Positive and False-Negative rates	Positive Percent Agreement (sensitivity) = True positive results / All positive results	
NPA: Drives the True- Negative and False- Positive rates	Negative Percent Agreement (specificity) = True negative results / All negative results	
Pre-test probability: Based on clinical opinion	Clinical probability that a person being tested has COVID-19 before the test is performed.	
Pre-test odds	= Pre-test probability/(1-Pre-test probability) = Probability person is infected/ Probability they are not	
Calculations	**Positive test**	**Negative test**
Likelihood ratio	Positive (LR+) = PPA / (1 - NPA) = True Pos Rate/False Pos Rate	Negative (LR-) = (1-PPA)/NPA = False Neg Rate/True Neg Rate
Post-test odds	= Pre-test odds x LR+	= Pre-test odds x LR-
Post-test probability: The probability that a person is infected	= Post test odds Pos Test / (Post-Test Odds Pos +1) - with a positive test	= Post test odds Neg Test / (Post-Test Odds Neg Test +1) - with a negative test

RESULTS

Ninety-two laboratories reported both PPA and NPA to the FIND database[15] as of October 17, 2020. We removed 19 results from two laboratories in one country that reported NPA of 100% based on only one negative

The authors compared the Information For Use (IFU) documents provided to FDA for two manufacturers[16,17], to five FIND[15] laboratory studies for manufacturer 1 (Mfg-1) and six FIND laboratory studies for manufacturer 2 (Mfg-2.) To calculate PPA, Positive Percent Agreement, Mfg-1 tested "30 contrived clinical nasopharyngeal (NP) swabs prepared by spiking clinical NP swab matrix with purified viral RNA containing target sequences from the SARS-CoV-2 genome at concentrations approximately 2x LOD (20 samples) and 5x LOD (10 samples)[16]." Mfg-2 tested "45 patient samples collected during COVID-19 pandemic in the US that had previously been characterized as positive for SARS-CoV-2 by an EUA RT-PCR test[17]." Mfg-1 reported PPA of 100% (30/30). Mfg-2 reported PPA of 97.8% (44/45).

To prove NPA, the Negative Percent Agreement, Mfg-1 reported that "Thirty Negative NP swab samples were also tested in this study.16 "Mfg-2' IFU reported testing 45 samples, saying "Fifteen of the 45 SARS-CoV-2negative NP swab specimens were collected before December 2019 and are expected to be negative for SARS-CoV-2. The others had previously been characterized as negative for SARS-CoV-2by an EUA RT-PCR test17. "Mfg-1 reported NPA of 100% (30/30). Mfg-2 reported NPA of 95.6% (43/45)16,17. These results were driven by each manufacturer's test methods, the type and number of samples tested plus the competency of staff and instrument performance at the manufacturers' sites.

Table 2 presents the data reported by the selected manufacturers and two laboratories using each test method. The number of known samples that each laboratory tested drives the confidence intervals around PPA and NPA which, in turn, drive the confidence intervals around likelihood ratios, which drive post-test probability and other metrics. Notice the wide variation in the number of known samples tested in rows 1 and 2. In row 3, notice that the labs A and B reported PPA values lower than Mfg-1 while Labs C and D reported higher PPA than Mfg-2. Sample size drives the confidence intervals around PPA, NPA and likelihood ratios. Confidence intervals for four studies range from below 10 to infinity. Pre-test probability x LR+ = post-test probability. With Pre-test probability of 3% x LR+ of 10 = post-test probability of 30%. If LR+ = infinity, post-test probability is 100%.

Table 3 presents the probable post-test interpretation of results for patients with pre-test probability of 3%. Red numbers in the table indicate variation from others and/or less-than-ideal test performance. Notice that a positive test results from Mfg-2 and Lab D indicate less than a 50% post-test probability of disease. Where Mfg-1 and Lab A both projected 100% post-test probability, confidence intervals show that could actually be as low as 18% or 7.5%; in Lab C, the reported 100% may actually be as low as 2.8% due to the low number of samples tested. Confidence intervals show that clinician may see only one to three true results for every of 10 positive tests reviewed. Lab A may produce as few as 1 true result in every 13.5; in Lab C, confidence intervals show that there is a risk of seeing only one true positive result in 35 reported true results.

When pre-test probability raises to 50% in Table 4 probable post-test probability rises to over 95% for all labs. Even with a negative test, post-test probability is approximately 20% in Labs A and B. With pre-test probability of 50%, only 8 of 10 negative tests are true for Labs A and B. Table 2 shows that confidence intervals for Lab C show a low possible positive likelihood ratio of 0.94 and a high possible negative likelihood ratio of

1.08. When pre-test probability is 50%, the odds are 1:1 that the patient is infected. Multiply the pre-test odds times the likelihood ratio to calculate post-test odds – which will be essentially unchanged in this case. The low range of post-test possibility with a positive test overlaps the high possibility with a negative test positive or negative test result, as the method was verified in Lab C so a test result from this laboratory may not be able to differentiate infected from non-infested patients. This is not due to an inherent weakness in the test method, but to the low number of samples used by Lab C to verify method performance in their hands.

The authors designed an online *'Clinician's Probability Calculator'* to create a report that could accompany each laboratory's test results to show clinicians the post-test probability of COVID-19 based on their clinical opinion of each patient's pre-test probability.

Each laboratory's report would vary based on the laboratory's chosen methodology and on the PPA, PNA and number of samples in their on-site method validation studies. The calculator overcomes the complexity of calculations that prohibit most laboratories from reporting post-test probability with confidence intervals. It is available at https://awesome-numbers.com/post-test-probability-calculator/. Reports contain data as shown in Table 3 and in Table 4, plus in the graphs with confidence intervals as shown in Figure 5.

Table 2 Method validation studies

	Mfg-1	Lab A	Lab B	Mfg-2	Lab C	Lab D
Known positives	30	46	33	45	5	220
Known negatives	30	15	546	45	3	261
PPA reported	100%	71.7%	78.8%	97.8%	100.0%	99.5%
Confidence intervals	88.0% - 100%	56.6% - 83.8%	61.2% -90.9%	87.8% -100%	54.6% - 100%	97.3 %- 100%
NPA reported	100%	100%	100%	95.60%	100%	95.80%
Confidence intervals	88.0% - 100%	78.5% - 100%	99.3% - 100%	84.5% - 100%	41.9% - 100%	92.5% - 97.9%
Pos likelihood ratio (LR+)	999.9	999.9	999.9	22.2	999.9	23.7
Confidence intervals	7.3 - 999.9	2.6 - 999.9	82.6 - 999.9	7.3 - 999.9	0.94 - 999.9	12.91 - 999.9
Neg likelihood ratio (LR-)	0.00	0.28	0.21	0.023	0.00	0.005
Confidence intervals	0 - 0.14	0.16 - 0.55	0.09 - 0.39	0 - 0.14	0 - 1.08	0.09 - 0.39

Table 3 Post-test probability of SARS-CoV-2: with 3% pre-test probability

Post-test probability of SARS-CoV-2 (Ideal is 100% with positive test; 0% with negative test)						
	Mfg-1	**Lab A**	**Lab B**	**Mfg-2**	**Lab C**	**Lab D**
With positive test	100%	100%	100%	41%	100%	42%
Confidence intervals	18.5% - 100%	7.5% - 100%	71.9% - 100%	14.9% - 100%	2.8% - 100%	28.5% - 59%
With negative test	0.0%	0.9%	0.7%	0.1%	0.0%	0.0%
Confidence intervals	0% - 0.4%	0.5% - 1.7%	0.3% - 1.2%	0% - 0.4%	0% - 3.2%	0% - 0.1%
Number of true results in every ten tests reviewed (ideal is ten of ten)						
Positive test	10	10	10	4.1	10	4.2
Confidence intervals	1.8 - 10.0	0.8 - 10.0	7.2 - 10.0	1.5 - 10.0	0.3 - 10.0	2.9 - 5.9
Negative test	10.0	9.9	9.9	10.0	10.0	10.0
Confidence intervals	10.0 - 10.0	9.8 - 10.0	9.9 - 10.0	10.0 - 10.0	9.7 - 10.0	10.0 - 10.0
One in x test results is/are true (ideal is one in one)						
Positive test	1.0	1.0	1.0	2.5	1.0	2.4
Confidence intervals	1.0 - 5.4	1.0 - 13.3	1.0 - 1.4	1.0 - 6.7	1.0 - 35.4	1.7 - 3.5
Negative test	1.0	1.0	1.0	1.0	1.0	1.0
Confidence intervals	1.0 - 1.0	1.0 - 1.0	1.0 - 1.0	1.0 - 1.0	1.0 - 1.0	1.0 - 1.0

Table 4 Post-test probability of SARS-CoV-2: with 50% pre-test probability

Post-test probability of SARS-CoV-2 (Ideal is 100% with positive test; 0% with negative test)						
	Mfg-1	**Lab A**	**Lab B**	**Mfg-2**	**Lab C**	**Lab D**
With positive test	100%	100%	100%	96%	100%	96%
Confidence intervals	88% - 100%	72% - 100%	99% - 100%	85% - 100%	49% - 100%	93% - 98%
With negative test	0.00%	22.10%	17.50%	2.20%	0.00%	0.50%
Confidence intervals	0% - 12%	14% - 36%	8% - 28%	0% - 13%	0% - 52%	0% - 3%
Number of true results in every ten tests reviewed (ideal is ten of ten)						
Positive test	10	10	10	9.6	10	9.6
Confidence intervals	8.8 - 10	7.2 - 10	9.9 - 10	8.5 - 10	4.8 - 10	9.3 - 9.8
Negative test	10	7.8	8.3	8.7	10	9.9
Confidence intervals	8.8 - 10	6.4 - 8.6	7.2 - 9.2	8.7 - 9.8	4.8 - 10	9.7 - 10
One in x test results is/are true (ideal is one in one)						
Positive test	1.0	1.0	1.0	1.0	1.0	1.0
Confidence intervals	1.0 - 1.1	1.0 - 1.4	1.0 – 1.0	1.0 - 1.2	1.0 - 2.1	1.0 - 1.1
Negative test	1.0	1.3	1.2	1.0	1.0	1.0
Confidence intervals	1.0 - 1.1	1.2 -1.6	1.1 - 1.4	1.0 - 1.1	1.0 - 2.1	1.0 - 1.0

DISCUSSION

Importance of PPA (sensitivity) and NPA (specificity)

PPA, the Positive Percent Agreement (sensitivity), drives the rate of true positive and false negative test results. NPA, Negative Percent Agreement (specificity), drives the rate of true negative and false positive test results. PPA and NPA combine to drive the probability, number and cost of false-positive and -negative test results[4]. PPA and PNA are typically used by laboratory directors to compare inherent method quality and select test methods. They can also be used to calculate likelihood ratios that in turn drive post-test probability of COVID-19 disease plus the graphs and other metrics displayed in Figure 5 and Tables 3 and 4.

Test methods are often verified by manufacturers under ideal conditions with hospital or contrived samples containing higher viral loads than those from asymptomatic individuals living in the community. As such, PPA and NPA in test laboratories might differ significantly from values reported by manufacturers. Notice in Figure-3 that none of the five laboratories reporting to FIND15 attained the 100% PPA claimed in the FDA IFU by Manufacturer 1[16]. In contrast, laboratories C and D reported higher PPA values than Manufacturer 2[17]. Thus, the PPA and NPA values reported by manufacturers cannot be assumed to accurately reflect performance in each laboratory.

PPA and NPA do not help clinicians decide if a specific positive or negative test result is true. PPA and NPA can be converted to likelihood ratios which can be used to convert clinical pre-test probability of disease for a specific patient to post-test probability.

Figure 1 Known samples tested

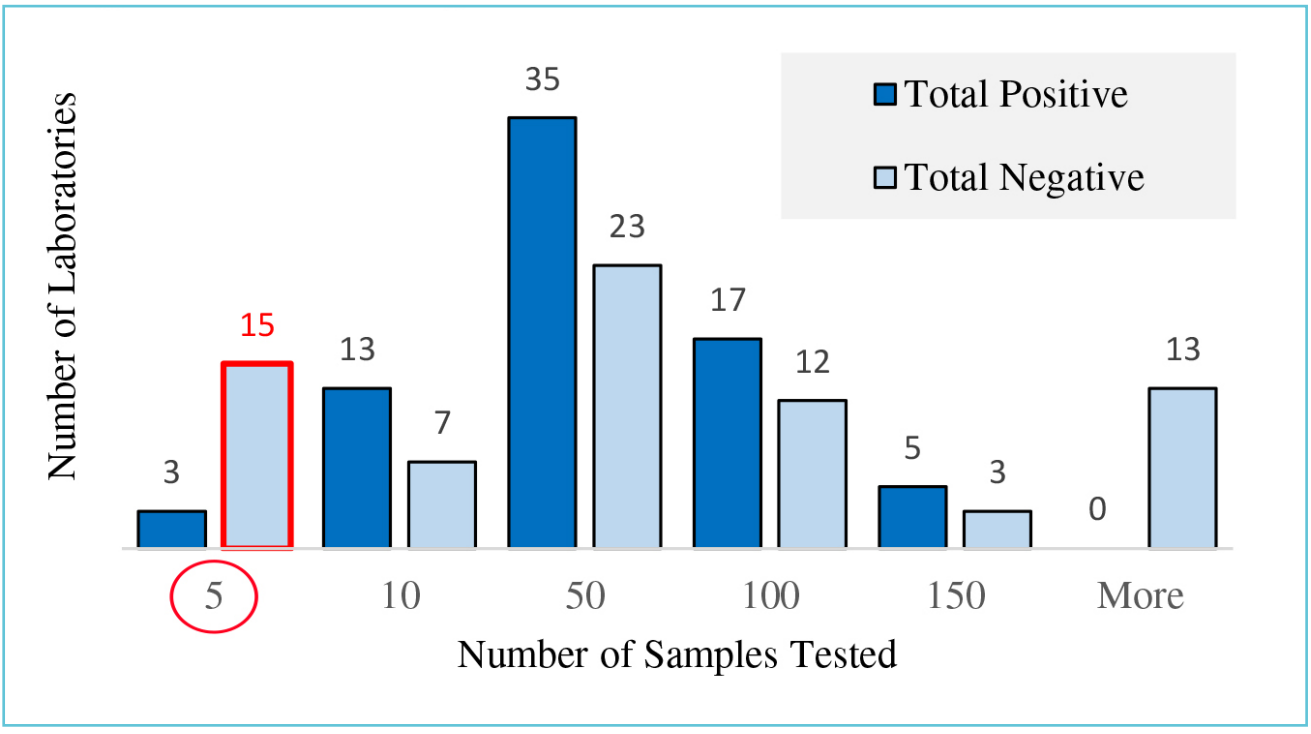

Figure 1 Shows the number of known positive and negative samples reported in each laboratory's study. Fifteen of the laboratories (21%) tested fewer than five known negative samples. (Data available in supplemental material include individual lab results and the source of known positive samples.)

Figure 2 PPA and NPA by study

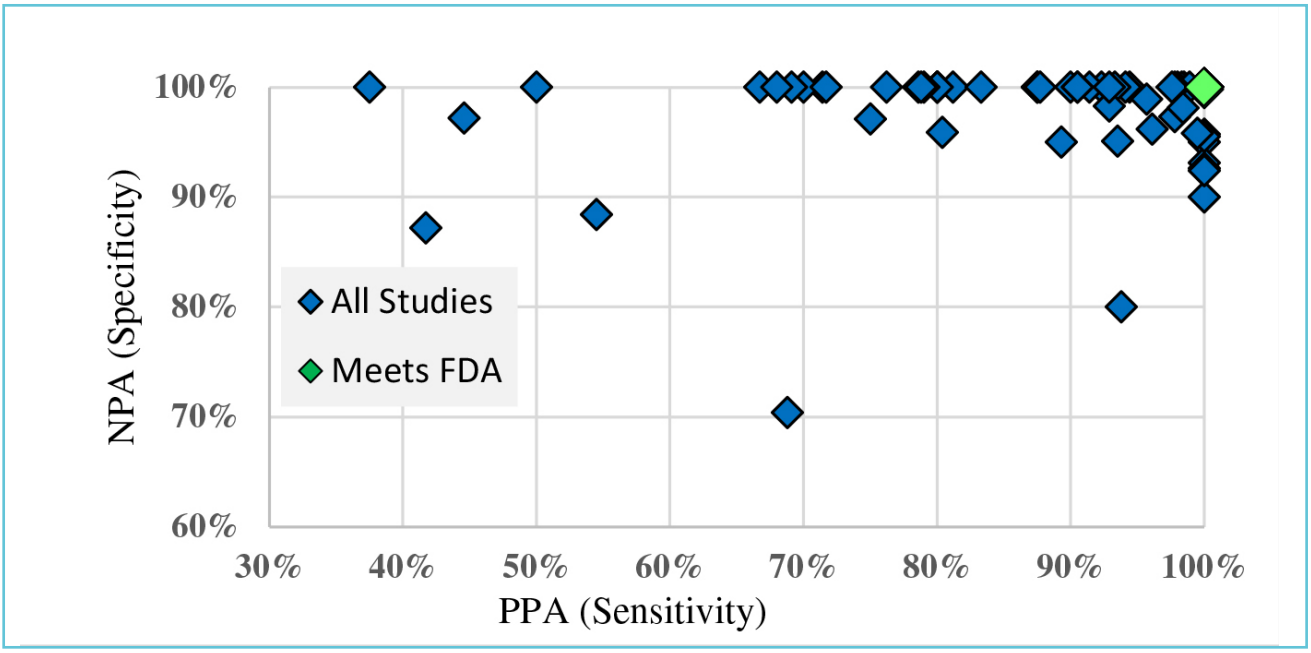

Figure 2 shows the PPA and NPA for 73 studies reported to FIND.[15] Method validation studies showed PPA from 17% to 100% and NPA from 70.4% to 100%.

Manufacturer A reported PPA and NPA of 100%; Manufacturer B reported PPA of 97.8% and NPA of 95.6% to FDA based on 60 and 90 known samples.

Laboratory results from the same test methods did not mirror each other or the manufacturer. Only 15 studies (20.5%) met the FDA recommendations. FDA defines the acceptance criteria for the performance as 95% agreement at 1x-2x Limit of Detection (LoD), and 100% agreement at all other concentrations and for negative specimens.[18]

Relevance of likelihood ratios

Likelihood ratios allow one to convert pre-test to post-test odds of infection.[7] When pre-test probability is 50%, the odds are 1:1 that the patient is infected. One of every two people with 'these' clinical symptoms is expected to be positive before testing (50%). If the positive likelihood ratio is approximately 24, as in Lab D in Table 3, multiplying the pre-test odds by the positive likelihood ratio produces post-test odds of 24:1. Twenty-four of every 25 people with a positive test are actually infected; 24/25 = 96% post-test probability.

Importance of number of known samples tested

The number of known positive and negative samples tested determines the confidence intervals around PPA and NPA[14]. Figure 1 and Table 2 illustrate the dramatic difference in number of samples tested by individual sites reporting to FIND[15] Labs A, B and C each reported 100% NPA. Lab A made that assessment by testing 15 known negative samples, while Lab B tested 546 known negatives and Lab C tested only three. The lower limit of confidence for NPA in Lab A is 78.5% compared to 99.3% in Lab B and only 41.9% in Lab C (Table 2.) The low number of known samples tested in Lab C does not allow this lab to verify acceptable method performance with confidence.

Impact of confidence intervals

Confidence intervals determine the range of possibilities for PPA and NPA, which drive likelihood ratios that drive post-test probability of COVID-19

with positive and negative test results. Post-test probability drives the number of true and false positive and negative tests in every 10 positive or negative results seen, and how many positive or negative test results would be seen to find one true test result. Confidence intervals allow users to visualize the gap between the post-test probability that a positive, or negative, test indicates an infected person.

Value of graphs and metrics reported by the Probability Calculator

Instead of either taking all positive or negative test results at face value or developing personal experience to 'guess' if results are true or false, clinicians can visualize a reliable scientific range of possibilities. Glancing at the six graphs in Figure 5 clarifies that when pre-test probability is only 3%, the probability of a person having COVID-19, even with a positive test, is less than 50% - except in Lab B where they tested enough samples to prove test reliability. These graphics and data eliminate the use of Fagan's Nomogram8, which is typically used with likelihood ratios but is cumbersome for front-line use and does not include confidence intervals.

Laboratory directors and public health officials who are challenged to select and verify test methods can clearly see the ability of each test to confirm, or rule out, SARS-CoV-2 infections. Lab C shows no gap at all between the range of possibilities that a positive or negative test indicates an infected person. The test has not been verified to provide useful information by testing only five known-positive and three known-negative samples. Laboratory directors and clinicians can have little confidence in the values reported in such circumstances.

Figure 3 PPA & NPA for Mfg-1 and Mfg-2

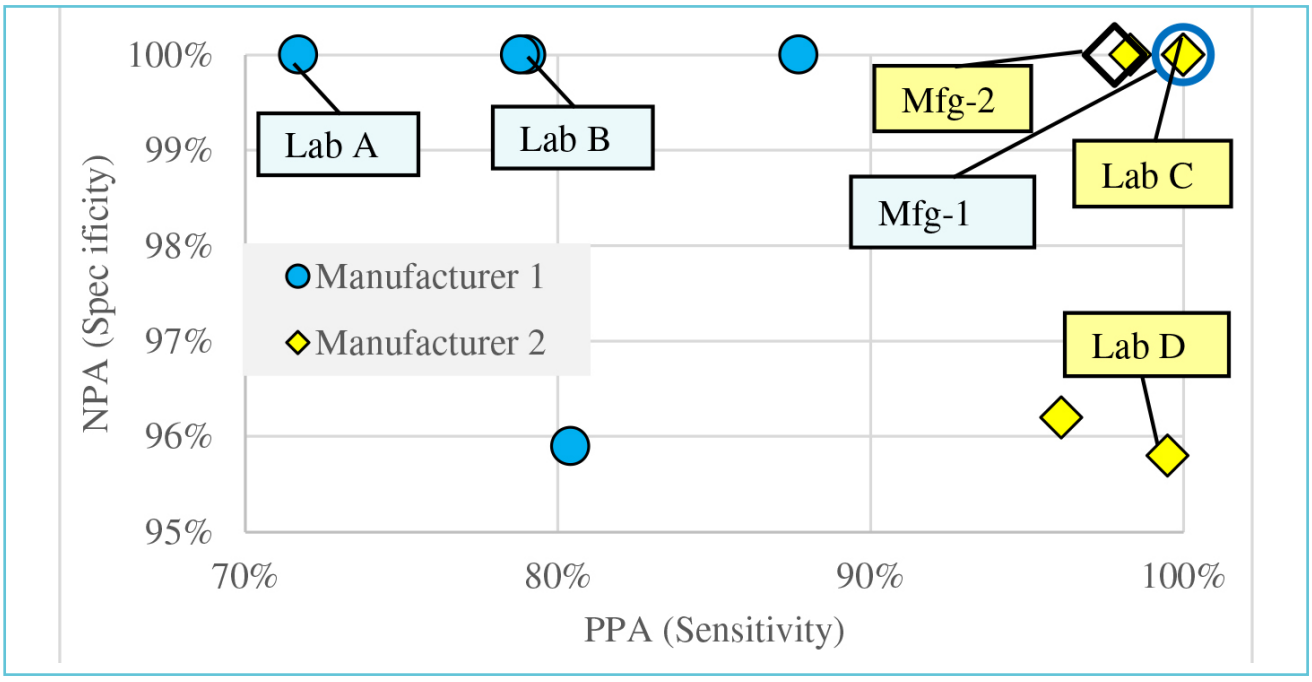

Figure 3 shows the reported PPA on the x-axis, and NPA on the y-axis, by Manufacturers 1 and 2, and in the FIND studies[15] for all labs reporting studies from the same manufacturers.[16,17]

The circles representing 'Manufacturer 1' labs are coloured blue; the manufacturer is shown as the clear circle. The diamonds represent 'Manufacturer 2'; labs are coloured yellow; the manufacturer is shown as the clear diamond.

Labs A, B, C and D are examined in greater detail in Tables 3, 4 and 5.

Clinicians can benefit from understanding the number of true and false positive results they can expect to see in every ten positive or negative results. With 3% pre-test probability, clinicians may see as few as one or two true positives in every ten positive test results according to the Manufacturer-1 and Lab A, while Lab B can be relied on to produce over seven of ten true positives (Table 3). Knowing the frequency of true test results reported could impact test selection and interpretation. This information, however, is not available by only examining the reported PPA and NPA values.

In the USA, Clinical Laboratory Improvement Amendments (CLIA) mandates that laboratory director responsibilities include ensuring that your laboratory develops and uses a quality system approach to laboratory testing that provides accurate and reliable patient test results[19].

Accuracy is the number of true results as a portion of all test results created[20]. The authors were shocked to discover that most laboratories are not required to verify that they can, at least, reproduce PPA and NPA claims from manufacturers. This does not preclude the laboratory director from performing this study as part of good lab practice. In fact, Stephanie L. Mitchell et al published an article in the Journal of Clinical Microbiology[21] outlining a process to verify method PPA and NPA with ten positive and negative samples. In order to ensure method accuracy, we recommend that each testing laboratory confirm PPA and NPA with sufficient known samples to provide reliable post-test probability of disease. We concur that each report should be accompanied by a statement from the laboratory indicating that test performance has been verified; the Clinician's Probability Calculator fulfils this need.

Figure 4 Known samples tested for Mfg-1 and Mfg-2

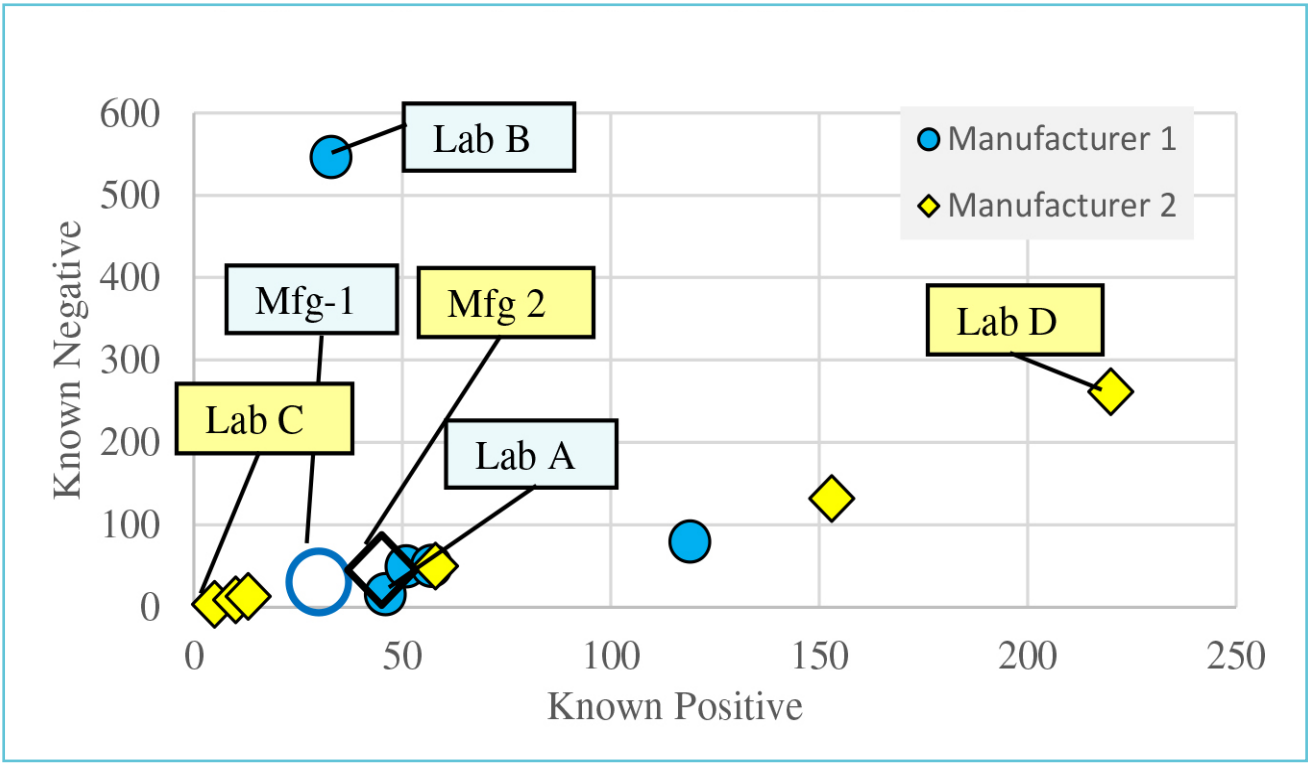

Figure 4 shows the number of known samples tested by Manufacturers 1 and 2[16,17], and in the FIND studies[15] for the labs reporting studies from the same manufacturers.

Figure 5 **Probability Calculator results from Manufacturer 1 and 2, plus Labs A, B, C and D**

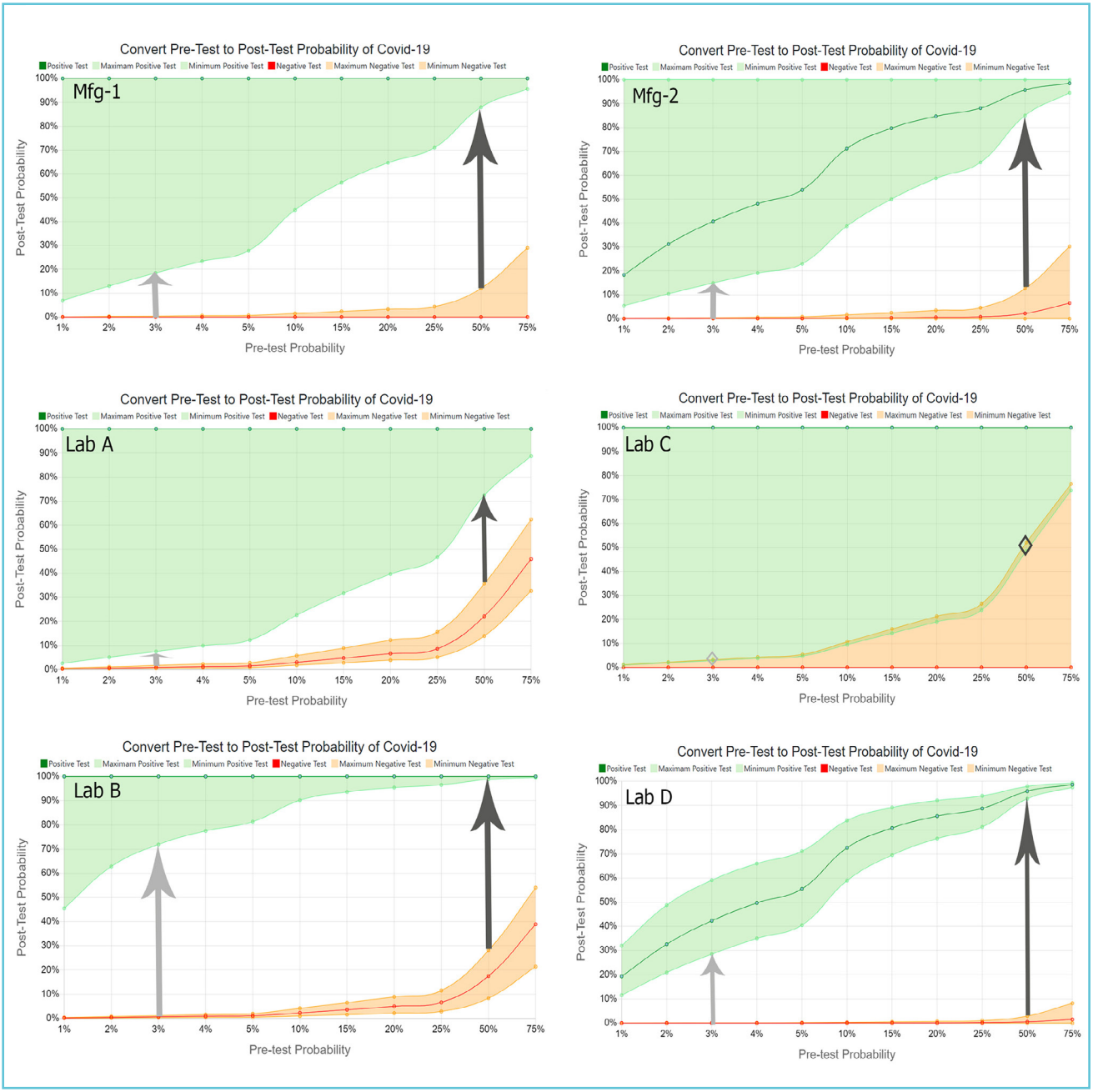

Figure 5 shows Probability Calculator graphs from Manufacturer 1 and 2, plus Labs A and B who reported data from Manufacturer 1, and Labs C and D who reported data from Manufacturer 2.

In the graphic, the x-axis is the pre-test probability, as estimated by the clinician or public health professional. The Y-axis is the post-test probability. The shaded green area shows confidence intervals that a positive SARS-CoV-2 test result indicates an infected person. The pale orange shaded area shows confidence intervals that a negative SARS-CoV-2 test indicates an infected person (false negatives.)

The arrows show the gap between the highest probability that a negative test represents an infected person and lowest probability with a positive test.

CONCLUSION

In spite of all possible measures taken, false positive and false negative SARS-CoV-2 test results are cannot be avoided[2,3]. A positive or negative test result from one laboratory has a different probability for the presence of disease than the same result from another laboratory. Post-test probability, likelihood ratios and confidence intervals can help answer the question: "Does this person have COVID-19, or not?" by converting the physician or other healthcare professional's clinical estimate of pre-test probability to post-test probability. If the pre-test probability is below 5%, a positive test result may only raise that probability to less than 50%. A negative test with some methods in some labs may still convey a 20% post-test probability of disease. Ranges of probabilities differ depending on proven method PPA and NPA in each laboratory. The authors recommend that testing laboratories verify PPA and NPA of their SARS-CoV-2 test method with sufficient sample numbers to verify acceptable performance and create a report with the Clinician's Probability Calculator (https://awesome-numbers.com/post-test-probability-calculator) to assist with interpretation of test results.

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Prevalence of aminotransferase macroenzymes in rheumatoid arthritis patients and impact on their management

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CASE REPORT

Introduction

Rheumatoid arthritis (RA) treatment can be hepatotoxic, but liver enzymes can be falsely elevated due to macroenzyme presence. Macroenzymes are often found in autoimmune diseases, but prevalence and effect on treatment is unclear. This study aimed to determine aminotransferase macroenzyme prevalence and effect in RA patients.

Materials and methods

This study included consecutive RA patients without liver disease sent for laboratory tests. Samples with elevated AST or ALT were processed for macroenzymes. Presence was determined using polyethylene glycol precipitation (PEG).

Results

Out of 126 patients, 21 had elevated aminotransferase levels. Due to liver disease, 6 patients were excluded, another 3 were unavailable for informed consent, leaving 12 patients for inclusion. Out of 12 patients, 1 had increased AST levels, 2 increased ALT levels, and 9 both. Macro-ALT was detected in 5/11 patients, 1 also had macro-AST. Out of 5 patients with macroenzymes, treatment change was seen in 3/5 patients, imaging in 2/5, both in 2/5.

Conclusion

Elevated liver enzymes in RA patients is not always indicative of hepatotoxicity, as shown by the fact that about half of patients in our study had macroenzymes detected. Before assuming drug hepatotoxicity and changing treatment or ordering imaging, rheumatologists could consider macroenzyme presence.

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INTRODUCTION

Macroenzymes are serum enzymes bound by serum components, namely immunoglobulins, where research has found various enzymes (such as aspartate [AST] and alanine transferases [ALT], lactate dehydrogenase [LDH], creatinine kinase [CK], amylase [AMY], and lipase [LIP]) form such complexes causing falsely elevated values, and often are found in autoimmune diseases (1,2).

Rheumatoid arthritis (RA) is one such autoimmune disease where macroenzymes can be found (1,2). RA is a chronic inflammatory disease, exact cause is unknown, which manifests as symmetrical joint destruction, especially synovial joints (3). Therapeutic drug of choice, methotrexate, as well as other commonly used drugs, have well-documented hepatotoxicity (4,5). Elevated liver enzymes may lead to change in treatment or additional diagnostics, which may be unnecessary, or even detrimental, considering macroenzymes may be to blame, as seen in one example of a case of macro-AST which lead to an invasive liver biopsy (6).

This prospective study aimed to evaluate and determine the prevalence of aminotransferase (AT) macroenzyme complexes in RA patients. A secondary goal was to evaluate the rate of unnecessary changes in treatment or additional imaging.

MATERIALS AND METHODS

This study included consecutive RA patients with increased AST and/or ALT levels without known liver disease, based on laboratory requisitions with a diagnosis of RA as sent by rheumatologists during followups from Rheumatology Outpatient Clinics at Clinical Hospital Center Rijeka between 16th May and 14th of Dec 2018. AST and ALT were measured on a Beckman Coulter AU5800 (Beckman Coulter, California, USA) biochemistry analyser using the IFCC Reference Method modified without pyridoxal phosphate, at 37°C. The Croatian Chamber of Medical Biochemistry recommended, age and gender specific, ALT and AST reference ranges were used (Table 1). Macroenzyme presence was determined using polyethylene glycol precipitation (PEG) according to Levitt and Ellis (7) with a 1:2 25% PEG solution. PEG solution was prepared by adding 2.5 g of PEG 6000 (for synthesis) solution (Mercks KGaA, Darmstadt, Germany) to 6 mL of deionised water, after the PEG 6000 had dissolved, deionised water was added to the 10 mL mark in the measuring tube. Solution was kept at 4°C. For testing macroenzyme presence, 200 µL of patient serum was pipetted in a tube, then another 200 µL of PEG solution was added and vortexed for 10 secs. The mixture was incubated in a water bath at 37°C for 10 mins before being centrifuged at 3000 rpm for 20 mins at room temperature. For a blank, 200 µL of deionised

water was added instead of PEG solution. The sample and blank probes were simultaneously treated the same way. PEG-precipitable activity (PPA) was calculated by measuring aminotransferase levels in the probe supernatants, and using the formula: %PPA = 100 x ((activity blank x activity PEG)/activity blank). Electrophoresis was not used — besides being unavailable, a strong correlation exists between the methods (8). Cut-off values for PPA according to Davidson and Watson (9) were used, which are cut-off of 76% PPA for macro-ALT and cut-off of 54% PPA for macro-AST.

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Clinical Hospital Centre Rijeka. All participants have provided informed consent for inclusion in the study.

Table 1 AST and ALT reference values as recommended by the Croatian Chamber of Medical Biochemistry (2004)

Test	Recommended method and/or procedure	Recommended method and/or procedure	Unit	References		
				Sex	Age (years)	Interval
Alanine-aminotransferase (ALT)	UV photometry, IFCC method, 37°C, Tris buffer, L-alanine, α-ketoglutarate, pyridoxal phosphate, nicotinamide adenine dinucleotide (NADH), lactate dehydrogenase, pH 7,15	UV photometry, 37°C, L-alanine without pyridoxal phosphate, Tris buffer	U/L	Male Female Male Female Male Female Male Female Male Female	0-2 0-2 3-7 3-7 8-12 8-12 13-19 13-19 ≥ 20 ≥ 20	11-46 11-46 9-20 9-20 11-37 11-37 10-33 10-29 12-48 10-36
Aspartate aminotransferase (AST)	UV photometry, IFCC method, 37°C, Tris buffer, L-aspartate, α-ketoglutarate, pyridoxal phosphate, nicotinamide adenine dinucleotide (NADH), malate dehydrogenase, lactate dehydrogenase pH 7,65	UV photometry, 37°C, L-aspartate without pyridoxal phosphate, Tris buffer	U/L	Male Female Male Female Male Female Male Female Male Female	0-2 0-2 3-7 3-7 8-12 8-12 13-19 13-19 ≥ 20 ≥ 20	26-75 26-75 24-49 24-49 14-39 14-39 11-38 14-32 11-38 8-30

RESULTS

Out of 126 RA patients, 21 had elevated AT levels. A total of 6 patients were excluded due to liver disease or conditions which could cause elevated levels, as noted in medical documentation (4 with non-alcoholic fatty liver disease [NAFLD], 1 pancreatic cancer,1 unspecified liver lesion), and another 3 patients were excluded as they were unavailable to obtain informed consent for inclusion in the study, leaving a total of 12 patients for inclusion. Demographically, median patient age was 63 (40 to 78), 2 patients were male, and 10 female. Out of 11 patients, 1 had increased AST levels, 2 increased ALT levels, and 9 both. Macro-ALT was detected in 5/11 patients, 1 of which also had macro-AST. Due to technical issues with the analyser, 1 patient was excluded since the sample could not be treated in the same way as the others.

A change in treatment was observed in 5/12 patients, additional imaging was ordered in 6/12 patients, both in 4/12 patients, and no change or imaging in 5/12 patients. Of patients with macroenzymes, change in treatment was seen in 3/5 patients, imaging was ordered in 3/5 patients, both in 2/5 patients, no action in 1/5 patients (Table 2). Liver biopsy or other invasive procedures were not noted.

Examining the macroenzyme patients further, one patient with both complexes present was

Table 2 Breakdown of AST and ALT values, AST and ALT PPA, change in treatment or further imaging by patient

Patient	AST (U/L)	ALT (U/L)	PPA AST (%)	PPA ALT (%)	Change in treatment	Further imaging
1	61	135	53,85	76,67	Yes	No
2	60	84	53,33	80,95	Yes	Yes
3	52	54	71,43	85,71	Yes	Yes
4	48	31	50,00	62,50	Yes	Yes
5	42	54	50,00	80,77	No	No
6	40	51	50,00	66,67	No	No
7	40	41	11,11	37,50	No	No
8	39	67	47,37	68,75	No	No
9	38	56	50,00	84,62	No	Yes
10	25	41	0,00	50,00	No	No
11	23	43	42,86	69,23	Yes	Yes

diagnosed with methotrexate induced hepatotoxicity, and treatment was discontinued. Treatment was subsequently reinstated after imaging results were found to be normal. Another patient was also diagnosed with methotrexate induced hepatotoxicity, and treatment has been postponed for the time being. Methotrexate was temporarily discontinued for a third patient for 3 weeks, and continued after follow up laboratory test results were shown to be static, with no change in AT levels; no imaging was done. The final two patients with complexes present were without change in treatment, but one had an ultrasound done yearly to monitor for liver changes, and the other had no imaging done within the last year.

DISCUSSION

Although it is known that macroenzymes are present in autoimmune diseases such as RA (1,2), an exact prevalence is unclear. Unfortunately, our study did not yield enough of a sample size to determine the prevalence of macroenzymes in RA, this is a clear limitation, but it did confirm that macroenzymes are present. It should be noted there is a possibility that some requisitions were incorrectly labelled with diagnosis of RA, however, all patients tested in our study had a diagnosis of RA either confirmed or suspected at the time.

With only 21/126 RA patients with elevated liver enzymes in our study, 6 of which with known liver disease, it could be commented that although hepatotoxicity of drugs in RA is known (4,5), it is well-managed. Still, with examples in the literature such as ordering invasive procedures, that is, liver biopsy (6), and keeping in mind that treatment which may be adequate or beneficial is often changed if hepatotoxicity is suspected, the importance of recognising and detecting possible macroenzymes remains relevant. About half of the patients with elevated AT had either some form of change in treatment, either pausing or discontinuation; imaging ordered, that is, abdominal ultrasound; or both. It is possible that the patients with macroenzymes did not require any change in treatment or imaging done. If macroenzymes are to blame for the elevated liver enzymes, then it is clear how such laboratory results can influence management. However, it should be noted that macroenzymes can be present without elevating laboratory results outside of reference ranges (1), and any acute or dramatic change warrants further investigation.

Considering that PEG is available in a number of diagnostic laboratories, and the test is simple, inexpensive, and non-invasive, testing for AT macroenzyme presence in patients with RA, or other autoimmune diseases, may be warranted as a differential diagnosis for elevated AT levels, especially when considering drug hepatotoxicity as changing treatment which is adequate or beneficial, or ordering further tests, especially invasive tests such as liver biopsy, should be avoided.

To clarify, the PPA cut-off values for macro-AST and ALT used were taken, as mentioned, from a study by Davidson and Watson (9). The study tested several enzymes, taking 40 patients with elevated levels, and measured PPA after excluding macroenzyme using electrophoresis (9). By calculating mean enzyme and PEG-precipitable activity, reference ranges for each enzyme were proposed, for AST 18 to 53 U/L and for ALT 38 to 76 U/L (9), for our study, the upper limit of reference ranges were used.

In comparison, according to Davidson and Watson the cut-off value for PPA for macroamylase is 60 % (9), and an accepted value for macroprolactin is 50 % (10), both of which are routinely used in our laboratory, however, these differences are not explained.

In conclusion, elevated liver enzymes in RA patients may not always be indicative of hepatotoxicity, as shown by the fact that about half of patients in our study had macroenzymes detected. Before assuming drug hepatotoxicity and changing treatment or ordering other diagnostics, rheumatologists and laboratory personnel could consider aminotransferase macroenzyme presence.

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Malignant hyperthermia syndrome: a clinical case report

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CASE REPORT

Malignant hyperthermia is a pharmacogenetic disorder. It manifests as a hypercatabolic skeletal muscle syndrome linked to inhaled volatile anesthetics or depolarizing muscle relaxants. Its clinical signs and symptoms are tachycardia, hyperthermia, hypercapnia, acidosis, muscle rigidity, rhabdomyolysis, hyperkalemia, arrhythmia and renal failure. Mortality without specific treatment is 80% and decreases to 5% with the use of dantrolene sodium.

This article presents the case of a 39-year-old patient admitted to the Intensive Care Unit for malignant hyperthermia after surgery for septoplasty plus turbinoplasty.

INTRODUCTION

Malignant hyperthermia (MH) is an inherited pharmacogenetic disorder of the skeletal musculature, characterized by an anesthesia-related hypermetabolic state (1, 2).

The pathophysiological mechanism is associated with mutation of the RYR1, CACNS1S and STAC3 genes (3, 4), responsible for controlling intracellular calcium homeostasis.

In susceptible individuals, the triggering stimulus causes hyperactivation of the receptors, resulting in uncontrolled release of Ca^{++} from the endoplasmic reticulum (ER) of muscle cells, leading to increased intracytoplasmic Ca^{++}, responsible for enzymatic activation leading to decreased ATP and O_2 consumption and increased anaerobic metabolism, resulting in increased heat and lactic acidosis (5).

Clinical signs and symptoms during the crisis is characterized by tachycardia, hypercapnia, arrhythmia, muscular contracture, cyanosis, metabolic and respiratory acidosis, lactic acidosis, hyperthermia, coagulopathy and rhabdomyolysis (3,6,7).

Mortality without treatment amounts to 80%, decreasing to 5% with supportive measures and effective treatment, which consists of the suspension of halogenated agents, hyperventilation with 100% O_2 and the administration of dantrolene sodium (DS), a muscle relaxant that inhibits the release of Ca^{++} from the ER by acting on RYR1 (2,8,9).

Diagnosis is purely clinical, while post-event confirmation is made by the halothane-caffeine contracture test (CHCT) or genetic study of the mutations of the genes involved (3,10).

CLINICAL CASE

A 39-year-old male patient, with no personal history of interest, was admitted for scheduled surgery for septoplasty plus turbinoplasty.

Anesthetic induction was performed with midazolam, propofol and remifentanil. Neuromuscular relaxation was performed with succinylcholine (100 mg) and rocuronium (50 mg), and hypnosis with desflurane, due to difficult manual ventilation.

The surgery was uneventful and the patient was afebrile. At the end of the surgery, a rapidly progressive rise of EtCO2 (CO_2 at the end of expiration) was observed, reaching values of up to 130 mmHg, tachycardia and axillary hyperthermia 39.5 ºC. When malignant hyperthermia was suspected, desflurane was stopped, physical maneuvers were performed to cool the patient and specific treatment was started with dantrolene sodium, with an initial dose of 250 mg i.v. (2.5 mg/kg), plus continuous perfusion with propofol and cisatracurium. A bladder catheter was placed, diuretics were prescribed and temperature was monitored.

Initial laboratory tests showed mixed acidosis, hyperkalemia, hypocalcemia and renal failure, so calcium bicarbonate, dextrose 5% and insulin were administered, improving $EtCO_2$ and temperature.

Once the patient was stabilized, it was decided to transfer him to the Intensive Care Unit (ICU).

On arrival at the ICU the patient was under the effects of anesthesia, presenting isochoric and normoreactive pupils, muscle hypertrophy, normothermic, tachycardic, good bilateral ventilation, bladder catheterization with myoglobinuria and no edema. He was maintained on mechanical ventilation.

A new analytical control was performed, highlighting: severe hypoglycemia 0.83 mmol/L, hypocalcemia, normalization of hyperkalemia, mild renal failure creatinine 140 **µmol/L** and persistence of acidosis. After 6 hours, a progressive increase in transaminases, lactate dehydrogenase (LDH) and creatinine kinase (CK) was detected,

Table 1 Timeline of laboratory tests

	Basal	6 hours	24 hours	36 hours	2 day	3 day	5 day	6 day	Reference range
Markers of severe metabolic acidosis									
pH	7.05	7.24	7.35	7.37		7.40			7.35 - 7.45
pCO_2 mmHg	84	57	56	48		53			40 - 55
pO_2 mmHg	322	230	55	115		29			
Bicarbonate mmol/L	23.2	24.4	30	27.5		32.4			21 - 26
Base excess mmol/L	-9	-3	2.7	1.8		6.1			-2.5 – 2.5
$SatO_2$ %	99.9	99.7	87	99		55			60 - 85
Lactate mmol/L	5.2	2.2	2.9	1.9		1.9			0.5 – 2
Clinical chemical									
CK U/L		30 930	88 930		112 860		3 460	1 890	46 – 171
LDH U/L		910	1 580			1 114	317	318	120 – 246
ALT (GPT) U/L		150	243		492	529	433	434	10 – 49
AST (GOT) U/L		390	1 023		1 926	1 533	482	279	14 – 35
Creatinine (µmol/L)	150	150	140		140	100	90	90	60 - 100
Potassium (mmol/L)	7.2	5.2	5			4.1	4.2	4.3	3.5 – 5.1
Calcium (mmol/L)	1.67	1.85	1.87		1.95	2.02	2.22	2.12	2.17 –2.59

pCO_2: partial pressure of carbon dioxide (mmHg); pO_2: partial pressure of oxygen (mmHg); SaO2: oxygen saturation; CK: creatinine kinase; LDH: lactate dehydrogenase; ALT: alanine aminotransferase; AST: aspartate aminotransferase.

with a maximum value at 48 hours after the onset of the crisis of 112 860 U/L (Table 1).

Serum therapy was increased with resolution of ionic alterations and renal function, but hepatic alterations and muscle destruction persisted for days. A new dose of dantrolene was not required.

The patient had a subsequent good evolution, allowing withdrawal of sedation and extubation at 24 hours. He was discharged from the ICU 48 hours after the crisis, with adequate blood glucose levels.

A genetic study was requested from the reference laboratory, where the c.6856C>G p.(Leu2286Val) mutation in the RYR1 gene was detected. Massive sequencing was used for analysis, using Agilent's CCP17 Sure Select panel. The analysis was performed on the Illumina NextSeq sequencer. This mutation is described in the clinical database of the American College of medical genetics and genomics as a probably pathogenic variant associated with malignant hyperthermia.

DISCUSSION

MH is a pharmacogenetic alteration that manifests as a hypermetabolic response after exposure to inhaled anesthetics (isoflurane, halothane, sevoflurane, desflurane and enflurane), and muscle relaxants such as succinylcholine (1), although it can also be produced by heat, infections, emotional stress, statin therapy and strenuous exercise (3). This reaction occurs in individuals with a certain genetic predisposition. Since susceptible patients do not present phenotypic alterations before anesthesia, it is impossible to diagnose them before exposure or before specific tests are performed.

Anesthetics: nitrous oxide, local anesthetics, propofol, etomidate, thiopental, ketamine, opioids, benzodiazepines, non-depolarizing muscle relaxants are considered safe in MH susceptible patients (2,7,9).

The incidence of MH is 1/50 000 to 1/250 000 in adults and 1/15 000 in children. The actual prevalence is difficult to define because there are patients with no or mild clinical reactions. In addition, the penetrance of the inherited trait is variable and incomplete (1,2).

MH has an autosomal dominant pattern of inheritance. Most of the cases described are due to mutations in three genes: RYR1 (ryanodine receptor type 1), CACNS1S (dihydropyridine receptor), and STAC3. It is estimated that 70% of cases are caused by mutations in the RYR1 gene (1,11,12,13). As discussed above, our patient was heterozygous for the RYR1 gene mutation.

Ryanodine receptors are large (560 kDa) ion channels involved in intracellular calcium release, especially in the sarcoplasmic reticulum. There are three isoforms that are variably distributed in tissues, with the RYR1 isoform predominating in skeletal muscle. In the case of our patient, the mutation described above is associated with a missense-type change that predicts the substitution of an amino acid leucine for valine at position 2286 of the protein.

When the receptor is mutated, it releases excess calcium once activated by anesthetic agents. This results in sustained muscle contraction, altered calcium homeostasis and a hypermetabolic state, especially anaerobic, with lactate production, increased temperature and CO_2 and oxygen consumption. This leads to rhabdomyolysis, hyperkalemia, hypocalcemia, myoglobinuria, elevated CK and hypernatremia (9).

Ionic disturbances are due to loss of function of the cell membrane, on the one hand there is a release of enzymes and electrolytes, especially potassium into the intercellular space. On the other hand, this release is compensated by a flow of water into the cellular interior which causes a state of hypovolaemia in patients, resulting in a haemoconcentration of various analytes such as sodium.

MH may appear early with succinylcholine or late with inhaled anesthetics. In the case described, it was attributed to the mixture of succinylcholine and desflurane. One of the earliest clinical manifestations of MH that should alert the anesthesiologist is increased $EtCO_2$. Hypercapnia is the most specific symptom, being found in 90% of cases (14).

Other associated signs may include cyanosis, metabolic and respiratory acidosis, lactic acidosis and increased CK. Peak CK values are reached hours after the onset of the crisis. In this case, the patient reached values of 112 860 U/L 48 hours after surgery, with a subsequent decrease.

The diagnosis should be confirmed using The Clinical Grading Scale (CSG) for MH developed by Larach (9). A score above 50 classifies the episode as almost certainly malignant hyperthermia, as was the case presented.

Following the European Malignant Hyperthermia Group Guidelines (EMHG) (15), once the condition is diagnosed, treatment should be initiated as soon as possible, progressively decreasing the anesthetic agent. The drug used for MH is dantrolene sodium. Dantrolene is a muscle relaxant that acts at the level of the RYR1 receptor, decreasing intracellular calcium availability and slowing massive skeletal muscle contraction. Initially 2.5 mg/kg should be administered as an intravenous bolus, and this dose should be repeated every 3-5 min. until the signs are controlled, maintaining thereafter the administration of 1 mg/kg every 6 hours to prevent recurrence of crises. In the case presented, only one dose was needed, without presenting subsequent crises. Simultaneously, treatment of hyperthermia, hyperkalemia, acidosis, renal failure and arrhythmias should be started (2,15). Once the crisis has been controlled, the patient should be monitored and transferred to the ICU for at least 24 hours, due to the risk of relapse.

Confirmation of MH is performed by HCT and is indicated when a patient has had a previous suspicious reaction or in patients with a family history (10).

The genetic susceptibility described MH justifies the performance of the genetic study to search for the presence of mutations and subsequent genetic counseling in families with a history (13).

LEARNING POINTS

The laboratory has a key role in early diagnosis for the administration of effective treatment: dantrolene sodium.

The most common clinical manifestations are nonspecific and mild, but associated with exposure to triggering agents, will be sufficient for initial suspicion of MH.

Triggering agents are inhaled anesthetics and depolarizing muscle relaxants.

Confirmation of susceptibility will depend on the result of the halothane-caffeine contracture test (HCTC), indicated three months after the crisis.

The genetic study of the disease aims at a presymptomatic diagnosis, without the need for biopsy, and at assessing new mutations.

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