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Editor-in-chief: Prof. János Kappelmayer, MD, PhD

Faculty of Medicine, University of Debrecen, Hungary

e-mail: ejifcc@ifcc.org

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Foreword: Measurably better healthcare – signs of a (r)evolution in progress towards a new academic science?

Guest editors: Tim J. James¹, Ellie Dow²

¹ Department of Clinical Biochemistry, Oxford University Hospitals NHS Foundation Trust, United Kingdom

² Diagnostics Laboratories, Ninewells Hospital, NHS Tayside, United Kingdom

ARTICLE INFO

Corresponding author:

Tim J. James
Department of Clinical Biochemistry
John Radcliffe Hospital
OX3 9DU, Oxford
United Kingdom
E-mail: Tim.james@ouh.nhs.uk

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FOREWORD

Welcome to this special edition of the eJIFCC where as guest editors we have the pleasure of sharing with you work from around the world highlighting new and successful ways of working, from local to regional implementation examples. These examples have all earned recognition in the global *UNIVANTS of Healthcare Excellence™* program (1) and represent a range of clinical environments, from emergency care through to the community setting, where there are impacts on population health.

The late Howard Morris, former president of the IFCC (one of the prestigious partner organisations to the UNIVANTS of Healthcare Excellence program), had an aspiration to have a journal dedicated to '*measurably better health care*'. But what is this and why did this hugely respected figure in laboratory medicine think this was important?

Perhaps this can best be defined by exploring what we mean by *measurement* in this context and also what we mean by *better* in health care and specifically in laboratory medicine.

It is more usual, particularly in the current financial climate, to examine cost effectiveness of laboratory testing solely within the silo of the laboratory. However, the concept is wider than this, has greater complexity, and is more difficult to assess when trying to capture clinical outcome benefits accurately. Extra costs in the laboratory can be rationalised as these may impact favourably elsewhere, for example in reducing drug budgets (see Hoenle et al in this edition), through avoidance of other expensive diagnostics, by improving the time to diagnosis (see Lucas et al in this edition) and hence, patient flow through pathways to definitive treatment. Standard measures of diagnostic accuracy cannot capture this complexity, although they provide the gateway into test introduction into practice. Examples of these outcomes in this edition include measures of patient management (length of stay), equity of access for hard to reach populations (see Curtis et al, the Kidney Check programme in this edition), early disease detection and improved patient identification for eligibility for invasive diagnostics which have long waiting times: all of which may be considered better for the patient.

Better can also be defined in terms of health-care economics. Unfortunately financial reviews of laboratory services often focus solely on cost, rather than value. An integral part of our laboratory leadership role is therefore to evangelise and explain this to those defining budgets at the executive level of healthcare. It is no surprise therefore that the application process for UNIVANTS requires the engagement of senior hospital management to support the application team. In this regard, the European Health Management Association (EHMA) is also a *founding* partner (and thus, one of many judge organizations) to the UNIVANTS of Healthcare Excellence awards. Engagement at these levels increases the understanding of the value of laboratory services rather than solely the cost generally of health care.

The concept of value in health care has been championed by many, including in the UK, by Sir Muir Gray (2) and this has impacted on government policy. The IFCC has also recognised the importance of value through the establishment of a committee dedicated to this work: the *IFCC-WASPALM Committee for the Value Proposition in Laboratory Medicine* (3). Committee members Prof. Chris Price and Dr. Andrew St John have provided an introduction (4) for those less familiar with this in a review article where they explain how to ‘unlock’ the potential of this concept for laboratory leaders which they summarise as:

‘The value proposition provides a guide for successful implementation of a test. Although it can address both adoption and implementation, it highlights that the requirements for test implementation are quite different to those of adoption, with an emphasis on real-world evidence and outcomes.’

Laboratories cannot judge value solely on their own. This is apparent by the inclusion of clinicians in all the winning submissions to the *UNIVANTS of Healthcare Excellence Awards*, and also in the articles we present in this issue. As providers of laboratory testing, we need the input of service users to fully understand the impact on patient care. Laboratories working in co-production with clinicians and multi-disciplinary teams are thus ideally placed to tap into the value agenda. The breadth of healthcare scope across which laboratories can impact are exemplified in this edition by the papers of Martin Than (ACS pathway, urgent secondary care) and Judith Strachan (FIT pathway, primary: secondary care interface). For a representative clinician’s view on working with laboratories, we invite you to read ‘Valued Clinical Leaders Share Perspectives on the Importance of Laboratory Medicine’ in which those whose teams have successfully partnered with laboratories share their experience (5).

The *UNIVANTS of Healthcare Excellence* awards, besides facilitating a sharing of ideas, also provide a checklist of good practice ideas for laboratories to review in order to adopt the concepts of working in a value added fashion, as described in more detail in the article by Ravalico and Strain (6) in this issue. This is a useful pointer for a way of working which is new to many of us. There are, of course, other sources of inspiration and guidance, for example, the work of the NICE Diagnostics Committee in the UK, which explores cost effectiveness of laboratory tests, or the IFCC committee's work on the value proposition (3). All contribute in different, but complementary, ways to encourage ongoing quality improvements.

The IFCC and others (7) recognise that laboratories are not good at fully evaluating and measuring outcomes in terms of standard health economic measures (and laboratories may not have been included in such assessments). It is therefore important for future developments to engage with health economists, who should ideally be fully embedded in health care. We need to understand both the micro-economic impact within individual laboratories, as well as the macro-economic population impact. The lack of awareness of health economic modelling, to demonstrate cost-effectiveness, combined with the increasing cost of health care show how important it is for current and future laboratorians to be economically educated. A good start would be to ensure this is included in training programmes for all laboratory disciplines and professions.

Howard Morris was indeed prescient when he recognised this:

“We need to appreciate that what we are doing in some ways is creating a new academic science... a new way of thinking that has not been done before. I think UNIVANTS is the future of Laboratory Medicine and could even be its own journal one day.”

Professor Howard Morris, IFCC President at the March 3rd, 2019 UNIVANTS of Healthcare Executive Partner Meeting

This special edition is dedicated to his memory.

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Laboratory medicine and healthcare excellence – till death do us part

Colleen Strain^{1,2}, Tricia H. Ravalico^{2,3}

¹ Scientific Leadership and Education, Core Diagnostics, Scientific and Medical Affairs, Abbott, Canada

² Program Leads, UNIVANTS of Healthcare Excellence Awards

³ Scientific Leadership and Education, Core Diagnostics, Scientific and Medical Affairs, Abbott, United States

ARTICLE INFO

Corresponding author:

Colleen Strain
Abbott
Core Diagnostics
7115 Millcreek Dr.
Mississauga, ON L5N 3R3
Canada
E-mail: Colleen.Strain@abbott.com

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ABSTRACT

The union between laboratory medicine and healthcare excellence is strong, interconnected and has stood the test of time. This partnership is essential in the quest for value-based health care, expanding the strategic role of the clinical laboratory from traditional, transactional models to strategic ones that expedite or activate new cascades of care.

This paper reviews outcomes and key trends following global recognition of integrated clinical care teams for exemplary outcomes of measurably better health care. In all cases, laboratory medicine was either a key contributor or leader in predictive risk management, preventative health, and integration of clinical care through active synthesis of relevant data: data that are too often under-used, under-recognized, or even missing in traditional models of care.

Outcomes connect multi-disciplinary teams with favorable key performance indicators across patients,

payors, clinicians and health systems, as well as top disease burdens and unmet gaps of care. Results affirm the possibilities ahead with proactive engagement across healthcare professionals including the vital and active role of laboratory medicine. With the future upon us, it is incumbent upon all healthcare professionals to work together, learn from others, champion health outcomes and join in a pledge for healthcare excellence.



INTRODUCTION

Partnerships that are built to last often require continuous effort, mutual appreciation, creativity, and commitment to making things better. The best partnerships not only complement one another but lead to growth. The marriage between laboratory medicine and healthcare excellence is no exception. Both interconnected entities are vital to the health of our communities and to the future of medicine.

Like-minded pathologists and clinical laboratory leaders have long urged healthcare professionals across the globe to strategically engage laboratory medicine for value-based health care [1-3], with value defined in terms of the outcomes achieved for patients relative to the money spent [2]. Excellent best practices for improving healthcare outcomes subsequently emerged, highlighting successful examples of laboratory-led healthcare projects that have re-engineered healthcare delivery pathways and the practice of medicine [4-6].

The insights from the UNIVANTS of Healthcare Excellence award program have been equally as inspiring, linking improved key performance indicators (KPIs) for patients, payors, clinicians and health systems through strategic engagement of laboratory medicine within integrated clinical care teams, which were unified across

disciplines in order to achieve measurably better outcomes [7].

This paper reviews the most common themes, disease areas and outcomes associated with the top-performing, award winning teams with recognized best practices from the UNIVANTS of Healthcare Excellence award program. In all cases, innovative or avant-garde healthcare professionals transformed traditional standards of care to achieve exceptional outcomes; outcomes that would not have been possible without the clinical laboratory. Thus, the connectedness of laboratory medicine to healthcare excellence is bi-directional. Laboratory leaders can drive healthcare excellence, just as the need for further healthcare excellence is a stimulus for innovations in laboratory medicine. Both entities are not only intertwined and a complement to one another, but also reflect opportunities for joint growth.

The trends and findings identified through this analysis offer multiple benefits. First, they increase awareness of existing best practices of measurably better health care. Second, the outcomes can serve as an inspiring call to action for others to emulate similar best practices or create new ones through integration of clinical care teams across their health system(s). Third, the findings identify areas of unmet needs whereby the successful integration of laboratory medicine hasn't been recognized yet by the program, enticing new care teams to quantify and share their success. Fourth, the key performance indicators highlighted in this report present alternative or additive approaches for quantifying the value of laboratory medicine in healthcare settings. Finally, the findings collectively underscore the importance of healthcare excellence and the need for healthcare professionals to unify across disciplines for the betterment of value-based health care.

THE UNIVANTS OF HEALTHCARE EXCELLENCE AWARD PROGRAM

The UNIVANTS of Healthcare Excellence awards inspire and recognize best practices in health care. Founded by Abbott in 2018 and made possible through strategic partnerships with seven other leading healthcare organizations worldwide, the program accepts nominations from integrated clinical care teams who have achieved measurably better health care. Eligible applications are scored across process attributes, in addition to impact scores that are calculated from submitted quantitative and qualitative metrics in the form of KPIs. Applications must involve laboratorians and healthcare teams with care initiatives that have been implemented into clinical practice, leading to measurable benefits for patients, payors, clinicians and health systems/administration. The award program is product-agnostic, open to all healthcare professionals, and standardized using online forms for nominations and scoring. Abbott has no role in the scoring of submitted applications, instead nominated experts across each of the seven partner organizations serve as judges and must score every application.

Some prestigious program partners include the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC), AACC (formerly known as the American Association of Clinical Chemistry), the European Health Management Association (EHMA), Modern Healthcare, the Healthcare Information and Management Systems Society (HIMSS), the National Association of Healthcare Quality (NAHQ), and the Institute of Health Economics (IHE); each in partnership with Abbott. Among many prestigious benefits, healthcare teams recognized with UNIVANTS of Healthcare Excellence awards earn widespread global amplification of their winning best practice(s), enabling education and replication across the world.

WINNING TEAMS AND BEST PRACTICES

The winning teams and associated best practices in the program's inaugural year have been summarized previously [7], with three teams receiving top recognition and earning the title of 2019 UNIVANTS of Healthcare Excellence winner. Seven teams also received global recognition for distinction with two additional teams receiving global recognition for achievement. The number of recognized teams doubled in the program's second year, underscoring a substantial increase in worldwide awareness of the program, as well as a potential increase in the number healthcare teams across the globe who are more readily measuring the effectiveness of their integrated clinical care initiatives. This is further substantiated by a 44% increase in the number of countries actively engaged on the program website (97 countries in year 1 to 141 countries in year 2). As outlined in Figure 1, the winning teams for 2020 included three top global winners, nine teams of distinction, and twelve teams of achievement. In addition, and among the 24 teams with recognition in 2020, five teams were highlighted as top area winners for best practices in (1) Asia Pacific, (2) Europe, (3) Latin American and Caribbean, (4) Middle East and Africa and (5) North America. More details across all 36 teams with recognition from the UNIVANTS of the Healthcare Excellence Program and their associated best practices from 2019 and 2020 can be found at www.UnivantsHCE.com.

METHODS

All nominations submitted to the UNIVANTS of Healthcare Excellence Program are assessed against minimum program eligibility and scored by a panel of judges, as previously described. For the purposes of this evaluation, all teams with a recognized best practice in 2019 and 2020 had their submissions further evaluated for industry

insights in accordance with Table 1. The attributes included, but were not limited to, leading causes of death worldwide [9, 10], as well as top industry trends in health care [11-14]. In addition, each best practice was also categorized for the dominant change agent, defined as the singular most influential impetus, power, or driving force behind the care initiative without

which the team could not have attained its project mission or measurable outcomes. Only one dominant change agent was attributed to each best practice. The latter recognizes that dominant change agents are either new test methods (i.e., new information), new insights associated with previously existing information (i.e., application of informatics), or new processes.

Figure 1 Winning teams of the 2020 UNIVANTS of Healthcare Excellence awards, including Top Global Winners (3), Distinction (9) and Achievement (12)

UNIVANTS OF HEALTHCARE EXCELLENCE GLOBAL WINNERS	
Reducing Patient Risk and Enhancing Care through the Development and Implementation of a New Chest Pain Pathway, Expedited by and for the COVID-19 Era – Canterbury District Health Board	* ASIA PACIFIC AREA WINNER
Early Diagnosis and Improved Management of Patients with Diabetes through Strategic and Automated Test Algorithms via Primary Care – Hospital Universitari Sant Joan d'Alacant	* EUROPE AREA WINNER
Kidney Check: The Next Generation of Surveillance for Hypertension, Diabetes and Chronic Kidney Disease – Chronic Disease Innovation Centre, Seven Oaks General Hospital	* NORTH AMERICA AREA WINNER
UNIVANTS OF HEALTHCARE EXCELLENCE RECOGNITION OF DISTINCTION	
Reducing Medical Errors and Enhancing Patient Care through Pathology Lead Strategic Activation of Point-of-Care Testing in an Emerging Market – Aga Khan University Hospital, Nairobi	
Early Detection and Management of Gestational Diabetes Mellitus for Improved Outcomes of Mothers and their Babies – Hospital Clinico San Carlos	
Reducing Catastrophic Adverse Events in Patients with Hemorrhagic Shock through Early Recognition of Risk and System-Wide Automatic Alerts – Hospital Israelita Albert Einstein	* LATIN AMERICA AREA WINNER
Reduction of Inpatient Daily Blood Draws with Data Science and Clinical Collaboration – St. Paul's Hospital	
Reducing Post-Operative Complications in Cardiac Surgery Patients – Hospital Virgen Macarena	
Use of Faecal Immunochemical Tests (FIT) Unlocks the Door to Efficient and Effective Investigation of Patients with New Bowel Symptoms – NHS Tayside	
Novel Collaborative Approach among Public and Private Sectors for Streamlined SARS-CoV-2 Testing towards Optimized Patient Outcome during COVID-19 Pandemic – Dubai Health Authority	* MIDDLE EAST & AFRICA AREA WINNER
Improved Safety for Patients with Indeterminant Pulmonary Nodules through Optimized Diagnostic Pathways for Lung Cancer – The First Affiliated Hospital, Sun Yat-sen University	
Enhanced Identification and Care for Patients with Undetected HCV and/or HIV via Opt-Out ED Screening with Active Education and Linkage to Care – University of Alabama at Birmingham Hospital	
UNIVANTS OF HEALTHCARE EXCELLENCE RECOGNITION OF ACHIEVEMENT	
Improving Patient Experiences via Reliable Pre-Surgical Biomarker Risk Assessments in Patients Undergoing Eye Surgery – St. Petersburg Hospital Number Two	
Improving Population Health through Screening for Hepatitis C to Enable Treatment for Undetected Viral Infections – Biomédica de Referencia	
Improving Care and Overall Experience for Patients who Present to a Tanzania Clinic with Suspected Cardiovascular Diseases – Faith Medical Tanzania Clinics	
Optimized Detection and Management of Thyroid Dysfunction During Pregnancy for Improving Maternal and Offspring Outcomes – Hospital Virgen de la Luz	
Procalcitonin: A Successful Clinical Formula for the Early Recognition and Management of Sepsis in the Emergency Department – The Princess Alexandra Hospital NHS Trust	
Maintain High Quality Patient Care During the COVID-19 Pandemic – Institut für Medizinische und Chemische Labordiagnostik, Mein Hanusch Krankenhaus	
Maximizing Delivery Method and Clinical Resources for Timely Patient Communication of COVID-19 Status – Nova Scotia Health	
Laboratory-Led Company-Wide Screening Programs for Safe, Back to Work Strategies during COVID-19 Pandemic in Saudi Arabia – Dr. Suliman Al Habib Medical Group	
COVID-19: Using Data, Innovation, and Collaboration to Support Better Patient Outcomes – North West London Pathology	
Increased Detection of Acute Myocardial Infarction in Women Using Sex-Specific Upper Reference Limits in Clinical Pathways for Patients Presenting with Suspected Acute Coronary Syndrome – Kokilaben Dhirubhai Ambani Hospital & Medical Research Institute	
Strategic SARS-CoV-2 Testing for Risk Mitigation and Optimal Health of Healthcare Workers and Patients – Marienhospital	
Enhanced Discovery of Unidentified Comorbidities and Diagnosis Through the use of Diagnostic Logics Empowered by Laboratory Medicine and Informatics – Seirei Hamamatsu HP	

Table 1 Attribute evaluation for each recognized best practice

Attribute	Criteria	Evaluation		
Dominant Change Agent			<i>Select only 1</i>	
Implementation of New Test Methods	Does this care initiative require the adoption and implementation of new biomarkers and/or test methods that were not previously used in clinical care at this institution to achieve the measurable success?			
Informatics	Is use of informatics likely the only way to achieve the best practice outcomes? Does this best practice strategically use informatics to automate, and/or perform reflexive testing, and/or calculate risk score critical to care pathways?			
Process Change	Was there a change to the standard of care? Were there changes to how existing information was communicated or acted upon?			
Disease States and Areas of Focus			Indicate all that apply	
Disease State(s)	Liver, Sepsis, Cardiac, Oncology, Infectious Disease, Endocrine, Diabetes, Kidney, Prenatal, Trauma, Respiratory, Fertility, Neurology			
Area(s) of Focus	Acute, Chronic, Prevention, Primary Care, Long-term Care, In-Patient Care, Women's Health, Clinical Informatics, Point of Care, Transfusion, Hematology, Molecular, Pediatric, Geriatric			
Emerging Trends			Yes	No
Laboratory Stewardship	Did this care initiative more accurately improve the ordering, retrieval, and interpretation of appropriate laboratory tests? Was the problem of over or under utilization of laboratory tests addressed? [8]			
Customized Reference Ranges	Were new, normal ranges established and implemented into clinical practice? Did implementation enable change to patient outcomes?			
Quality System	Did this care initiative more accurately improve quality control, quality improvements and/or involve new procedures or certifications related to quality in order to achieve the measurable outcomes?			
Patient Engagement	Were patients (or potential future patients) directly involved in new ways for health management, diagnoses or treatment?			
Screening	Does this care initiative involve strategic selection and/or wide-spread testing for specific disease and/or wellness areas?			
Surgical Relevance	Does this care initiative more accurately assess pre, post or peri-operative risk and/or action?			

**UNDERLYING CHANGE AGENTS
 ACROSS TOP PERFORMING TEAMS**

Healthcare excellence can happen in many ways. The route taken to achieve a measurable difference in health outcomes will undoubtedly vary by institution, location, patient type and more. Success involves a combination of teamwork, innovation thinking, and a commitment to drive change. Change in turn gets fueled by new information, new insights and/or new processes, as the single most influential force behind the

care initiative in order to achieve measurable outcomes.

Across both years of the UNIVANTS of Healthcare Excellence award program, new processes were the most common agent of change, with approximately 52% (Figure 2) of the recognized best practices involving changes to the delivery of care, without implementation of new biomarkers or algorithms.

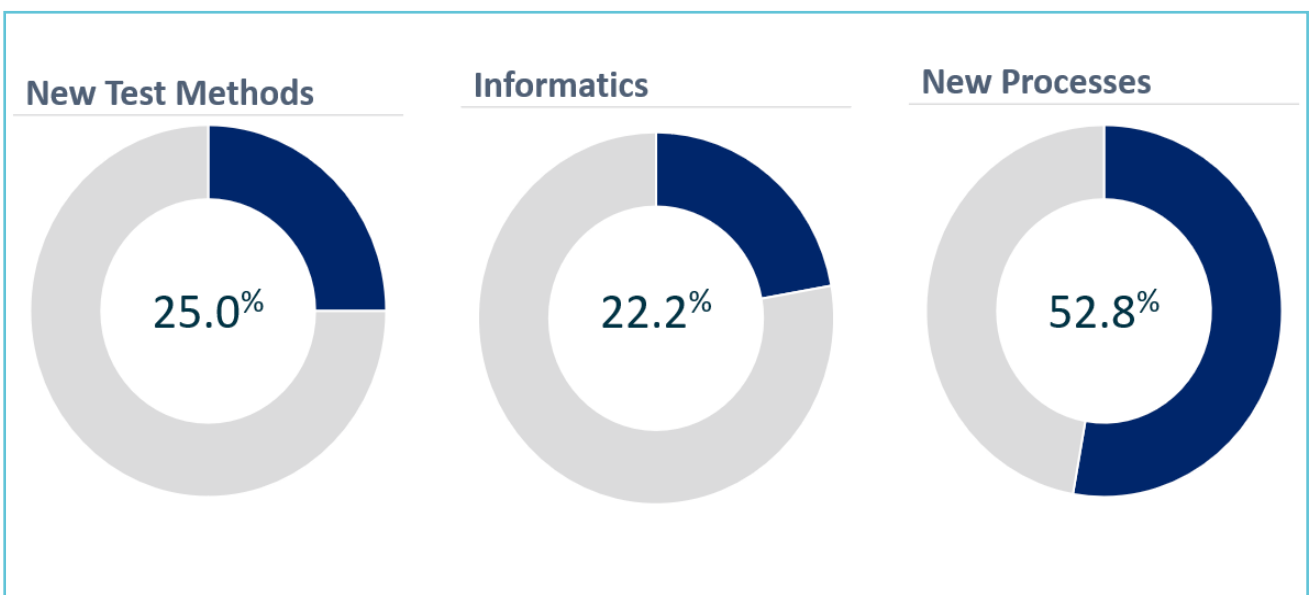
Examples include expedited triage for patients with chest pain [15, 16], improving the timely

communication of COVID-19 status through activation of online patient portals [17], and maximizing patient care via comprehensive or new quality systems [18] or enhanced quality processes [19]. Other dominant agents of change included the adoption of new test methods (25%) and new insights (22%) driven by implementation of informatics or clinical decision support. Thus, while it may be common to believe that implementation of new biomarkers into care is the customary way to innovate, even small changes within current systems can have long-lasting and substantial impact.

Not surprisingly, the COVID-19 pandemic has substantially increased the rates of new test methods implemented into clinical care between 2019 (16.7% of the recognized best practices) and 2020 (37.5% of the recognized best practices), as many institutions implemented newly developed SARS-CoV-2 assays into clinical care. Implementation of new test methods with instant

and sustained demand, such as SARS-CoV-2 assays, require innovative thinking to overcome capacity challenges [20], while ensuring patient-centric care [21, 22]. Traditional implementation of novel biomarkers can be equally as complicated, requiring wide-spread education, demand creation, and activation of consistent care pathways. However, best practices in this area have had proven success. Examples include implementing procalcitonin into clinical decision-making for the early recognition and management of sepsis [23, 24], use of placental growth factor (PLGF) for early identification of preeclampsia [25, 26], introduction of faecal immunochemical tests (FIT) to investigate patients with new bowel symptoms [27, 28], and implementation of viscoelastic point-of-care testing following cardiopulmonary bypass for reducing post-operative complications [29]. Collectively, teams working together can facilitate rapid adoption and transformational delivery of care.

Figure 2 Dominant change agents across recognized best practices through the UNIVANTS of Healthcare Excellence awards*



* Nine of thirty-six care initiatives involved the implementation of new test methods into clinical care as the main agent of change. Eight of thirty-six best practices were predominantly powered by clinical decision support or algorithms for actionable change in clinical care. While all thirty-six care initiatives had some level of process change, nineteen had process as the leading change agent.

Use of informatics and/or clinical decision support continues to emerge with time. Offering synthesis of data, either longitudinally or across biomarkers at single points in time can enhance patient diagnosis [4, 30-32], monitoring [5, 33-34] and/or care [35, 36]. These trends collectively suggest that while there will always be a time and place for novel test methods and/or biomarkers, innovation and measurable differences can be also achieved through strategic application of informatics and process changes, enabling immediate and actionable insights for resolving existing gaps in care.

PREVAILING DISEASE STATES AND AREAS OF FOCUS

Care gaps exist in medicine today across most disease areas with opportunities to improve or expedite care regardless of the disease burden. It is not surprising, however, that care teams often focus on areas with substantial unmet needs, enabling improvements to patient experiences, reducing clinical uncertainty, improving staff satisfaction, and/or lowering overall healthcare costs. Across and between award years, the disease states associated with the best practices for the award-winning teams include infectious disease, cardiovascular disease, kidney disease and prenatal care (Figure 3). While cardiovascular disease and kidney disease continue to be strong focuses globally, approaches to improving outcomes vary widely. Patient-centric initiatives in the field of cardiovascular disease span best practices in expedited triage of patients presenting with chest pain [15, 16, 37], long-term risk prediction [38, 39] and reducing cardiac complications in patients undergoing cardiac [29] and non-cardiac surgery [40, 41]. Strategies for improving outcomes related to kidney disease include identification of acute kidney injury [42] managing patients undergoing treatment with chronic kidney disease [35, 36] and reducing risk of dialysis in underserved

communities through early screening via point of care [43-45]. In terms of infectious disease, and beyond the aforementioned SARS-CoV-2 test method adoption, are leading best practices focused on hepatitis C virus (HCV) identification and elimination with strategies including highly successful awareness campaigns [46] as well as Opt-out [47-49] screening programs for earlier detection and enhanced linkage to care.

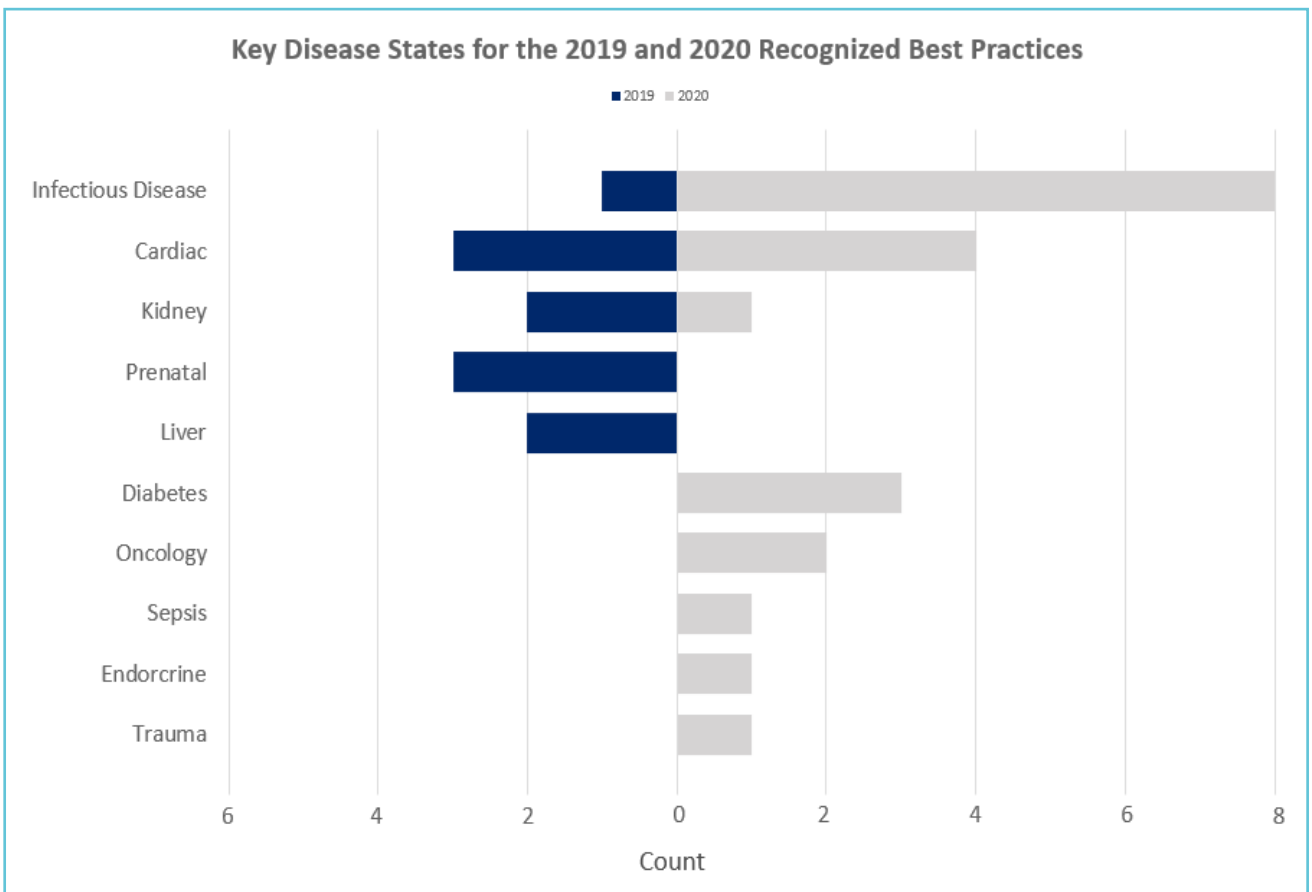
While commonalities prevail across years in the top four disease areas, differences can also be noted. Specifically, best practices in several new disease categories emerged in 2020, including but not limited to more strategic identification and management of patients with diabetes [5, 33], expedited decision-making for patients with suspected cancer [32], and improved identification and management of potential bleeding due to trauma [50, 51] (Figure 3).

In the years ahead, further expansion of categories is expected, including best practices that address other areas of unmet needs, including but not limited to fertility, respiratory disease and traumatic brain injury. Current gaps are not likely driven by an absence of engagement or use of laboratory medicine in these specialties, but rather the absence of award awareness and/or interdisciplinary connections necessary to quantify success or ensure award eligibility. This highlights new opportunities for care teams to further collaborate and measurably impact patient care.

LABORATORY INSIGHTS FOLLOWING TWO YEARS OF REFLECTION

Not all of the best practices submitted to the UNIVANTS of Healthcare Excellence award program involve laboratorians as the primary applicant. In fact, many of the top-performing teams were led by clinicians who approached laboratory medicine for help in solving gaps in care. Other superior care initiatives, however, did originate

Figure 3 Common and unique disease states associated with recognized best practices across the first two years of UNIVANTS of Healthcare Excellence awards.*



* Not graphed, but noteworthy, was the absence of recognized best practices in the fields of respirology, fertility and neurology.

and thrive through the leadership of the clinical laboratory. Multiple trends have emerged from the latter including some level of laboratory stewardship (Figure 4), which accounts for 19.4% (year 1: 25.0%, year 2: 16.7%) of all teams with recognized best practices. Ensuring the right tests are used for the right patients at the right time has broad relevance both within and beyond the lab.

Another key area of pathology-led excellence is the establishment and implementation of outcome-based reference ranges. Too often, generic reference ranges are used inappropriately in clinical care. Doing so can limit disease detection

and challenge potential treatment or wellness. One stand-out example is the more accurate classification of the thyroid status in pregnant mothers, using locally established, outcome-based reference ranges for thyroid stimulating hormone [52].

A final theme and long-standing focus of clinical laboratories is the crucial requirement of high-quality laboratory testing. Whether it is pathology-led oversight of point of care testing [19] or a complete redesign for a system-wide quality culture in an emerging market [18], the relevance of laboratory medicine and its impact to patient care remains vital and evident.

STANDOUT KEY PERFORMANCE INDICATORS (KPIs)

Measurement of outcomes is a common practice and core competency within laboratory medicine. Measurement of health system outcomes, however, is not. Often, the connection between laboratory medicine to measured KPIs outside the clinical laboratory are speculative or confounded at best. Experts have long tried to associate the value of laboratory testing with the value of the profession. In reality, these two entities, while intertwined, are also mutually exclusive. Laboratory professionals are uniquely positioned for strategic brainstorming irrespective of the implementation of new test methods. Similarly, successful implementation of new test methods within the core laboratory does not necessarily mean successful implementation into clinical care. For these reasons, trends associated with KPIs across the two years of the UNIVANTs of Healthcare Excellence Awards can be insightful, highlighting what is possible, connected, and measurable.

As outlined in Figure 4a, the most frequently measured KPI across recognized best practices in 2019 was improved clinical confidence. This outcome to most will be somewhat expected, as the power of laboratory data has long been recognized for its value in guiding clinical decisions.

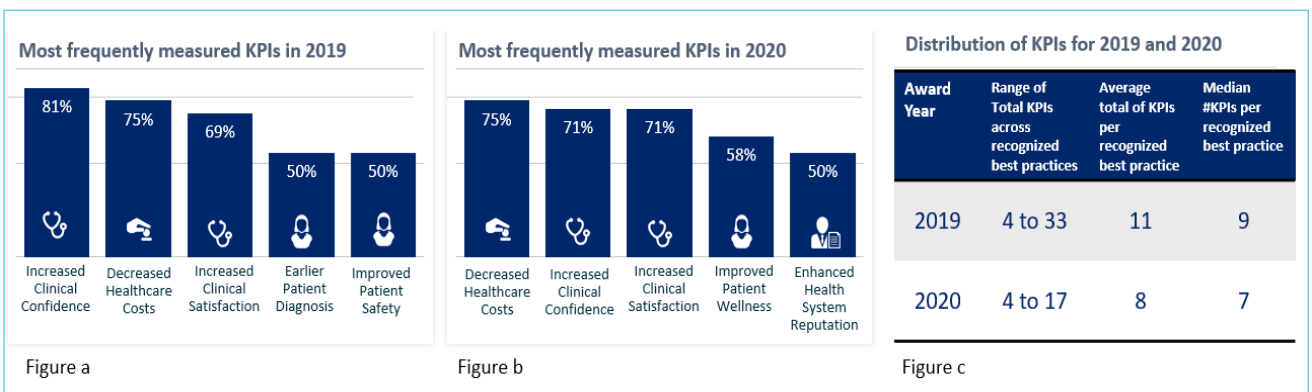
Interestingly, the most frequently measured KPI across recognized best practices in 2020 was reducing overall healthcare costs; surpassing the KPI of clinical confidence. Thus, more teams have either begun to more frequently connect the downstream value of laboratory medicine beyond clinical stakeholders, or perhaps they are more readily beginning to quantify it.

It is worthy to also note that the median number of submitted KPIs across both years reflect a near doubling of the minimum requirements for eligibility (Figure 4c). In addition, multiple best practices across consecutive years far surpassed the minimum requirement of 4 KPIs. This highlights the rewarding potential for measurable excellence from inter-connected teams working together towards common goals.

DISCUSSION AND A PLEDGE FOR HEALTHCARE EXCELLENCE

It has been said that “communication to a relationship is like oxygen to life. Without communication, relationships die.” In kind, so do marriages and long before ‘death does them part.’ Thus, commitments to any partnership require effort, time, trust and yes, communication. A joint commitment for healthcare excellence is no different. Healthcare professionals must work together, trust and communicate with one another,

Figure 4 (a, b, c) Distribution analysis of KPIs associated with the UNIVANTs of Healthcare Excellence awards



appreciate and problem-solve with one another to achieve common goals. Opportunities to do that vary; across regions, health systems, disease states, processes and populations. Those that do it well achieve measurably better health care, and ideally, also achieve recognition both locally and globally for their best practice of elevating patient care.

The trends and findings of this paper suggest that the UNIVANTS of Healthcare Excellence program has been successful in recognizing teams for healthcare excellence whereby laboratory medicine has contributed in a measurable way. Even amidst the unprecedented COVID-19 pandemic, healthcare excellence has been thriving. Of note, in both years of the program at least one of the top three winning teams involved best practices in the field of kidney medicine. Further, cardio-renal care initiatives comprised 28% of all recognized best practices, surpassing infectious disease by 3%. Given the collective global burden of cardiac and renal diseases, in addition to substantial opportunities for improved detection and prevention, as well as the close connection of biomarkers to measurably better health care in these fields, this finding is not surprising. What is surprising is that HCV elimination strategies comprised 8% of all recognized teams, including best practices from England, Mexico and the United States. This favorably reinforces the global goal of HCV elimination by 2030 [53]. With approximately 30% more disease states with recognized best practices in 2020 compared to 2019, opportunities continue to emerge for measurably better health care.

A limitation of the trends and findings presented in this paper is that they were limited to the 36 best practices with recognition associated with the UNIVANTS of Healthcare Excellence awards. The award program however is global, spans engagement from over 141 countries and involves high-quality, diverse initiatives with recognition only to those with peer-approved

acknowledgement from seven prestigious healthcare organizations. Thus, while limited in total number, the themes and trends associated with the first two years of the program are genuine and reflect measurably better outcomes of healthcare excellence relevant to unmet clinical care gaps in health care today.

It is the intent of the UNIVANTS program and the hope of these authors that the award program continues to thrive with wide-reaching examples of excellence across the globe, while inspiring new and complementary best practices at other healthcare facilities that desire similar success. The quest for healthcare excellence is upon us and the way to achieve measurably better healthcare is to engage laboratory medicine, work across disciplines and lead with action and by example in value-based health care. We invite readers to join in this community of best practices, pledge to healthcare excellence, and inspire others to do the same.



A parodical Pledge for Healthcare Excellence

From this day forward, for better (and not worse), in sickness and in health, for patients and the community, for unborn babies to the elderly, to save and to heal, I commit to healthcare excellence all the days of my life. To be inclusive and innovative, and being open and strategic; all while maximizing the value of laboratory medicine until death do us part.



CONCLUSION

Life and death decisions are made every day. Healthcare professionals carry that burden and become the ‘oxygen’ to millions of patients in need. In the quest to do more, for patients and healthy communities, we must work together to achieve healthcare excellence; maximizing health

through laboratory insights, measuring success across stakeholders with quantitative and qualitative KPIs, and sharing those best practices with the UNIVANTS of the Healthcare Excellence award program. We are in this together, until death do us part.

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Procalcitonin (PCT) level in the emergency department identifies a high-risk cohort for all patients treated for possible sepsis

Georgia Lucas*, Angela Bartolf*, Nicholas Kroll, Agampodi-Umanda De Thabrew, Zoya Murtaza, Siddarth Kumar, Abrar Gani, Andrea Annoni, Marie Parsons, Helen Pardoe

Princess Alexandra Hospital NHS Trust Harlow, United Kingdom

* Georgia Lucas and Angela Bartolf are both joint first authors

ARTICLE INFO

Corresponding author:

Helen Pardoe
Princess Alexandra Hospital NHS Trust
Harlow
United Kingdom
Phone: +44-1279-444455
E-mail: helen.pardoe1@nhs.net

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ABSTRACT

What is already known?

1. The benefits of measuring PCT in the Emergency Department (ED) are not yet fully characterised.
2. PCT is widely used in the intensive care setting to guide antimicrobial prescribing.

What this adds?

Measurement of PCT as a routine in the emergency department for all patients treated for possible sepsis identifies a high-risk cohort.

Key improvement in patient care

1. A PCT measurement of $>0.2\mu\text{g/L}$ in the Emergency Department identifies a patient at increased risk of deterioration and of in-hospital death.



Background

Early recognition and management of sepsis in the Emergency Department (ED) is a clinical challenge. Our aim was to determine if measuring the biomarker PCT in patients with suspected sepsis enables the identification of patients at increased risk of deterioration or in-hospital death in the ED setting of a district general hospital in the United Kingdom.

Methods

A prospective observational study was conducted on all patients aged 18 and over presenting to ED fulfilling NICE criteria for moderate to high risk of sepsis admitted to hospital. Patients had a PCT test alongside the sepsis six protocol. PCT was measured using Brahms's chemiluminescent micro particle assay (CMIA) for the quantitative determination of PCT in human serum and plasma on the Abbott Alinity I analytical platform. The cost per test was approximately 13 GBP.

The analysis was performed on patients having a PCT in ED over a 7-month period, with in-depth scrutiny of an appropriate subgroup. A high level quality improvement (QI) approach was used in the study.

Results

A total of 1242 patients were included in the study. Mean/median age was 67.9/72, (range 18-102). 88.7% of deaths occurred in patients over 65 years of age. 42.4% (n=532) had a PCT level in ED of >0.2 ug/L. This identified a high risk group with a 2.4 fold increase in mortality rate (7.7%:18.2% p value <0.001). The median length of stay (LOS) was 5 (IQR 9) and 8 days (IQR 11) in patients with a first PCT of ≤0.2 ug/L versus >0.2 ug/L respectively.

Conclusion

An immediate PCT on patients presenting to ED with signs of sepsis in a non-specialised acute trust identifies those patients at an increased risk of deterioration and in hospital death.



INTRODUCTION

Sepsis is responsible for approximately 37,000 deaths and 100,000 hospital admissions per year in the UK (1). Early recognition of sepsis in the ED is a clinical challenge due to the variability in presentation (2). ED staff need a quick, reliable test to diagnose sepsis and identify those patients at high risk of deterioration.

Procalcitonin (PCT) is a biochemical marker of bacterial sepsis which has excellent diagnostic and prognostic value to identify bacterial sepsis early and alert clinicians regarding disease severity (3). It can also be used to monitor response to antimicrobial treatment. Whilst PCT results can guide clinical decision making, they cannot replace standard sepsis management. Internationally, PCT is used widely in intensive care (ICU) (4) with serial PCT levels guiding continuation of antimicrobial treatment (Procalcitonin Guided Antimicrobial Therapy –PGAT) using the BRAHMs criteria (5). PGAT as described by Schuetz et al (5) is based on a cut off of 0.25ug/L. However, the cut off used in this study was 0.2ug/L reflecting the fact that the local laboratory LIMS system reports PCT measurements to only one decimal place.

Our aim was to discover if measuring PCT in patients with suspected sepsis would allow us to identify those at increased risk of deterioration or death.

MATERIALS AND METHODS

Patients presenting to the ED at the Princess Alexandra Hospital Trust, a UK district general hospital, fulfilling the NICE 2016 (6) criteria for moderate to severe sepsis had a PCT blood test on triage alongside the sepsis six protocol between August 2019 and February 2020. A second PCT was recommended 24-36 hours later (Figure 1). PCT results were available within 60 minutes of receipt in the laboratory for ED samples and within four hours of receipt in the laboratory for samples received from inpatient wards. PCT was measured using Brahms's chemiluminescent micro particle assay (CMIA) for the quantitative determination of PCT in human serum and plasma on the Abbott Alinity I analytical platform. PCT levels were reported to one decimal place (ug/L). The result reproducibility was acceptable with within run imprecision of 2.9%, 3% and 2.5% determined using internal quality control (IQC) materials with concentrations 0.18, 1.79 and 64ug/L respectively. Between assay imprecision was tested at two levels 0.18 and 64ug/L and was shown to be 4% and 5% respectively. The cost per test (reagents only) was approximately 13GBP. The performance of the PCT assay was monitored using the Welsh External Quality Assurance Scheme (WEQAS) and has performed acceptably when compared to other laboratories performing PCT assays who are subscribed to the scheme. Overall lab SDI score 0.05, with a median all laboratory SDI score of 0.30.

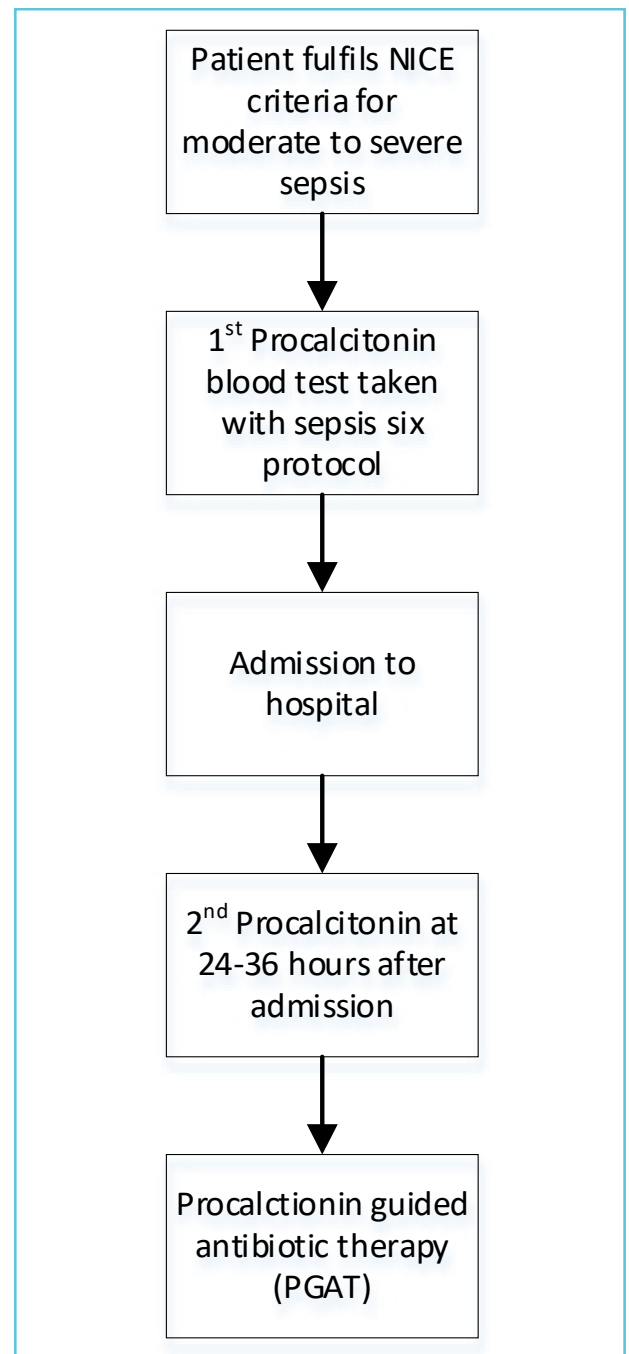
Outcome data was collected from local digital clinical systems. All patients 18 years old or above with at least one PCT test in ED were included in the sample.

A Plan-Do-Study-Act (PDSA) approach using the Institute of Healthcare Improvement quality improvement (QI) model was used to optimise staff understanding and engagement with the protocol (Figure 1). PCT was introduced as

a routine diagnostic test for the investigation of sepsis following local governance approval.

Adherence to the protocol for the second PCT blood test was poor. This can be attributed to a number of system factors including high medical staff turnover, patient ward changes, phlebotomy

Figure 1 Recommended protocols



arrangements and PCT measurement not yet being embedded within the hospital culture. A decision was made to run an additional PDSA cycle to try to increase adherence to the Procalcitonin protocol. There was a period of intensive teaching and training for ward staff highlighting the importance of the second PCT test and intervention from the laboratory to ensure the phlebotomy team bled requests for the second PCT.

Subgroup analysis data was collected on the patients presenting between 1st September 2019 and 31st October 2019 as this was the period following increased education and the direct laboratory intervention. Analysis was performed on the following outcome measures (OM): compliance with protocol, confirmed diagnosis, antibiotic usage, length of stay (LOS), ITU admission, and readmission.

Results were analysed in Microsoft Excel 2016, retrospective Chi Squared was used to calculate p-value. Binomial confidence intervals (CI) were used for mortality and Z and T scores used for all other CI.

RESULTS

A total of 1242 patients were included in the study (male:female 610:632) following the exclusion of 16 patients due to the lack of a valid PCT measurement in ED.

The mortality rate was 12.2% (95% CI 10.3%-14.0%). Mortality rate in patients with PCT >0.2 ug/L was 18.2% (95% CI 14.9% to 21.5%) compared to 7.7% (95% CI 5.7% to 9.7%) when PCT ≤0.2 ug/L (p value: <0.001 retrospective Chi Squared) (Table 1). 62% of patients within the study population were >65 years old, with 88.7% of deaths occurring in this age group.

Subgroup analysis (264 patients) identified the following: Patients with a final diagnosis of sepsis had a mean PCT of 5.6 ug/L (95% CI 0.7 to 10.5). 28.8% (76 patients) completed the

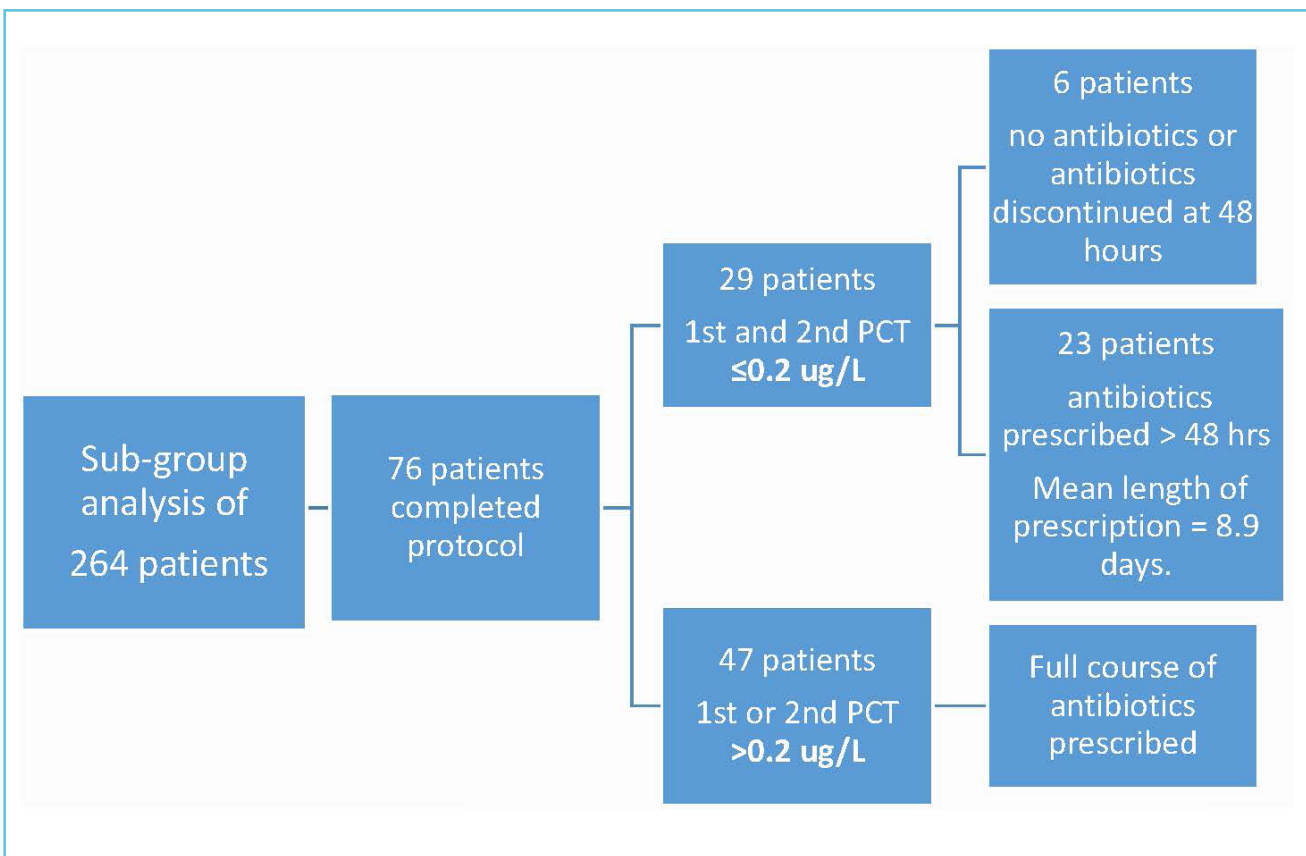
protocol (Figure 2); of those who completed the protocol, 47(61.8%) had at least one PCT of >0.2 ug/L and were prescribed a full course of antibiotics as per local antimicrobial prescribing guidelines (Figure 2). 38.2% (29 patients) had both PCT levels of ≤0.2 ug/L. For prescribers following the B.R.A.H.M.S criteria for Procalcitonin guided antibiotic therapy (PGAT), two PCT levels of ≤0.2ug/L >24 hours apart indicates that the source of symptoms is highly unlikely to be bacterial sepsis. Only 6 of our patients had their antibiotics de-escalated within 48 hours of admission. The remaining 23 of these 29 patients (79.3%) were prescribed antibiotics with a mean antibiotic duration of 8.9 days (95% CI 7.2 to 10.6). For these 23 patients antimicrobial therapy is likely to yield little or no benefit.

The most frequent first line antibiotics prescribed were Co-Amoxiclav and Piptazobactam. Gentamicin was the most frequent second line prescription. Potential antibiotic cost reduction was estimated. Our first step was to assume our prescribers had followed the BRAHMS algorithm in the antimicrobial prescribing for these 23 patients. Theoretical application of the BRAHMS criteria to de-escalate antibiotic prescription after 2 PCT tests of ≤0.2ug/l demonstrated a potential cost saving of approximately 44GBP per patient. The calculation was based on the average cost for 1 day's usage, multiplied by the number of days antibiotics were prescribed. This reflects the cost of the drug only; in reality, the costs will be much higher when factors such as staff time (medical/nursing/pharmacy) and overheads are taken into account.

The median LOS was 5(IQR 9) and 8 days (IQR 11) in patients with a first PCT of ≤0.2 ug/L versus >0.2 ug/L respectively. Data samples were too small to identify any significant correlation between ED levels of PCT and ITU admission or hospital readmission.

Table 1 The association of PCT in ED and patient mortality			
Patient group	Deaths	Discharges	Mortality
Patient group = 1242 patients, 610:632 Male:Female			
All	151	1091	12.2% 95% CI (10.3%-14.0%)
PCT in ED ≤ 0.2 ug/L	55	660	7.7% 95% CI (5.7%-9.7%)
PCT in ED > 0.2 ug/L	96	431	18.2% 95% CI (14.9%-21.5%)

Figure 2 Observational study profile*



* Subgroup analysis was performed over the collection period 01/09/2019-31/10/2019, as compliance with the second PCT measurement was highest during this period. This was following the additional PDSA cycle to highlight the importance of the second PCT measurement to clinical staff.

DISCUSSION

PCT is not routinely measured on patients with signs of sepsis in ED in the UK. Our study conducted in the emergency department stands out from the published literature on PCT where the target population is in the critical care setting (8). We have shown that for patients in ED with signs of sepsis, a PCT >0.2 ug/L at presentation is a prognostic indicator for a significantly increased risk of in hospital death. ED is a high volume, high risk area in the treatment of patients with sepsis. A PCT level of 0.2 ug/L was chosen as the cut-off to align with BRAHMS criteria (<0.25 ug/L) to ensure clear guidance to clinicians. Raised mortality was observed in PDSA cycle 1 in those patients with an ED PCT level greater than 0.2ug/L and there was clinical concern that a higher cut off would potentially be clinically unsafe in an ED setting. Early identification of a high risk cohort of patients can help alert the clinical teams to an increased need for monitoring and early review by a senior clinician in a patient who may at first appear clinically stable. Early identification of high-risk patients could mean that intensive monitoring and treatment is initiated at an earlier point in the development of sepsis, potentially reducing secondary organ damage and reducing the number of deaths from sepsis.

The study was performed when COVID-19 was present in the population, but the subgroup analysis was completed before the COVID-19 pandemic, indicating that the results are applicable to routine ED practice (9).

PCT as a routine diagnostic test for investigation of sepsis in ED was successfully introduced using a QI program. Use of PCT in the non-ICU setting to guide antibiotic prescribing was more challenging. Completion of the 2nd PCT test did not exceed 29%. High medical staff turnover, patient ward changes and phlebotomy arrangements and the fact the PCT use was not embedded in

current practice were responsible system factors identified for low compliance with performing the 2nd PCT test. Automation of the 2nd PCT at ordercomms level was considered the single most effective way to improve compliance, but was not achieved.

PGAT supports good antimicrobial stewardship; however, in our study compliance with PGAT was only 20.7% for de-escalation of treatment. Our study suggests that there may be a potential to reduce antimicrobial costs by using the BRAHMS criteria to guide antibiotic de-escalation in the non-ICU setting. Larger studies with higher levels of compliance with PGAT for de-escalation of treatment are required to confirm the findings of our study. Resistance of prescribers at all levels to apply evidence based PGAT to prescribing practice was identified as the prime factor causing low compliance with PGAT (10). In our hospital the staff continued to rely on a more familiar, less specific biomarker, namely C-reactive protein (CRP). Education and digital clinical decision support are two key strategies that hospitals could utilise to improve compliance with PGAT. Engaging education programmes delivered by PCT ambassadors such as training meetings, short videos and tea trolley training can encourage adoption of change (11). Digital clinical decision support could also encourage behaviour change by automated ordering of the second PCT, preventing the daily ordering of CRP analysis and prompts and alerts associated with antibiotic prescribing. If the hospital culture transitioned to the use of PCT evidence based prescribing practice in non-ICU patients, the benefits of PCT measurement in ED would be further enhanced (12).

CONCLUSION

A Procalcitonin level >0.2 ug/L in patients presenting to the Emergency Department with signs of sepsis identifies a patient cohort at increased

risk of in hospital death. Early senior review and enhanced monitoring for signs of deterioration of these patients has the potential to reduce the numbers of deaths from sepsis.



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Reducing patient risk and enhancing care through the development and implementation of a new chest pain pathway, expedited by and for the COVID-19 era

Martin P. Than¹, John W. Pickering^{1,2}, Philip Adamson⁴, Thomas Clendon⁴, Christopher M. Florkowski³, John Lainchbury⁴, Jacques Loubser¹, Alison Nankivel⁴, Sally J. Aldous⁴

¹ Department of Emergency Medicine, Christchurch Hospital, Christchurch, New Zealand

² Department of Medicine, University of Otago Christchurch, Christchurch, New Zealand

³ Canterbury Health Laboratories, Christchurch Hospital, Christchurch, New Zealand

⁴ Cardiology Department, Christchurch Hospital, Christchurch, New Zealand

* On behalf of the Christchurch COVID pandemic chest pain pathway initiative members and wider stakeholder group

ARTICLE INFO

Corresponding author:

Dr. Martin Than
21 Taylors Mistake Road
Sumner, Christchurch 8081
New Zealand
E-mail: martinthan@xtra.co.nz

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ABSTRACT

The COVID-19 pandemic raised major concerns relating to hospital capacity and cross-infection patients and staff in the Emergency Department (ED) of a metropolitan hospital servicing a population of ~500,000. We determined to reduce length of stay and admissions in patients presenting with symptoms of possible myocardial infarction; the most common presentation group.

After establishing stakeholder consensus, the existing accelerated diagnostic pathway (ADP) based on the ED Assessment of Chest-pain Score (EDACS), electrocardiogram, and troponin measurements with a high-sensitivity assay (hs-cTn) on presentation and two hours later (EDACS-ADP) was modified to stream

patients following an initial troponin measure as follows: (i) to a very-low risk group who could be discharged home without follow-up or further testing, and (ii) to a low-risk group who could be discharged with next-day follow-up community troponin testing. Simulations were run in an extensive research database to determine appropriate hs-cTnI and EDACS thresholds for risk classification. This COVID-ADP was developed in ~2-weeks and was implemented in the ED within a further 3-weeks.

A comparison of all chest pain presentations for the 3 months prior to implementation of the COVID-ADP to 3 months following implementation showed that there was a 64.7% increase in patients having only one troponin test in the ED, a 30-minute reduction of mean length of stay of people discharged home from the ED, and a 24.3% reduction in hospital admissions of patients ultimately diagnosed with non-cardiac chest pain.



INTRODUCTION

On 23 March 2020, New Zealand entered a stringent lockdown because of rising Sars-Cov2 cases nationally. Hospitals and their Emergency departments (EDs) began preparations for an influx of cases. Major concerns included cross-infection of patients and staff in the ED and bed space availability. Patients presenting with symptoms of chest pain and possible acute myocardial infarction (AMI) are one of the more common presentation groups to the ED accounting for approximately 5-15% of all presentations (1,2). We recognised that being able to reduce the length of stay in the ED of this patient group by expediting discharge of low-risk patients could reduce the risk of cross-infection and free up staff for dealing with more serious illnesses.

Christchurch Hospital has been a prominent developer of Chest Pain pathways. This has included running the world's first randomised controlled trial (RCT) evaluating a structured clinical pathway against usual care (3), and then the development of and subsequent validation in a second RCT of the Emergency Department Chest pain Score (EDACS) and pathway (4). In 2019 a modification of that pathway was implemented that used a troponin threshold of < 5ng/L (Abbott Architect – high sensitivity assay) to rule-out AMI after a single troponin measurement (5). This modification was based on a considerable body of evidence, which included locally collected data, that showed such a threshold safe and effective (6,7). The clinical approach at the time adopted a 'next day' community troponin test for patients discharged from the ED after a single troponin test.

The successive research studies had resulted in the creation of a large high-fidelity data set of laboratory and clinical variables for patients who had been assessed for possible AMI. We aimed to use this data to modify the existing pathway and to implement an expedited change of practice to reduce time spent in ED amongst these patients.

MATERIAL AND METHODS

This study measured the impact of a change practice, namely the implementation of a modified chest pain accelerated diagnostic pathway in the COVID era (the COVID-ADP). We present data from 3-months prior to the change of practice to 3-months post the change of practice. We will describe (a) pathway development, (b) pathway evaluation methods and (c) change management processes.

Pathway development

The COVID-ADP was developed by using a well characterised and high-fidelity data set of

patients who had presented to the Emergency Department at Christchurch Hospital with symptoms suggestive of AMI and in whom the attending physician intended to investigate for possible AMI.

This data set comprised four research studies during which patients were recruited with almost identical exclusion criteria which have been reported in detail elsewhere (3,4,8,9). Briefly, patients were excluded if <18 years, unable or unwilling to provide consent, a clear cause of symptoms other than AMI, ST segment Elevated Myocardial Infarction (STEMI), transfer from another hospital, pregnancy, unable to be followed-up, or staff considered recruitment inappropriate (e.g. receiving palliative care).

In all these studies participants had serial blood samples taken at the time of recruitment shortly after presentation (0h) and two hours later (2h). Blood was drawn into lithium-heparin tubes, immediately centrifuged, and stored at -80°C for later testing. Troponin concentrations were measured with a high-sensitivity Troponin I (hs-TnI) assay (Abbott ARCHITECT i2000 (Abbott Diagnostics, Chicago, Illinois).

The clinical troponin assay in use during the six-month quality improvement study was the same Abbott hs-TnI assay. Prior to implementation of the COVID-ADP all patients attending the ED with symptoms suggestive of AMI were assessed using the Emergency Department Assessment of Chest pain Score (EDACS) accelerated diagnostic pathway inclusive of a single troponin early rule-out (Figure 1).

We used the same definition of Major Adverse Cardiac Events (MACE) as with previous studies, either an AMI, cardiogenic shock, cardiac arrest, emergency revascularisation, ventricular arrhythmia requiring intervention, high-degree atrioventricular block needing intervention or death (unless clearly non-cardiac).

The Abbott ARCHITECT hs-cTnI assay has a limit of detection of 1.9 ng/L, and 99th percentile upper-reference-limits (URL) of 16 ng/L for Females and 34 ng/L for Males and an overall URL of 26 ng/L.

A priori we aimed to:

1. Identify an hs-cTnI threshold for use with a single troponin measure below which <1% of patients had a 30-d MACE,
2. Identify a group of low-risk patients where a second troponin measurement could be performed in the community. By consensus this group was to have approximately $\leq 5\%$ 30-d MACE,
3. Determine a minimum time threshold from symptom onset for early presenters before which required an ongoing observation period and serial cTn measurements,
4. Specify a change in troponin concentration threshold which would trigger a review by a Cardiologist in patients receiving a next-day community troponin measurement, and
5. Design the pathway to reduce duplication of assessment of patients by ED and Cardiology doctors.

We used a process of iterating troponin thresholds to determine thresholds which produced the necessary metrics.

Preference was given to using the pre-existing troponin threshold of 5 ng/L for single sample rule-out (aim 1) as this was already in use and has been well validated internationally (5,6). To aid clinical acceptability we determined to utilise one or more of the risk thresholds for EDACS already in use at Christchurch Hospital, namely EDACS <16 for low-risk, 16-20 for intermediate risk and ≥ 21 for high-risk (5). A consensus decision was made *a priori* that evidence of new ischaemia on an electrocardiogram would remain being defined as a high-risk feature.

Since staff members were unable to meet face-to-face except for direct patient care (during the pandemic lockdown), iterative changes to the pathway format were achieved using consensus achieved via successive videoconference meetings.

Pathway evaluation

To assess pathway performance we retrospectively measured for three months prior to implementation of the change of practice and for three months following the implementation of the COVID-ADP the numbers of patients who had one or serial troponin tests within the ED, the numbers of patients admitted to hospital, the diagnoses of admitted patients (ICD10 codes), the numbers of patients discharged from ED, the lengths of stay of patients in the ED, the numbers of patients receiving next-day community troponin tests, and the repeat presentations to ED of all patients. The pathway was

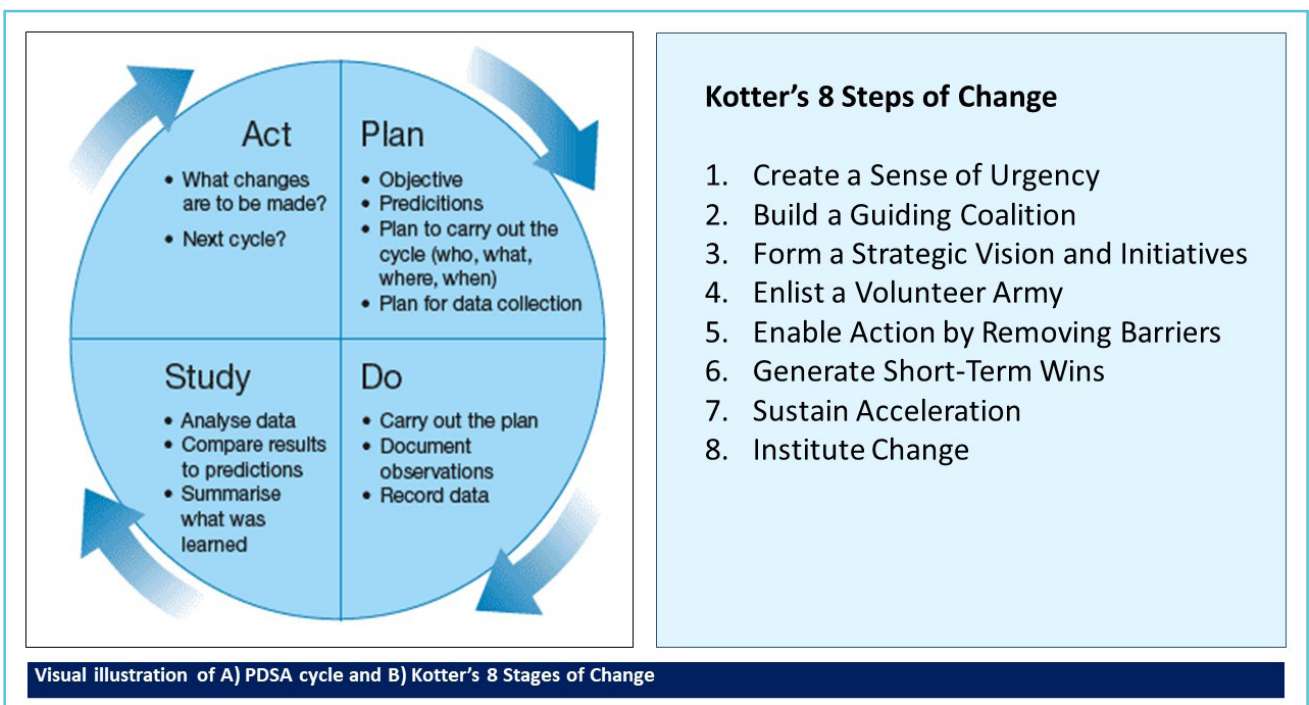
implemented on 6 May 2020. We compared the performance of the pathways from 6 February 2020 to 5 May 2020 (EDACS-ADP) and from 6 May 2020 to 6 August 2020 (COVID ADP). We excluded from the analysis all admitted patients with a myocardial infarction.

Our principal outcomes were length of stay, proportions of patients discharged from the ED, proportions of patients with single and serial troponin tests in the ED, proportions of patients admitted with an ultimate diagnosis of Unspecified or Other chest pain (ICD10 codes R07.3 and R07.4).

New Zealand has four COVID-19 alert levels (<https://covid19.govt.nz/alert-system/about-the-alert-system/> - last accessed 23 Nov 2020).

In levels 3 and 4, people are instructed to stay at home in their bubble other than for essential personal travel. Healthcare services are to use virtual, non-contact consultations where possible.

Figure 1 Change management process based on the Institute for Healthcare Improvement's PDSA Cycle and Kotter's 8 stages of change (11,12)



Supplementary Figure 1 Stakeholders and stakeholder groups involved

Emergency Department	Clinical staff, Clinical and Nursing Director, Pathway Developer, Nurse Educators, Research Nurses, phlebotomists, ward clerks Dr Martin Than Dr Jacques Loubser Dr James Weaver Tracey Williams Polly Grainger Kay Ratahi	Emergency Medicine Physician, Project Lead Emergency Medicine Physician, ED Co-lead Clinical IT Lead Clinical Nurse Specialist, Cardiology portfolio ED Pathways and Forms Specialist ED Supplies Specialist
Laboratory	A/Prof Chris Florkowski Vanessa Buchan	Clinical Chemist, Canterbury Health Laboratories Operations Manager, Canterbury Health Laboratories
Community Laboratory	Liaison via Vanessa Buchan through Service Level Alliance	Southern Community Laboratories
Cardiology Department	Dr Sally Aldous Dr John Lainchbury Dr Phil Adamson Dr Alison Nankivell Dr Thomas Clendon Margaret Cumming Rob Hallinan Chest Pain Unit nursing staff	Cardiologist Cardiologist Cardiologist Advanced Trainee, Cardiology Advanced Trainee, Cardiology Cardiology Charge Nurse Manager Cardiology Service Manager
Primary Care	Dr Andrew Meads Debbie Krute Cathy Cooper	Clinical Director, Primary Care Acute Demand Service Nurse Leader, Primary Care Acute Demand Service Nurse Leader, Primary Care Acute Demand Service
Research – Development of background dataset	<u>Christchurch Heart Institute</u> Prof Chris Frampton Prof A Mark Richards Prof Richard Troughton Lorraine Skelton <u>ED Science Group</u> Dr Joanna Young Antony Watson Felicity Turner Alieke Dierckx	Biochemist Cardiologist Cardiologist Nurse Manager Data Collection Data Collection Data Collection Project Administrator
Data Science	Prof John Pickering <u>Canterbury District Health Board Data Warehouse (Decision Support)</u> Scott Maxwell Melanie Browne Lesley Hamel Soledad Labbe-Hubbard Valentyna Sylevych	Acute Care Research Fellow Data Warehouse Manager Information Analyst Project Specialist Project Specialist Performance Reporting Analyst
Management	Carolyn Gullery Dr Greg Hamilton Harue Akimoto	General Manager Planning & Funding and Decision Support Change Transition Manager, Planning & Funding Management Accountant
Exercise Stress Test / ECG Departments	ECG Technicians Nursing staff	

At level four all businesses are closed except for essential businesses and all gatherings are cancelled and public venues closed.

All of New Zealand entered alert level 3 at 13:30 on 23 March 2020 and level 4 at midnight 25 March 2020. A state of emergency was declared on 24 March 2020. At midnight on 27 April New Zealand moved from alert level 4 to level 3 and from midnight of 13 May to level 2 and the state of emergency expired. Level 2 allows normal gatherings with <100 people.

All confidence intervals are 95% confidence intervals calculated using bootstrapping. The statistical calculations were made in R version 3.5 (10).

Change management process

The management of change was based on the principles set out by the well-established Plan-Do-Study-Act (PDSA) cycle model for improvement from the Institute for Healthcare Improvement (IHI), Figure 1 (11). It is a simple yet powerful tool for accelerating quality improvement. Once a team has set an aim, established its membership, and developed measures to determine whether a change leads to an improvement, then testing the change in the real work setting is possible.

The PDSA cycle is shorthand for testing a change—by planning it, trying it, observing the results, and acting on what is learned. We also used the principles based upon the 8-step process for leading change to plan the change management process (12). Many stakeholder relationships had already been established from previous ‘chest-pain’ pathway initiatives.

A revised stakeholder analysis was conducted (Supplementary Figure 1). After the decision logic for the new pathway was established and before full deployment occurred there was limited management of a number of cases by a small ‘super-user’ clinician group which helped

to establish the practicality of the new approach and potential problems. For the first six weeks after deployment there were targeted stakeholder discussions, approximately weekly, to troubleshoot individual patient cases and/or clinician behaviours, after which a more ad hoc review process was adopted. All cases where a patient did not attend planned community follow-up troponin were reviewed by a Cardiology and/or Emergency Medicine Specialist and patient management decisions made according to their clinical judgement.

RESULTS

COVID-ADP development

There were 2416 subjects in the dataset used to develop the COVID-19 pathway of whom 38.2% were female and the mean age was 63 years (Table 1). Of these patients 452 (18.7%) had a MACE within 30d.

Amongst patients with EDACS < 16 and no new ischaemia on ECG there were 697 28.8% (95%CI: 27.1% to 30.6%) of all patients) patients with hs-cTnI <5 ng/L on first blood sampling (0h) with three (0.4% (0% to 1%)) 30d MACE. All were NSTEMI at initial hospital visit. The two-hour hs-cTnI concentrations for these three patients were 6, 17, and 225 ng/L all presenting ≥5h post-symptom onset. The overall strategy EDACS <16, no new ischaemia on ECG and 0h hs-cTnI <5 had a predicted sensitivity of 99.3% (95%CI: 98.1% to 99.8%) and Negative Predictive Value (NPV) or 99.6% (98.7% to 99.9%) (Aim 1).

Another 138 (5.7% (4.8% to 6.7%)) patients had a 0h hs-cTnI 5-14 ng/L with a three (2.2% (0 to 4.8%)) 30d MACE (Aim 2). The 30d MACE rate amongst the remaining 100 (4.1% (3.4% to 4.9%)) of all patients) was 51% (41.3% to 61.0%). We determined patients in this group were to have an additional 2h troponin measurement and be assessed by Cardiology.

Demographic	Value
Age, years	63 +/- 13
Females	923 (38.2%)
Ethnicity	
New Zealand Māori	85 (3.5%)
Pacific	21 (0.9%)
New Zealand European	1745 (72.2%)
Other	268 (11.1%)
Unknown/Refuse to answer/Missing	297 (12.3%)
Diastolic Blood Pressure (mmHg)	81 +/- 14
Systolic Blood Pressure (mmHg)	147 +/- 26
Respiratory rate (breaths/minute)	17.2 +/- 3.5
O2 saturation (%)	97.3 +/- 1.9
Creatinine (umol/L)	93 +/- 30
Potassium (mmol/L)	4.1 +/- 0.5
White Cell Count (G/L)	7.8 +/- 2.6
Kilip class	
0	615 (25.6%)
I	1732 (72.0%)
II	55 (2.3%)
III	2 (0.1%)
Family history of Cardiovascular disease	1311 (54.3%)
History of Coronary artery disease	852 (35.3%)
History of Heart Failure	152 (6.3%)

History of Diabetes Mellitus	361 (15.0%)
History of Hypertension	1329 (55.0%)
History of Smoking	367 (15.2%)
History of Dyslipidaemia	1342 (55.6%)
Diaphoresis	1087 (45.0%)
Pain on Palpation	177 (7.3%)
Pleuritic pain	368 (15.2%)
Pain radiates to Arm, Neck or Jaw	1161 (48.1%)

Amongst patient with EDACS ≥ 16 or new-ischaemia on ECG there were 613 (25.4% of all patients) with 0h hs-cTnI < 5 ng/L of whom 6 (1% (0.3% to 1.8%)) had a 30d MACE (5 index NSTEMI, 1 NSTEMI within subsequent 30d). The overall sensitivity for this sub-group was 98.7% (95%CI: 97.1% to 99.4%) and Negative Predictive Value (NPV) or 99.0% (97.9% to 99.6%). It was determined that these patients were to be discharged from ED with next-day follow-up troponin. Another 341 (21.1%) of patients had a 0h hs-cTnI 5-14 ng/L with a 8.2% (n=28) 30d MACE rate. This was considered too high for them to be all followed the next day, so they were further stratified by time from symptom onset < 3 h or > 3 h (Aim 3). In the ≤ 3 h cohort there were 95 patients with a 15.8% (8.6% to 23.0%) 30d MACE rate. We determined patients in this group were to have an additional 2h troponin measurement and be assessed by Cardiology. There were 246 with time from symptom onset > 3 h with a 5.3% (2.7% to 8.2%) MACE rate. It was determined that these patients were to be discharged from ED with next-day follow-up troponin.

The 30d MACE rate among the remaining 528 (21.8% (20.2% to 23.5%)) patients (i.e. those with 0h hs-cTnI > 14 ng/L) was 68.4% (64.4% to 72.2%). It was determined that these patients

were to be admitted to the Cardiology ward where they were to receive further troponin testing.

The change from using three EDACS strata (≤ 16 , 16-20, ≥ 21 ; Figure 2) to two EDACS strata (≤ 16 , > 16 ; Figure 2) reduce the need for both cardiology and emergency department teams to assess the same patients (compare Figures 2 and 3) (Aim 5). This resulted in predicted change in duplicate clinical assessment from 20% to 4%. In our development dataset 935 (38.7%) had EDACS < 16 , therefore in the COVID-ADP would be expected to be evaluated by ED physicians, whereas (61.3%) would be expected to be evaluated by Cardiology.

Overall 28.8% of patients could be discharged from the ED without follow-up on the basis of a single hs-cTnI with a 30d MACE rate of 0.4%. A further 41.2% could be discharged from the ED with next-day follow-up with a 4.9% 30d MACE rate. The final pathway is shown in figure 3. This meant that $\sim 70\%$ of patients would not require measurement of a second troponin measurement while in hospital.

The EDACS-ADP for patients having a next-day community test used the sex-specific URL or significant rise as a trigger for cardiology review. For the COVID-ADP we used the results of patients

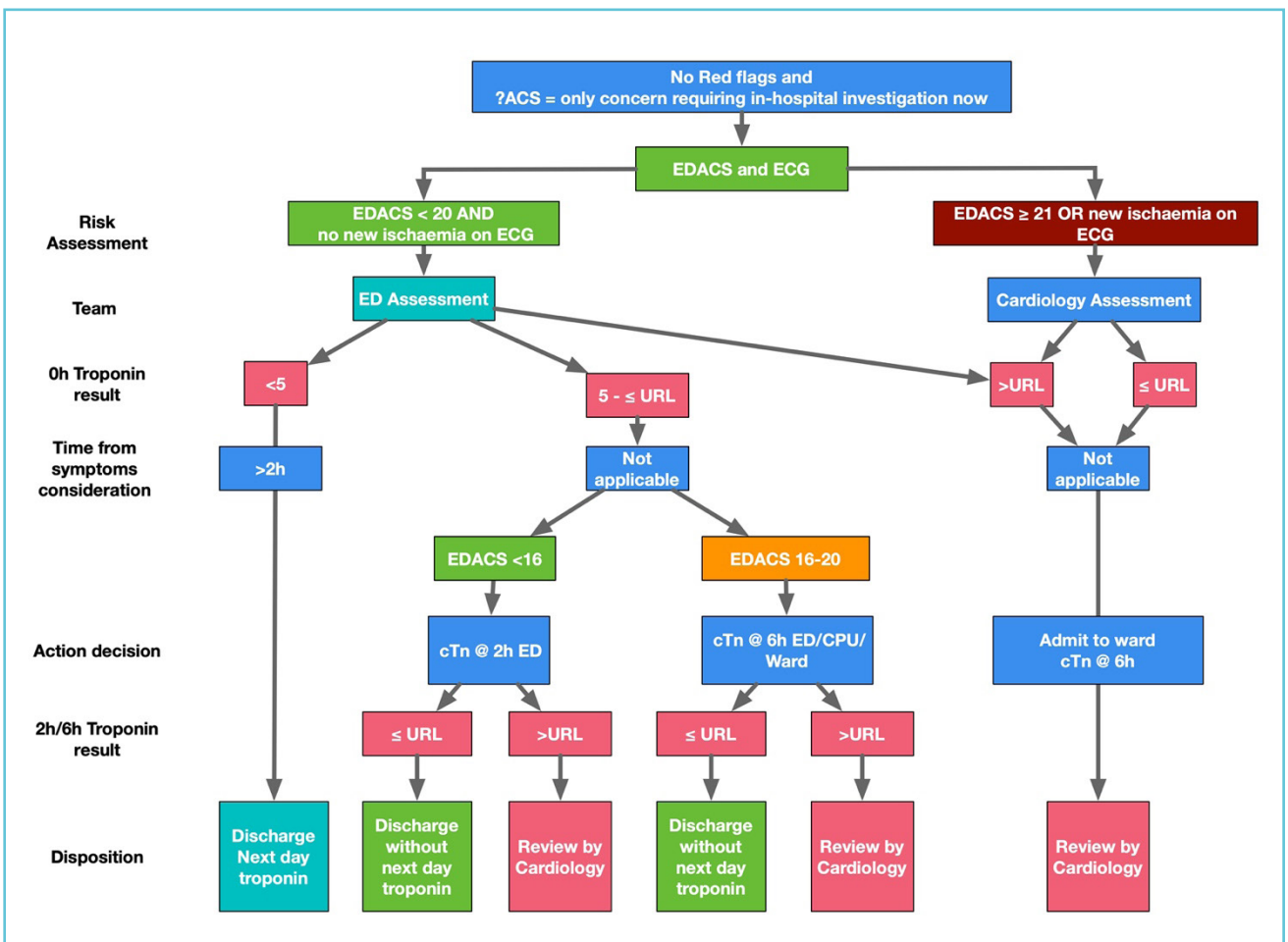
who had had a diagnosis of a MACE and serial troponin measurements with the first being 5-14 ng/L to determine a change in troponin concentration of ≥ 4 ng/L at which to trigger a review by Cardiology (Aim 4).

COVID-ADP implementation and performance

In the three months prior to COVID-ADP implementation 1,073 people presented with a primary complaint of Chest Pain compared with 1,343 post COVID-ADP implementation. The primary reason for the 25.2% increase post-implementation is that, during the period from

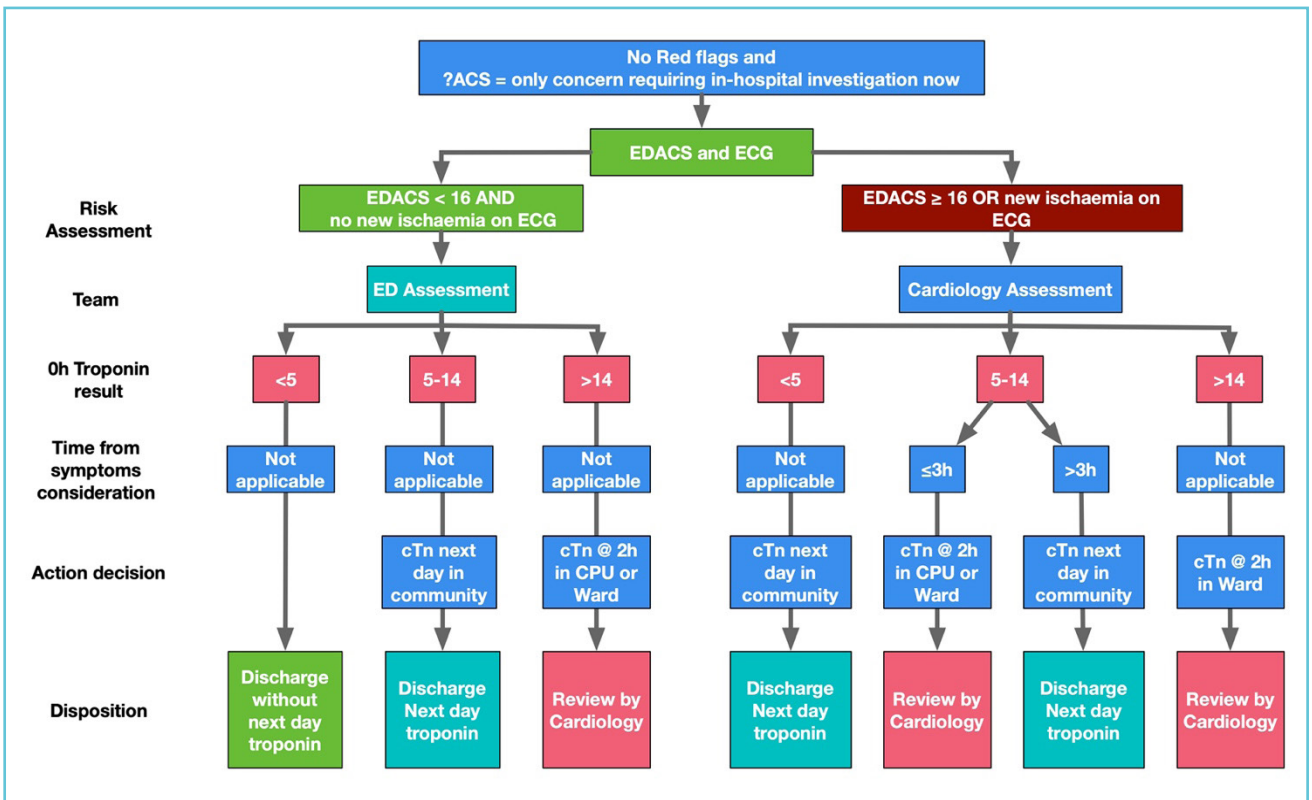
23 March to 13 May, New Zealand was under heavy COVID-19 lock-down restrictions. There could also be a seasonal effect. Despite this increase in Chest Pain presentations post-implementation there was an 8% reduction in the numbers of patients admitted who were admitted and ultimately diagnosed with Unspecified or Other chest pain. We accounted for the post-implementation increase in Chest Pain presentations by using the rate of Chest Pain presentations as a denominator. Consequently, the rate of Unspecified or Other chest pain admissions to Chest Pain presentations decreased from

Figure 2 The EDACS-ADP. The 2h cTn is 2h after the first blood draw for the 0h cTn. The 6h cTn is at least 6h after symptom onset or worst symptom if later



ACS: Acute Coronary Syndrome. cTn: cardiac Troponin. URL: Upper Reference Limit (Sex specific for hs-cTn; 16ng/L for females, 34ng/L for males). ECG: Electrocardiogram. EDACS: Emergency Department Assessment of Chest pain Score. CPU: Chest Pain Unit.

Figure 3 The COVID-ADP



ECG: Electrocardiogram. EDACS: Emergency Department Assessment of Chest pain Score.

12.3% to 9.3% representing an estimated 24.3% reduction in admissions with Unspecified or Other chest pain (non-cardiac).

In the target group of Chest Pain presenters discharged from the ED there was an immediate increase in the number with only a single troponin test in the ED, Figure 4. In the 3 months prior to the implementation of the COVID-ADP (EDACS-ADP era) 579 had a single troponin in the ED, in the 3 months with the COVID-ADP 954 had a single troponin representing a 64.7% (~1.6 fold) increase. To account for the reduced presentations during lockdown we looked at the proportion of patients with two troponin tests in the ED because a decrease in this proportion represents a decrease in the number of patients requiring further evaluation beyond the first blood test. Figure 5 illustrates that there was an immediate dramatic reduction, from a weekly

mean of 29.6% to a weekly mean of 11.7%, representing a 60% reduction in patients requiring 'two-troponin' evaluation for possible ACS.

The median (lower-quartile – upper-quartile) length of ED stay (LOS) of all patients with a troponin test in the ED reduced from 3.8h (2.8h – 4.9h) to 3.4h (2.6h – 4.6h). A Mann-Whitney test of length of stay (LOS) demonstrated that the before and after implementation distribution of lengths of stay are not the same ($p < 0.0001$). In the target group of those discharged from ED the median LOS prior to implementation was 3.7h (2.7h - 4.6h) compared to the post implementation LOS of 3.1h (2.4h – 4.1h). The mean LOS was 3.9h for the current pathway and 3.4h for the COVID-ADP suggesting an average time saving of 30 minutes per patient. The proportion of the target group patients discharged from ED within 2h increased post-implementation from

5.6% to 8.1%, a 44.6% increase. The proportion discharged from ED within 3h increased post-implementation from 32.7% to 44.2%, a 35.2% increase.

There were two patients who had an MI within 7 days of first presentation who had been discharged from the ED. One of these had self-discharged from the ED against medical advice. The other patient's initial hs-cTnI was less than the LoD. While this presentation was after implementation of the COVID-ADP they were equally eligible for early discharge under the former pathway. They presented 5 days later with more chest pain and an initial troponin concentration of 15 ng/L which rose to 21 ng/L.

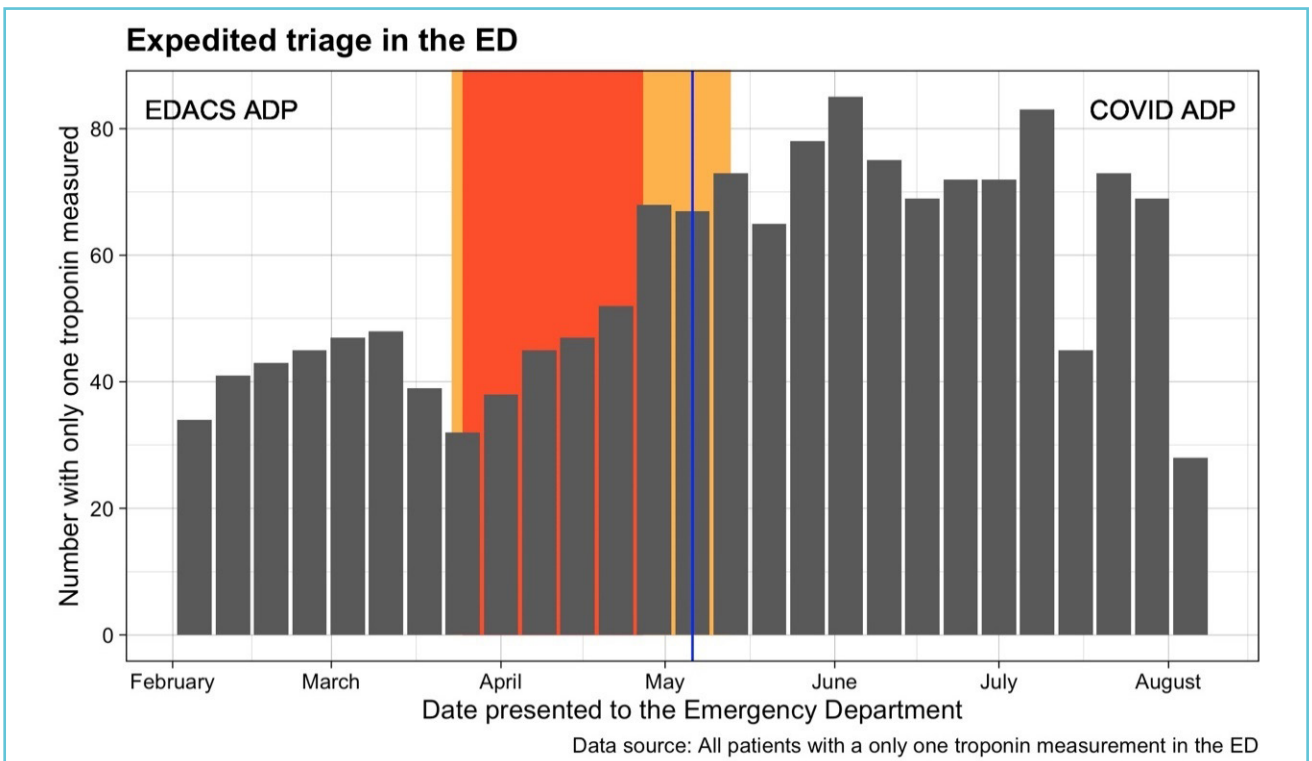
In 2019 there were 10,548 presentations to the ED with at least one troponin measurement. Of these 1,249 (11.8%) were admitted to hospital

and ultimately discharged after a mean 28h stay with a diagnosis of Unspecified or Other chest pain. If we apply our finding of a 24% reduction in admission of this patient group this would mean an annual 300 fewer patients spending a day in hospital. This would be a cost saving of NZ\$390,000. The 30-minute average reduction of time spent in ED translates to 4852 fewer hours of patient time in the ED per annum and an estimated saving of NZ\$146,000 bringing the total annual saving to the health system to over NZ\$0.5Million.

DISCUSSION

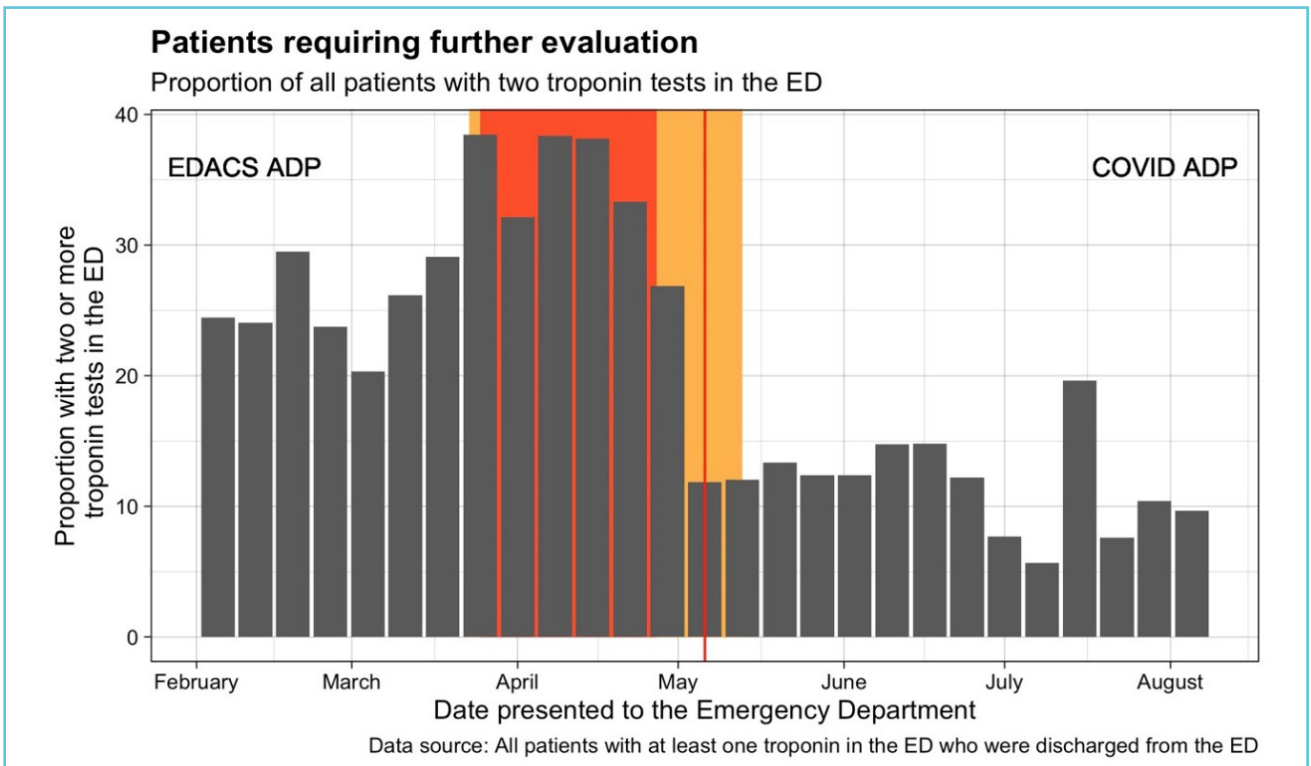
We have demonstrated that it was possible, in real life care, to make rapid changes to an accelerated diagnostic pathway which made an immediate and meaningful impact to patient care. We

Figure 4 More presenters had only one troponin measurement with the COVID-ADP compared to the EDACS ADP



Blue line: 6 May, date of implementation of COVID-ADP.
 Orange: New Zealand pandemic alert level 3; Red: Alert level 4.

Figure 5 Fewer of the presenters who were discharged home from the ED needed evaluation with a second troponin measurement with the COVID-ADP compared to the EDACS-ADP



Blue line: 6 May, date of implementation of COVID-ADP.
 Orange: New Zealand pandemic alert level 3; Red: Alert level 4.

were able to markedly reduce the use of repeat troponin testing in hospital which led to reduced time in ED and reduced admissions for patients without cardiac chest pain. This was important because we were able to reduce the potential risk of cross-infectivity and hospital resource burden for this common patient group.

There are a number of key take-aways from this project that inform rapid change management in general. *Firstly*, the objectives of the project (reduced length of stay and admission rates) were clearly established from the beginning by consensus. *Secondly*, it was agreed that reduction of serial testing would be the optimal way to achieve these objectives. *Thirdly*, we had access to high quality data enabling us to predict downstream event rates for the patients and so establish an

evidence base for proposed changes. *Fourthly*, we used wide cross-stakeholder consensus to agree specified actions for patients within different risk strata and then worked backwards using the data to determine how to identify which patients fitted within each risk group. *Fifthly*, we placed a high level of importance upon effective change management processes. *Sixthly*, the time invested in the preceding years to build meaningful and agile stakeholder relationships made possible the expedited change management processes in response to the pandemic situation.

Finally, video conferencing enabled robust discussion amongst multiple stakeholders when face to face meetings were not possible. Notably, by meeting remotely, it was possible to have a much more frequent meeting schedule than had

been previously possible when requiring coordination of schedule for face-to-face meetings. This, in itself, allowed an acceleration of previous decision-making and change-management processes.

This project has a number of strengths. Most importantly perhaps, our project describes what actually happened to patient care. We evaluated this project using data collected prospectively and routinely as part of healthcare delivery. Because we were able to base this change on extant well researched data and have shown it to be safe and effective, we believe that this project and its onward monitoring is both sustainable and transferable to other centres. Additionally, although not an original objective, the project reduced costs for the healthcare system.

There are some limitations. Firstly, the use of routinely collected data to evaluate the change required us to infer the group being assessed for possible myocardial infarction based on the measurement of troponin. Therefore, we may be overestimating the numbers of patients actually investigated for possible myocardial infarction. The same inference was used for both the time period before and after the COVID-ADP implementation, thus any overestimate will not affect our conclusions of a successful change of practice. Secondly, while the data sets used to derive the pathway have been well described in multiple publications in the literature and have only limited exclusions, they are nevertheless not exactly representative of all patients being evaluated for possible myocardial infarction.

CONCLUSION

Strong stakeholder relationships and change management processes, video conferencing and access to high quality data allowed rapid and agile re-design and implementation of a chest pain assessment pathway without face-to-face

contact. Significant meaningful impact was demonstrated resulting in the pathway being permanently adopted despite the relaxation of the easing of the alert levels and cessation of the need for an immediate response to the pandemic.



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Avoiding insufficient therapies and overdosing with co-reporting eGFRs (estimated glomerular filtration rate) for personalized drug therapy and improved outcomes – a simulation of the financial benefits

Adrian Hoenle^{1,2,3}, Karin Johanna Haase⁴, Sebastian Maus⁵,
Manfred Hofmann⁶, Matthias Orth¹

¹ Vinzenz von Paul Kliniken gGmbH, Institut für Laboratoriumsmedizin, Stuttgart, Germany

² Medizinische Fakultät Mannheim, Ruprecht Karls Universität, Mannheim, Germany

³ Vinzenz von Paul Kliniken gGmbH, HNO-Klinik, Stuttgart, Germany

⁴ Vinzenz von Paul Kliniken gGmbH, Apotheke, Stuttgart, Germany

⁵ Vinzenz von Paul Kliniken gGmbH, Klinik für Nephrologie, Stuttgart, Germany

⁶ Vinzenz von Paul Kliniken gGmbH, Klinik für Gynäkologie und Geburtshilfe, Stuttgart, Germany

ARTICLE INFO

Corresponding author:

Priv.-Doz. Dr. med. Matthias Orth
Institut für Laboratoriumsmedizin
Vinzenz von Paul Kliniken gGmbH
Postfach 103163
DE-70027 Stuttgart
Germany
E-mail: matthias.orth@vinzenz.de

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Orcid ID:

orcid.org/0000-0003-2881-8384

ABSTRACT

Patients with impaired renal function are at high risk for morbidity and mortality. Chronic kidney disease (CKD) even in the early stages can be associated with significant side effects of drug therapy, longer length of stay, and high costs. Correct assessment of renal function in the hospital is important to detect CKD, to avoid further damage to the kidneys, and to optimize pharmacological therapy. Current protocols for renal function testing in drug dosing are only creatinine based, are not robust enough, and can wrongly classify certain patients.

Goal of our simulation study is to optimize noninvasive renal function estimates and to allow for optimal dosing of pharmacological treatment without further

renal damage. Co-reporting of creatinine- and of cystatin C-derived estimated glomerular filtration rates (eGFR) allows a personalized approach for patients with large discrepancies in eGFR and it enabled us in detecting patients at high risk for side effects due to incorrect drug dosing. This approach might be highly effective for patients as well as for clinicians. In addition, we simulated the efficiency by estimating savings for the hospital administration and the payor with a benefit cost ratio of 58 to 1.



INTRODUCTION

Renal function declines over time in a physiological fashion and an eGFR of 35 ml/min 1.73 m² surface area only can be physiologic in nonagenarians (1). However, for dosing of drugs which are cleared by the kidneys, drug approval regulatory offices ask for a normal renal function (i.e., an eGFR >60 ml/min) to allow a normal dosing scheme (2), some drugs may not be used in patients with severe CKD or even in moderate CKD. In addition, a reduced renal function can be present in patients of all ages, is mostly completely asymptomatic, and often not known by the patient. Reduced kidney function is seen in chronic diseases of the kidney but also in patients admitted to the hospital with acute kidney injury (AKI). Therefore, in many hospital patients, the situation can be complex and complicated by “acute on chronic kidney disease” as seen for example in patients with hypovolemia, acute cardiac insufficiency, or acute infection (3).

The GFR can be measured based on the clearance of exogenous filtration markers, but due to its impracticability for routine application as well as complex issues with biological variation (4-6), the eGFR is calculated based on the serum or plasma concentration of biomarkers such as creatinine, cystatin C or other biomarkers (7) in the combination of demographic

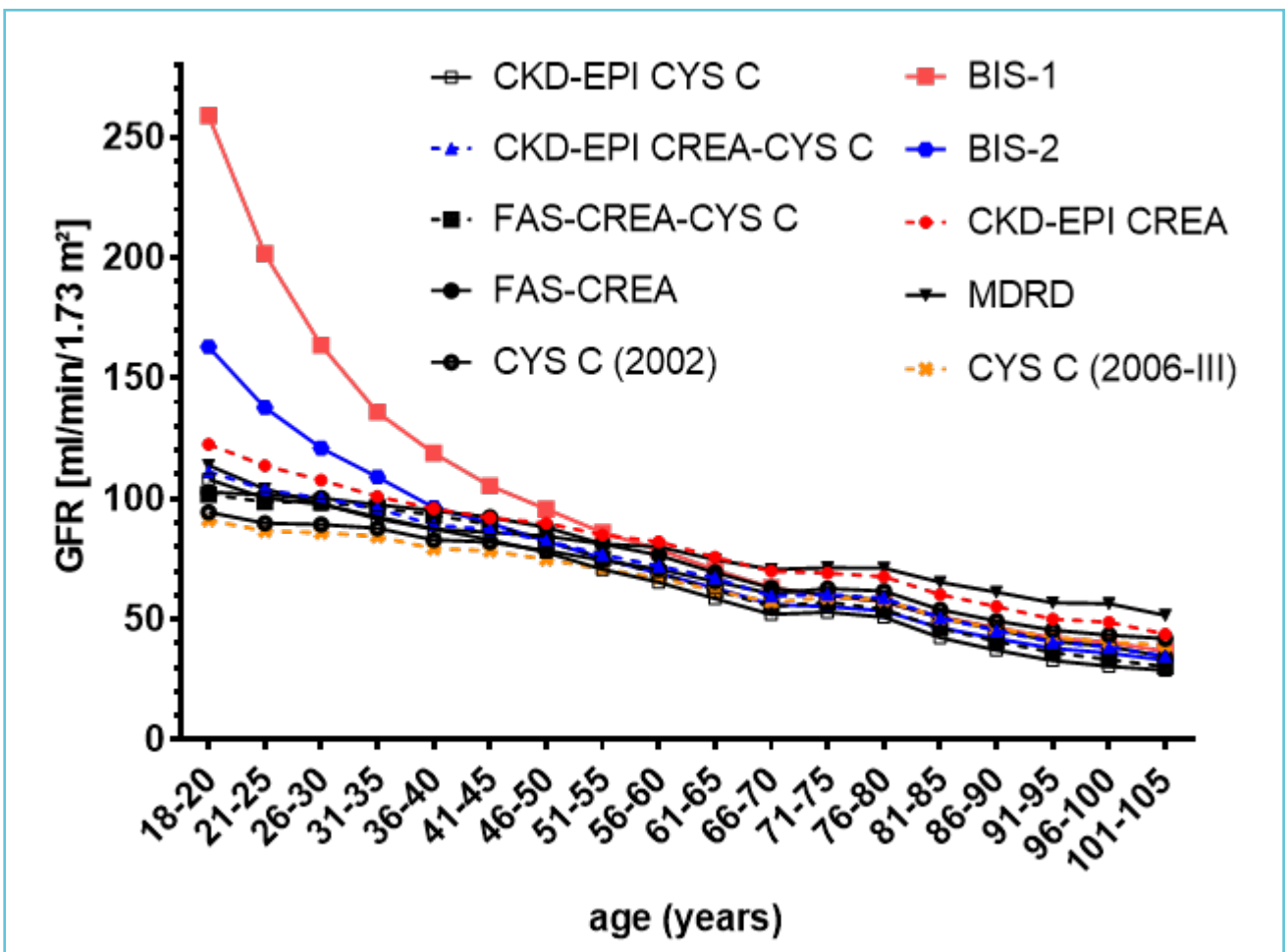
factors such as age, sex, and race. Several formulas are available for this calculation. The challenges with these formulas are several-fold: First, some of these formulas were derived from very selected populations (the formula used as standard for drug dosing, the creatinine-based Cockcroft-Gault equation, is based on 249 males only (8), and the Modification of Diet in Renal Disease (MDRD) equation is based on patients with renal disease only (9)). Like the newer Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula, these formulas are creatinine-based and are interfered by all factors affecting creatinine values such as age, body mass, drug intake, dietary protein intake, muscle mass, and ethnicity. Therefore, the application of a certain formula should not be transferred to a general population or to all hospital patients. Second, the formulas have been developed by optimizing the mean distance between the actual measured GFR (as determined by invasive methods) and the eGFR among all study subjects. This averaging does not exclude high and even exceedingly high differences to the real GFR in certain study subjects and patients, respectively (10). Third, the parameters used in these formulas must be highly standardized and after restandardization, formulas must be adjusted accordingly. It is a matter of discussion whether it is sufficient - e.g., after the restandardization of creatinine testing with SRM967 (11) - to adjust the eGFR formulas by a fixed factor or whether new studies employing the “gold standard” are needed. These issues are peculiar for the Cockcroft-Gault equation since the (non-standardized) creatinine method used in the development of the Cockcroft-Gault equation is no longer in use and samples from the study are not available to evaluate how the results might compare to the current standardized creatinine values and there is no version of the Cockcroft-Gault equation for use with standardized creatinine results, unlike to the

MDRD formula (12). While in many patients, there are little differences between eGFR estimations obtained by different formulas, in some patients and in dosing of some drugs with a narrow therapeutic range, the Cockcroft-Gault equation was less reliable in assessing the risk of kidney damage (13). However, many drug approval regulatory offices still oblige the use of the Cockcroft-Gault equation, with no comments on the creatinine standardization having occurred in the meantime.

Any approach to optimize a single eGFR formula suffers from mutual exclusive adjustments

either in relation to the GFR range or to the patients' age (14). Finally, most of the studies used for the development of these calculation were performed in patients of 65 years of age or younger. This patient group, however, is not representative of the patients treated in the hospital and the applicability of these formulas for the general hospital population is questionable (15). When different calculations are used to demonstrate the age-dependent decline in eGFR, all formulas can detect the decline by age but the differences among these formulas, even when only comparing the means, are huge (Figure 1).

Figure 1 Mean age-dependent decline of eGFR calculated by different estimations. Total number of patients n=63,383*



* For details of the formulae see CKD EPI CYS (21), FAS-CREA-CYS (26), BIS-I and II (40).

While creatinine is established for many decades (16), cystatin C has been used widely only after the standardization with ERM-DA471/IFCC in 2010 (17). Cystatin C is regarded to be more accurate than creatinine, with a reciprocal function between cystatin C and GFR. Some non-renal conditions such as high doses of glucocorticoids (18) or inflammation (i.e., increased C-reactive protein) have been shown to affect cystatin C concentrations (19). Effects of certain thyroid conditions on cystatin C concentrations were reported but could not be verified by other studies (20).

Aim of our study was to assess the feasibility of parallel reporting GFR estimates based on two independent biomarkers (creatinine and cystatin C) with automatic alerts in patients with significant discrepancies between both biomarkers followed by an individually-tailored approach employing a multidisciplinary team to adjust the drug doses in patients with certain chemotherapies (proof of principle). The study also included a simulation of the calculated monetary savings.

PATIENTS AND METHODS

In our hospital, cystatin C tests can be ordered for all patients. For eGFR requests in patients of 75 years of age and older, cystatin C testing is added automatically since the MDRD formula is less adequate in older persons.

The approach and the estimated benefits of dual reporting of creatinine and cystatin C derived eGFR was retrospectively validated in our chemotherapy patient cohort from 2018. Therefore, all patients from January 1, 2018 to December 31, 2018 treated at the Marienhospital Stuttgart which had requests for eGFR were included in the simulation.

Patients receiving certain chemotherapies (containing trastuzumab, cisplatin, carboplatin, oxaliplatin, or nivolumab) were identified according

to their prescriptions by the staff of the hospital pharmacy. We used the total mass (in grams) of the chemotherapy applied since the dosing in patients is rather individual during the repetitive administration (affected by weight, renal function, results of the blood count, number of repetitions). For the simulation, the average dose of a single drug was estimated by the total mass of the respective drug divided by the total number of patients receiving this drug. Drug prices were obtained by the "Rote Liste".

BIOMARKERS

Serum cystatin C (calibrated to ERM-DA471/IFCC, turbidimetric method), creatinine (Jaffé method), albumin and urea were measured on Architect ci8200 (Abbott GmbH, Wiesbaden, Germany) using Abbott reagents and Bio-Rad controls (Bio-Rad, München, Germany).

Biomarker data and demographics were captured from the laboratory information system (LIS) (LabCentre, i-Solutions, Bochum, Germany). Calculations and simulations were performed using IBM SPSS Statistics, Version 24 (IBM Corp., Armonk, N.Y., USA). To estimate the financial benefit, it was assumed that the renal function of patients receiving chemotherapy is comparable to the overall renal function of our hospital patients.

AUTOMATIC ALERTS

EGFR was calculated from cystatin C results by the CKD-EPI formula (21) and from creatinine, urea, and albumin by the modified MDRD formula, both without race adjustments in our predominantly Caucasian patients (9) (22). Patients were classified according to their eGFRs to the respective CKD stages. Patients with significant discrepant classification only according to the cystatin C- and creatinine-derived eGFR (such as CKD3a by creatinine-derived GFR and CKD4 by cystatin C-derived eGFR) receive an automatic

alert in the LIS. This alert triggers a personalized, individual adjustment of chemotherapy dosing by the pharmacists, the clinical pathologists and the nephrologists. Since the eGFR is mandatory in all patients receiving these chemotherapies, the pervasion of this personalized approach was complete.

RESULTS

The prevalence of impaired renal function in inpatients and patients treated as outpatients at a hospital is remarkably high: In our institution with about 35,000 inpatients per year and about 200,000 outpatients, ~33% have severely impaired renal function (CKD stages 3b, 4 and 5) (Figure 2).

The focus of the co-reporting approach is on patients with impaired renal function (CDK stage

3a and 3b). For patients with mildly decreased renal function (CKD 1 and 2) little challenges are expected by dosing drugs which are (partially) cleared by the kidneys. Patients with CKD stage 4 or 5 are found rather rarely and essentially all these patients are already aware about their severely impaired renal function.

32.9% of all patients in our hospital are in CKD stages 3A and 3B and of these, 18.6% have a significant (i.e., >15 ml/min) discrepancy between creatinine- and cystatin C-based eGFRs. This corresponds to 6.2% of the whole hospital population. In general, creatinine-based eGFRs overestimate the GFR compared to cystatin C-based GFRs (Figure 3). The difference between both GFR estimates in patients with CKD stages 3A and 3B was +4.5 mL/min (95% range -18.3 - +22.3 mL/min).

Figure 2 Number of patients according to the CKD stages in 2018.
Total number of patients n=63,383

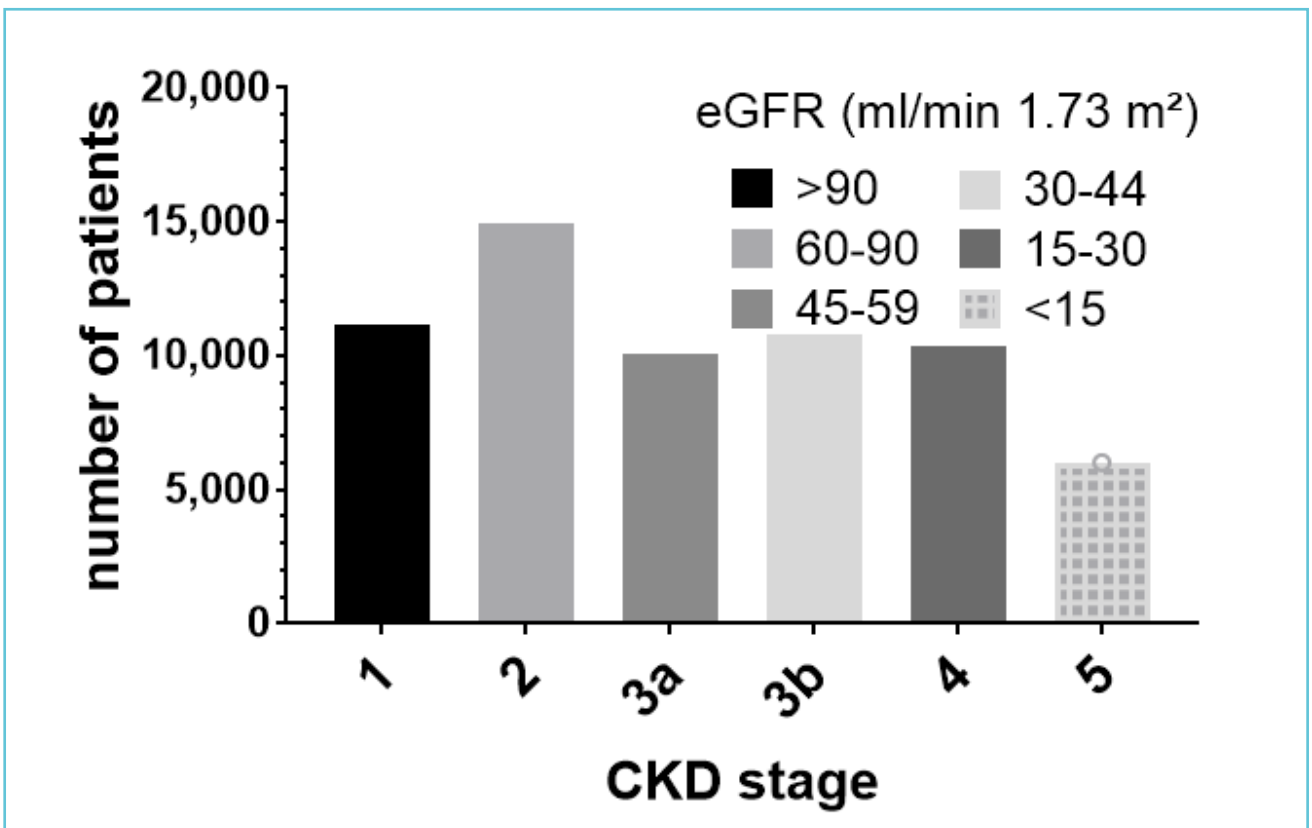
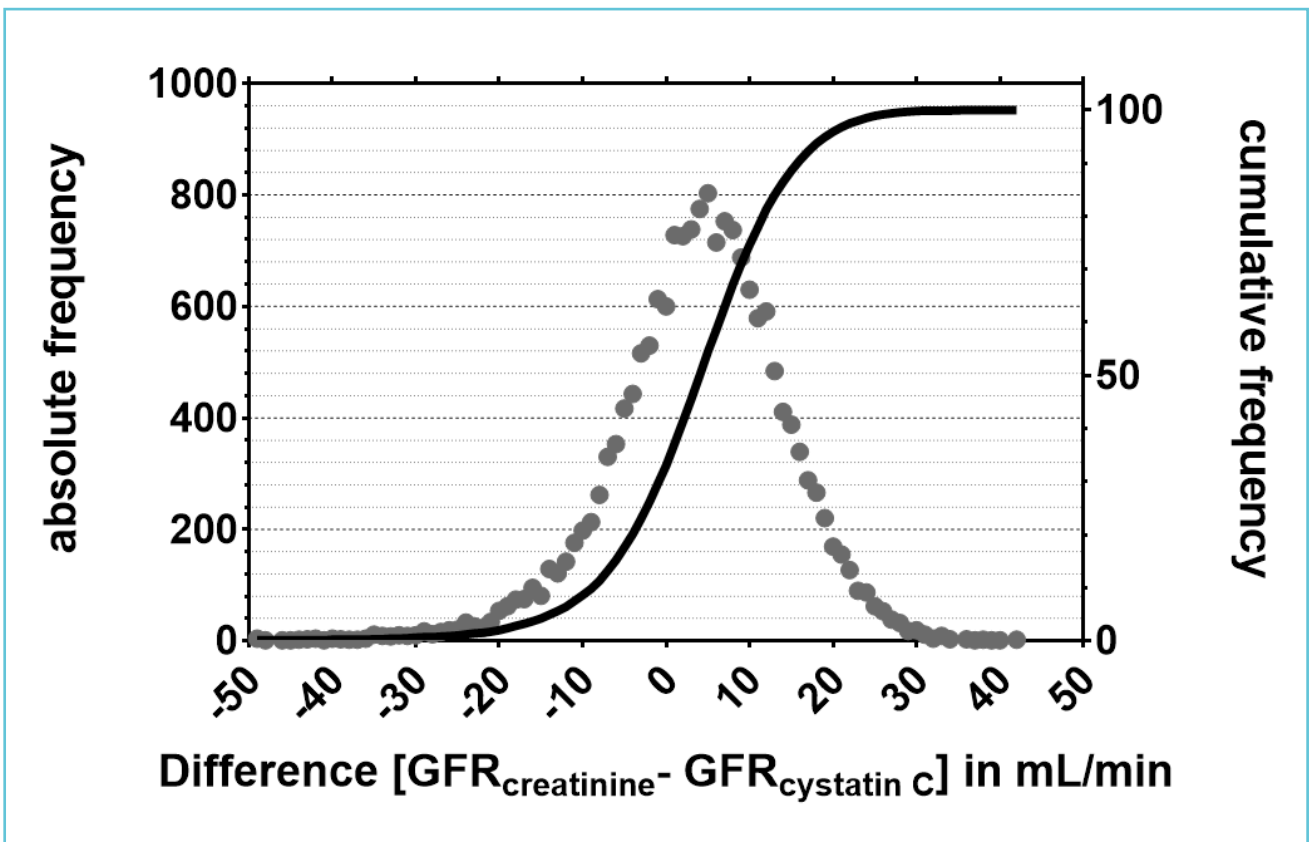


Figure 3 Individual difference and cumulative frequency between creatinine- and cystatin C-derived eGFR in patients with CKD stages 3A and 3B (as determined by creatinine-derived eGFR)



When these numbers are calculated in patients receiving chemotherapy in 2018, 193 of the total 606 patients were in CKD stages 3A and 3B and consequently 38 of these patients were at risk and could benefit from the dual reporting approach which avoids overdosing based on creatinine-based eGFRs only.

The monetary benefits of the adapted dosing scheme in 2018 were estimated by the total costs of the respective chemotherapies and the assumption, that co-reporting will lead to an overall lower dosage in 6.2% of patients. This value was estimated from the percentage of misclassification and the effects of the misclassification on the dosing of the chemotherapies of selected patients (n=20). The calculated monetary benefits are summarized in Figure 4. In total, the

savings would account to 105,000€ in direct drug costs alone in 2018.

DISCUSSION

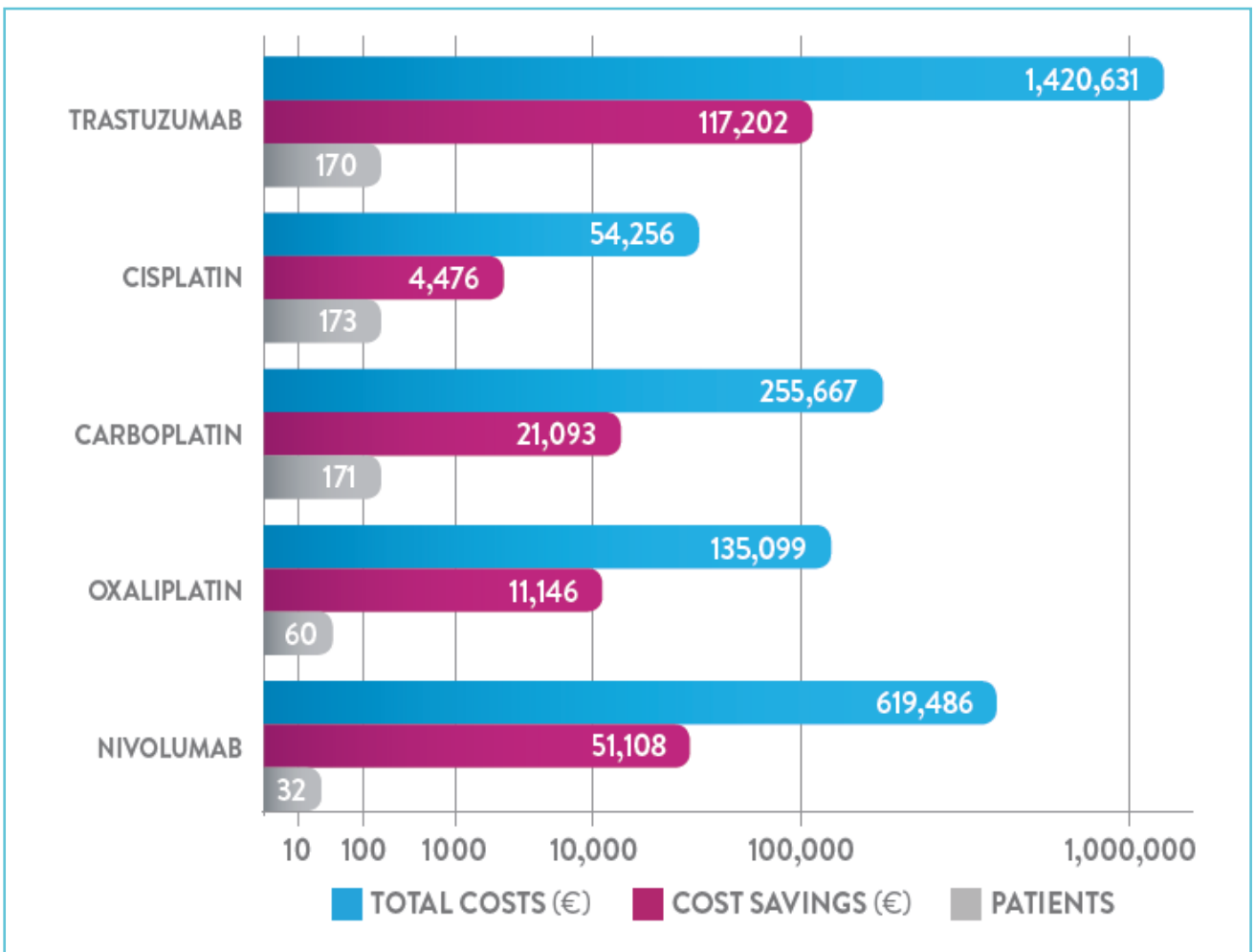
For drugs with a narrow therapeutic range like the chemotherapeutic drugs widely used, eGFR calculation can over- or underestimate renal function in patients with mild impaired renal function. The strong dependence on a single serum creatinine concentration in conventional dosing schemes poses several challenges such as significant (systematic) deviation from the true GFR (22, 23), significant biological variation (4), and unsuited dosing recommendation by the manufacturer of the drugs. In our simulations, parallel reporting of creatinine- and cystatin C-based eGFRs risk can mitigate false CKD

classification, and can improve accuracy of CKD staging and drug dosing for chemotherapeutic drugs as demonstrated in our simulation and applied as a routine approach in our hospital. According to our analysis for 2018, approximately 25% of the patients might benefit from this more accurate approach to determine GFR estimates as shown by the percentage of patients receiving altered dosing by an individualized approach.

The obvious benefits of this improved dosing regimen can be several-fold. First, we estimate that 1 out of 12 patients receiving chemotherapy

will avoid potentially lethal side effects by an optimized dosing regimen. Second, patients are more likely to comply with their treatment regimen containing highly toxic drugs when they are confident with the individual, patient-tailored dosing. When patients experience severe nausea or prolonged myelosuppression, their quality of life becomes further compromised and hinders sustained compliance. It is conceivable that the number of patients experiencing side effects of chemotherapy is decreased with corrected CKD classification and chemotherapy dosing. This concerns both the well-being of

Figure 4 Simulation of monetary benefits of adjusting chemotherapies by the individualized approach triggered by co-reporting of eGFRs*



* Please note the logarithmic scale.

the patients as well as the optimization of the time of the care givers since they must care less about treating unwanted side effects of chemotherapy such as heart failure, neuropathy, and renal failure (24). However, the calculation of the frequencies as well as the (additional) financial benefits of avoiding these detrimental side effects were far beyond the scope of this study. Fourth, most chemotherapeutic drugs (and their metabolites) have a narrow therapeutic range only. When a tool such as the Cockcroft-Gault equation is used for drug dosing, an inaccurate dosing is expected to occur in a substantial percentage of the patients and there is only little confidence by the care givers that the critical chemotherapy drugs are dosed correctly (13). An additional tool such as the co-reporting allows optimizing of patient treatments, and this leads to the expectation of less side effects in the patients (and their families) as well as less frustration in the care givers. Again, the calculation of the monetary benefits of the probably better confidence by the care givers and better adherence to the therapy by the patients was not performed during our study.

The implementation and governance of co-reporting is quite easy: Cystatin C testing can be performed by turbidimetry or nephelometry on essential all Clinical Chemistry analyzers (25) from serum samples already obtained before chemotherapy. The cost benefit analysis performed in 2018 in our hospital involving 606 patients showed that 1,800 € in Cystatin C testing (estimated costs for one test ~3,00 €) would account for savings of ~105,000 € in reduced chemotherapy drugs, which translates to a benefit:cost ratio of ~58:1. Co-reporting is not only highly effective but also extremely efficient. The benefits of the attending oncologists (such as higher confidence in producing less harm in their patients) and the benefits of the patients (such as less fear of unwanted side effects) are even not included in this monetary calculation.

Besides setting up the automatic alert in the LIS, some additional resources might be needed for the education of the benefits and caveats of using cystatin C for dosing of drugs in addition or as substitution of creatinine. It is obvious that GFR calculations based on more than one biomarker (7, 12) can diminish the rate of gross errors. However, given the legal background with the official approval of certain drug with a certain (only creatinine-derived) GFR, switching to a combined creatinine- (urea)-cystatin C-based eGFR (26) as a substitute for the creatinine-derived formula seemed to be too revolutionary. Therefore, we chose the co-reporting of creatinine- (urea)- based and cystatin C based eGFRs instead (27). This allows to focus on the subset of patients with very discrepant eGFRs and apply clinical knowledge and experiences in these selected patients for dosing of chemotherapeutics. In fact, this approach will use the cystatin C-derived GFR for dosing in essentially all patients: In most of the patients, both formulas (creatinine- and cystatin C-derived) do not differ significantly. When significant discrepancies are observed between both formulas, clinical expertise will be used to dose chemotherapy accordingly.

It is of particular interest, that cystatin C does not only allow dosing in patients with severely impaired creatin metabolism (such as myopathies, severe malnutrition) but is also a good marker for the shrunken pore syndrome (SPS) (28). SPS is characterized by a large difference between creatinine-derived GFR and cystatin C-derived GFR estimates (29) with a selective impairment of the glomerular filtration of 12- to 29 kDa molecules. Filtering of small molecules such as creatinine is not impaired but cystatin C and drugs and metabolites of drugs with a higher molecular weight are cleared less effectively in patients with SPS.

Improving the dosing of drugs by co-reporting is not restricted to patients with chemotherapy:

other drugs, in particular those which are markedly affected by renal function such as certain anticoagulants (30), antibiotics (31), or antidiabetic drugs (32) will also benefit from a dosing scheme reflecting closer the patients' renal function (33). The monetary benefit by saving drug doses will be smaller in these patients compared to patients with chemotherapy (due to the lower cost of a single dose) but the non-calculated benefits of avoiding side effects and the increase in quality of life (such as less bleeding events, no amelioration of renal function, fewer events of lactate acidosis) will compensate the costs (34) for cystatin C testing.

The limitations of these studies are the unavailability of a gold standard for glomerular function testing such as invasive GFR testing in our patients and no proof, that the optimized dosing of drugs has in fact benefited the patients. However, it is conceivable that chemotherapeutic drugs should be administered tailored to the individual patient characteristics as detailed as possible including weight and size (body surface), renal function, and liver function. This dosing is of particular concern in patients receiving an array of highly effective drugs and the complex interaction during co-administration of several drugs suggests that the optimized dosing regimen will reduce side effects and improve the expected effects of chemotherapy. One might argue that the registration of a drug such as by FDA or EMA restricts the use of a certain GFR-formula. However, it is highly conceivable that drug dosing is affected by renal function and that a certain GFR estimate is only a somehow inaccurate approximation of the real renal function (35, 36). The pharmacokinetics of some chemotherapeutic drugs are only moderately affected by renal function except in the case of a severe decrease of GFR (GFR <45ml/min). It is of certain interest that creatinine-derived GFR overestimate renal function in patients with a GFR <45 ml/min while cystatin C

underestimate GFRs in patients with normal renal function (37). Therefore, the benefits of co-reporting will be particular in patients with an impaired renal function – this patient population has the highest risk of side effects and of overdosing. We used the most frequently used method, the blanked Jaffé method, for creatinine testing. This method is known to be less reliable than enzymatic creatinine methods (38) but both creatinine methods suffer from significant discrepancies in many patients to the true GFR (39) even when the overall correlation between both methods is excellent.

Coreporting of creatinine and cystatin C testing can be introduced in essentially every clinical laboratory and programming these calculation and rule-based comments with standard IT tools is very straightforward. The detection of patients with large discrepancies is automatically triggered by the LIS or by middleware and is fully reliable.

Taken together, co-reporting of creatinine and cystatin C-derived eGFR may circumvent the known inaccuracies of creatinine only-derived GFR calculations, the use of which is mandatory by regulatory agencies. We suggest adding cystatin C-derived GFRs to the conventional creatinine-derived calculation with automatic alerts and use an interdisciplinary team when dosing chemotherapy.



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The use of faecal haemoglobin in deciding which patients presenting to primary care require further investigation (and how quickly) – the FIT approach

Judith A. Strachan¹, Craig Mowat²

¹ Department of Blood Sciences, Ninewells Hospital and Medical School, NHS Tayside, Dundee, Scotland, UK

² Department of Gastroenterology, Ninewells Hospital and Medical School, Dundee, Scotland, UK

ARTICLE INFO

Corresponding author:

Judith Strachan
Blood Sciences, NHS Tayside
Ninewells Hospital and Medical
School Dundee DD1 9SY
Scotland, United Kingdom
E-mail: judith.strachan@nhs.scot

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ORCID Ids:

Judith A Strachan 0000-0003-4528-1005
Craig Mowat 0000-0002-5021-415X

ABSTRACT

Patients presenting to general practitioners (GPs) with new bowel symptoms can be difficult to assess since symptoms are poor predictors of pathology. National Institute for Health and Care Excellence referral guidelines highlight features that may suggest colorectal cancer (CRC) including rectal bleeding, palpable mass, iron deficiency anaemia, but also non-specific symptoms such as weight loss. In those patients referred for investigation on the basis of symptoms alone the yield of CRC is low (2-3%). Faecal immunochemical tests (FIT) quantify faecal haemoglobin (f-Hb) and are widely used in bowel screening programmes. A number of groups have now studied the utility of FIT in patients attending primary care with new bowel symptoms. Studies have concluded that if the FIT is negative and clinical assessment and full blood count normal then the risk of underlying significant bowel disease (SBD) is extremely small. Furthermore, patients with f-Hb ≥ 400 $\mu\text{gHb/g}$ faeces have >50% risk of

SBD and should be investigated urgently. Thus, a single f-Hb requested by GPs provides both a reliable prediction of the absence of SBD, and an objective assessment of the need and urgency of further investigation.



Abbreviations (in alphabetical order)

CHI: Community Health Index

CRC: colorectal cancer

FIT: faecal immunochemical test

f-Hb: faecal haemoglobin concentration

GI: gastrointestinal

GP: general practitioner

IBD: inflammatory bowel disease

ICD: International Classification of Diseases

IDA: iron deficiency anaemia

NHS: National Health Service

NICE: National Institute for Health and Care Excellence

SBD: significant bowel disease



INTRODUCTION

Lower gastrointestinal (GI) symptoms are poor predictors of significant bowel disease (SBD), namely colorectal cancer (CRC), inflammatory bowel disease (IBD) or higher risk adenomas (HRA); and cannot be relied upon to differentiate between CRC and non-significant or functional disorders (1). Guidance on the “two week wait” (2WW) for urgent referral for further investigation of patients with symptoms suspicious of cancer was introduced in 2004 in England. There is evidence that this has led to a large increase in referrals, but no change in the overall survival (2). In addition, in a recent five-year national cohort study, patients from primary care practices with the highest urgent suspected cancer referral rates did not have a lower likelihood of late

stage diagnosis than those from practices with lower referral rates (3). There are an increasing number of complex guidelines available to general practitioners (GPs) to try and help with further decision making such as those from the National Institute for Health and Care Excellence (NICE) in England (4,5) and Scottish Government suspected cancer referral guidelines (6), but these are open to interpretation and have serious limitations.

Our local health care system in NHS Tayside, Scotland, serves a population of around 400 000. Each year approximately 4000 patients are referred from primary care for assessment of bowel symptoms via a dedicated referral portal, ensuring equity of access and a streamlined booking process. The percentage of referrals from GPs marked as ‘urgent’ or ‘urgent suspected cancer’ consistently runs at 35–40%. Referrals are triaged by consultant gastroenterologists; 75% are brought straight to investigation such as colonoscopy and the remainder seen in outpatient clinics. Demand for endoscopy services has continued to escalate due to the ageing population and increasing referrals with over 70,000 colonoscopies carried out every year in Scotland (7) with concerns about insufficient workforce to meet demand and increasing waiting lists. Furthermore, colonoscopies are not without issues. When patients undergo colonoscopy to investigate symptoms, the yield of significant bowel disease is low, with local audit revealing CRC in only 2% and IBD in 5%. Furthermore, colonoscopies are not 100% accurate with variations in the number of cancers reported post-colonoscopy by NHS providers in England (8) and there can be adverse patient events such as perforation and bleeding and although these are rare, the effect should not be underestimated (9).

New means of assessing patients in primary care were urgently needed to help GPs determine which patients need rapid investigation and, in turn, ease pressure on secondary care services.

Faecal immunochemical tests (FITs) for haemoglobin (Hb) are specific for intact human Hb and its early degradation products. *Quantitative* FIT, based upon latex agglutination immunoturbidimetry and giving a numerical result for the faecal Hb (f-Hb) concentration have been recommended over *qualitative tests* to remove reader variability, inter-batch variability and to improve the diagnostic accuracy of the test. The use of FIT is already well established in CRC screening programmes worldwide (10-13). There is increasingly compelling evidence that the use of *quantitative* FIT in patients presenting to GPs with new bowel symptoms suggest high specificity and negative predictive values (NPVs) for CRC including our own 6-month pilot study which showed that the negative predictive values of f-Hb for CRC, HRA and IBD were 100%, 97.8% and 98.4%, respectively (14-20). A recent very large study from the NICE FIT Steering Group concluded that in patients referred via the 2WW pathway in England, FIT was superior to symptoms in predicting pathology (21). However there is still lack of awareness and perceived barriers to using FIT as an investigative test in primary care (22) and there is an on-going need for good quality evidence to ensure confidence in the use of FIT in this context with data collation and shared learning required (23).

AIM

The aim of this project was to assess whether the use of FIT by primary care could more efficiently identify patients presenting with new bowel symptoms who required further investigation. In addition, could the use of FIT prevent patients being referred unnecessarily for invasive procedures.

METHODS

In the NHS Tayside Board area, FIT kits (Hitachi Chemical Diagnostics Systems Co., Ltd, Tokyo,

Japan, supplied by Alpha Labs Ltd, Eastleigh, Hants, UK) along with patient instruction leaflets, were made available to GP practices beginning in December 2015. GPs were recommended to request fHb to guide referral of patients with any lower GI symptoms. Uniquely combined with electronic test requesting (using Sunquest ICE) of a concomitant 'Colorectal Bundle' of a Full Blood Count and Anaemia Screen along with patient symptoms selected from a drop-down menu, this ensures high uptake of FIT testing and completeness of data. Patients are provided with a pictorial instruction leaflet and requested to return the completed FIT specimen collection device as soon as possible to the GP facility and, from there, the devices are delivered to Blood Sciences, Ninewells Hospital and Medical School, Dundee, at ambient temperature, by the routine sample collection service and, if required, stored at 4°C prior to analysis. Analyses are carried out Monday to Friday; most samples are analysed on the day of receipt. Results are reported electronically to the requesting GP after fHb measurement using one HM-JACKarc (Hitachi Chemical Diagnostics Systems) FIT system which has a limit of detection (LoD) of 2 µg/g, a limit of quantitation (LoQ) of 7 µg/g and an upper measurement limit of 400 µg/g (24). Samples with results above the upper measurement limit are therefore reported as >400 µg/g, and patients with f-Hb ≥ 10 µg/g are defined as worthy of further investigation as recommended in NICE DG30 (5). The reports also sign-post GPs to web-based advice that f-Hb <10 µg/g, in the absence of iron deficiency anaemia (IDA), severe persistent symptoms, or a rectal or abdominal mass, suggests that CRC is extremely unlikely.

Numerical FIT results were retrieved from the laboratory database and linked by means of the Community Health Index (CHI) number with the electronic patient record to access all correspondence, laboratory results, referrals to secondary care, colonoscopy findings, hospital

admissions and attendances at the primary care out-of-hours service. In addition, a *post-hoc* anonymised record linkage with the Scottish Cancer Registry (SCR) was carried out in order to identify any cases of CRC that had been overlooked (International Classification of Diseases [ICD] codes C18, C19 and C20). All cases of CRC were confirmed histologically. Ethical approval was in place to safeguard the record linkage. MedCalc statistical software (MedCalc Software, Mariakerke, Belgium) was employed for calculations. Regular newsletters were emailed to all GPs over the first year of offering the test. To gauge the impact of offering FIT as a routine test, a questionnaire was emailed to all NHS Tayside GPs in 2017 asking various questions about the service, including availability and use of FIT tests and asking for free-text comments.

RESULTS

The FIT service was introduced as a routine test in December 2015, and in the first year of routine use 5422 patients submitted 5660 FIT kits, of which 5372 were analysed (positivity: 22%). 2848 patients were referred immediately to secondary care and 3 with f-Hb <10 µg/g presented acutely within days with obstructing CRC. 1447 completed colonoscopy in whom overall prevalence of SBD was 21% (95 CRC (6.6%), 133 HRA (9.2%) and 68 IBD (4.7%)); in patients with f-Hb <10 µg/g it was 6.6% vs. 32.3% in patients with f-Hb ≥10 µg/g. 2521 patients were not immediately referred (95% had f-Hb <10 µg/g) of which four (0.2%) later developed CRC. Record linkage identified no additional CRC cases within a follow-up period of 23–35 months (25).

EFFECT ON PATIENT SAFETY

In the first year of introducing FIT as a standard test available to GPs, referrals in NHS Tayside from primary care via the Colorectal Pathway fell 9% and referrals to Gastroenterology fell 24%.

The overall reduction in referrals was therefore 15% (25). This was on a background of rising referrals over the last 5 years. This large drop in referrals meant that around 1000 patients were not referred in a 12 month period who would otherwise have been placed on the colonoscopy waiting list had FIT not been available to their GPs. For these patients, the availability of FIT meant that they did not have to undergo unnecessary colonoscopy.

Our approach has been well received within the local primary care community. 98% of the 179 GPs surveyed said that they had requested a FIT with 98% happy with the turnaround time of the result. GPs benefit from having quantitative results rapidly available along with clinical acumen to aid decision making. GPs and patients can therefore have a more informed discussion about further investigation with 32% of GPs stating that FIT testing always helps assess the risk of significant pathology and 63% saying that it helps most of the time. Using a FIT test appears very acceptable with a high rate of patient compliance – this is evident with over 70% of referrals including a FIT result with GPs reporting that when offered, 32% of patients are always willing to complete the test and 67.6% willing most of the time to complete a test.

Patients with a low FIT can be reassured that nothing immediate needs to be done, decreasing anxiety in this group while those with high results have, in many cases, led to more rapid investigations.

PATIENT DIAGNOSIS

For an individual patient, the impact is extremely significant. Firstly, a negative FIT test in the absence of other worrying signs/symptoms means that they are highly unlikely to have significant bowel disease. This means that they do not need an invasive and unpleasant colonoscopy and can be reassured that they do not have significant

disease thus reducing anxiety and a wait for further tests. For patients with on-going symptoms, advice and safety netting is available with repeat FIT testing if necessary. For patients with elevated FIT results, they may well be 'fast-tracked' to a more urgent investigations thus leading to a quicker diagnosis of significant bowel disease.

During the first year of FIT, analysis showed that at the vetting stage, 242 patients had the urgency of their referral altered by the consultant gastroenterologist prior to colonic investigation: 166 referrals were upgraded on the basis of the f-Hb $\geq 10 \mu\text{g/g}$ in which the yield of SBD was 33.7% (17 Colorectal Cancer, 14 Inflammatory Bowel Disease and 25 High Risk Adenomas). Forty-four patients had their referral downgraded based on f-Hb $< 10 \mu\text{g/g}$ from either 'urgent' or 'urgent suspected cancer' to 'routine'; only two of these patients had SBD (both HRA). Thirty-two patients who had f-Hb $< 10 \mu\text{g/g}$ were upgraded on the basis of symptoms and patient history only; three had HRA and one patient had IBD.

For individual patients and the vetting consultants, the ability to upgrade or downgrade referrals on the basis of the FIT result is very significant. Before the availability of FIT, symptoms were the main determinant of urgency of referral so knowledge of the FIT result is now integral to the vetting process. Our experience shows that upgraded referrals made on the basis of the FIT result, results in faster diagnosis of significant diseases in these patients. In contrast, downgrading does not significantly delay a diagnosis.

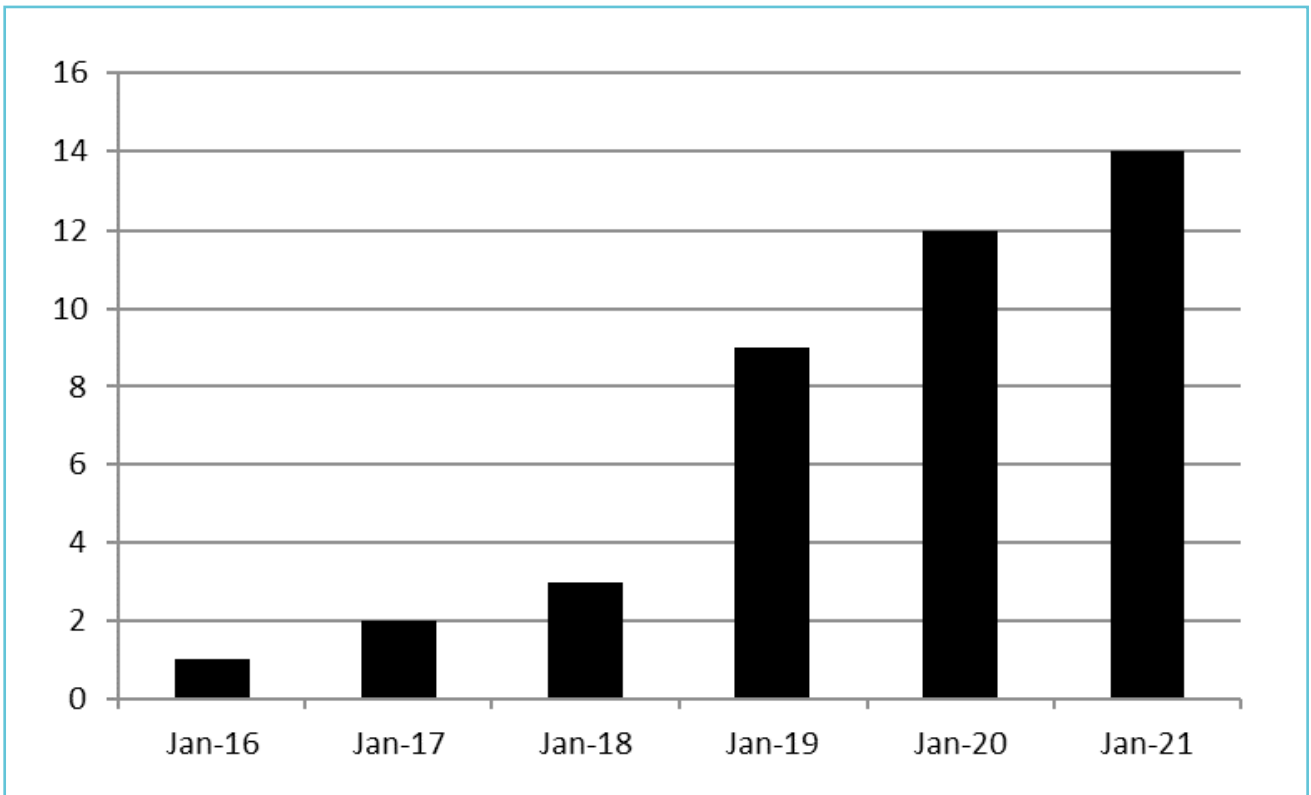
EFFECT ON OTHER HEALTH BOARDS

The roll out of FIT to all 14 Health Boards in Scotland has been accomplished over the last five years (Figure 1). This was initially via the creation of a Short Life Working Group and position statement in 2017 then facilitated with two key stakeholder meetings in 2018 and 2019 leading to collaborative working across Health Boards

both in terms of clinical approach and also laboratory processes.

The roll out of FIT across Scotland over the last five years has been of great benefit to laboratory colleagues across the country enabling more direct dialogue with other laboratories. Smaller laboratories can often feel quite isolated and the work undertaken to roll out FIT requesting has enabled them to be part of a national initiative. To date, there are four Health Boards performing their own FIT analysis using the same HM-JACKarc analytical platform, with the others sending kits on a daily basis to Tayside thus ensuring that there is rapid testing and reporting across the country. A common patient instruction leaflet has been widely used across the Health Boards, based on the Tayside version. NHS Tayside was a very early adopter in Scotland of NPEx software (an IT product to connect all UK labs through a single exchange hub) and our expertise and experience of this has greatly helped the roll out of FIT across the country. Where possible, electronic requesting of FIT from primary care has been encouraged. This work illustrates how diagnostic tests can be used effectively in clinical pathways and the interaction of clinicians and laboratory staff has led to the sharing of ideas, collaboration and interaction between all Health Boards in Scotland setting up this service. The service development has also in some cases led to technological changes in some boards too, with the introduction of NPEx to manage effective sample flow of referral tests between boards.

For clinicians across Scotland, the pioneering work undertaken by the laboratory and clinical team in Tayside has been transformative in improving diagnostic pathways for colorectal symptoms and the Tayside approach on the use of FIT has been adopted for local use with great enthusiasm and the benefits are now being seen in many areas. It has had the added benefit of more standardised requesting and referrals nationally.

Figure 1 Number of NHS Scotland Health Boards offering FIT by year

WIDER EFFECTS

Due to Tayside's pioneering work, FIT testing in primary care is now universally available in NHS Scotland. The service was in place pre-COVID, but its value to diagnostic services has been greatly emphasised during the recovery phase of COVID. Indeed, national consensus has been achieved on pathways and FIT thresholds for use in COVID service recovery as a direct consequence of the group's work (26). Furthermore, high risk patients (based on FIT ≥ 400 ug/g) have been prioritised for colonoscopy first. FIT has now been included in referral protocols by the Association of Coloproctology of GB and Ireland and has been incorporated into the new Colon Capsule Endoscopy (CCE) programme, allowing clinicians to triage low risk (based on FIT levels) patients to CCE.

The universal adoption of FIT along with associated clinical cut-off points and investigation

protocols across Scotland has had a significant impact on the investigation of patients presenting to primary care with new bowel symptoms across the whole country. It has meant equality of access for patients regardless of geography to diagnostic tests based on an objective measure (i.e. a FIT result) along with clinical assessment rather than on symptoms alone. Laboratory data and clinical outcomes have been shared for learning and future planning between the Scottish Health Boards. This has, in turn, led to the combining of data from three boards thus adding to the evidence for the use of FIT (27). This collaboration has also led to a consensus paper on the use of FIT as part of a national recovery strategy for colonoscopy services in symptomatic patients during the Covid-19 pandemic (26). Figure 2 shows the number of FIT tests analysed by Tayside over the last year. Following a marked reduction during the first wave of the COVID-19

pandemic, there has been a sharp increase in FIT requests since the guidance was published in early July 2020.

This common approach is very rare outside national bowel screening programmes and has been encouraged and supported by Scottish Government who has recognised the benefits for service delivery and patients.

SUMMARY

To our knowledge, we are the first area in the United Kingdom to introduce daily FIT testing to Primary Care for ALL age ranges and with ANY new bowel symptoms as an adjunct to clinical judgement and as an integral part of the colorectal referral pathway. Results are reported electronically back to GPs with signposting to local clinical advice and suggesting urgent referral if

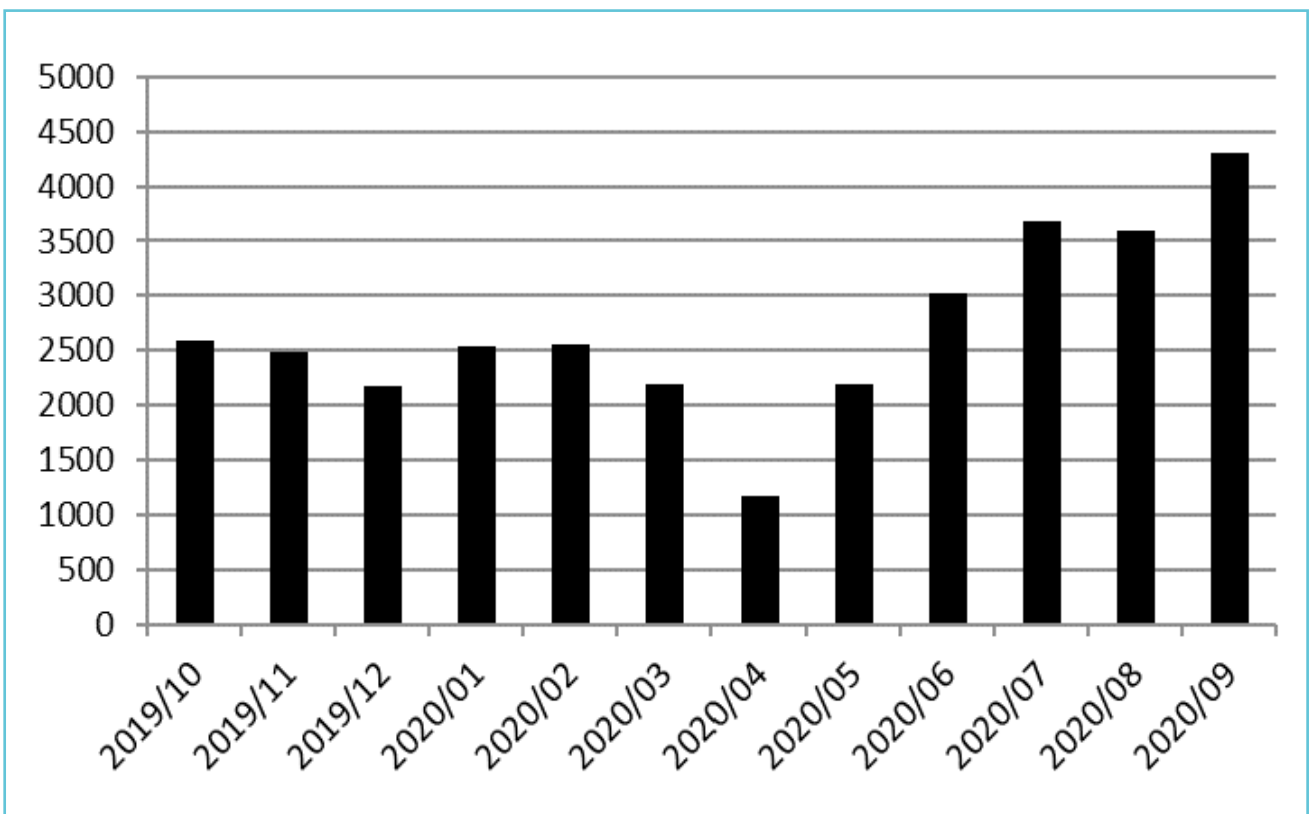
appropriate for high FIT results. FIT results are available to the gastroenterologists vetting requests thus providing added information to the clinical details. This approach has been rolled out to all 14 Scottish Health Boards over the last five years utilising the same analytical platform and clinical action limits and, in our opinion, is the one of the very few routine laboratory test to achieve uniform use in NHS Scotland.



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Figure 2 Number of FIT requests analysed by Blood Sciences, NHS Tayside from October 2019 to September 2020



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The Kidney Check program – championing patient-centered, culturally safe, preventive kidney care in Canada’s rural and remote Indigenous communities

Sarah Curtis¹, David Collister^{1,10}, Heather Martin¹, Abdul Razaq Sokoro^{3,4,5}, Lorraine McLeod^{7,9}, Caroline Chartrand⁹, Barry Lavalley⁹, Cathy Woods⁶, Adeera Levin^{6,8}, Paul Komenda^{1,2,6}

¹ Chronic Disease Innovation Centre, Seven Oaks Hospital, Winnipeg, Manitoba, Canada

² Max Rady Department of Medicine and Community Health Sciences, University of Manitoba, Winnipeg, Canada

³ Department of Internal Medicine, University of Manitoba, Winnipeg, Canada

⁴ Department of Pathology, University of Manitoba, Winnipeg, Canada

⁵ Shared health, Diagnostic Services, Winnipeg, Manitoba, Canada

⁶ CanSOLVE CKD Network

⁷ First Nations Health and Social Secretariat of Manitoba, Canada

⁸ The University of British Columbia, Vancouver, Canada

⁹ Diabetes Integration Project, Winnipeg, Manitoba, Canada

¹⁰ Population Health Research Institute, McMaster University, Hamilton, Ontario, Canada

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Corresponding author:

Paul Komenda MD, MHA
Chronic Disease Innovation Centre
Seven Oaks Hospital
2300 McPhillips St.
Winnipeg, MB R2V 3M3
Canada
E-mail: paulkomenda@yahoo.com

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ARTICLE

INTRODUCTION

The health status of First Nations, Inuit and Metis peoples reflects a disparate sociopolitical and environmental context inextricably linked to Canada’s colonial history. This health inequity is exemplified by the disproportionate burden of chronic diseases such as diabetes, hypertension, and chronic kidney disease (CKD) affecting Indigenous communities. Frequently diagnosed at a younger age and greater severity than non-Indigenous groups, the increasing prevalence of

these conditions is of particular concern in rural and remote Indigenous communities (1, 2). Often marginalized from mainstream health-care services (geographically, economically, or culturally), many of these communities lack the preventive health benefits associated with continuity of care (3). Consequently, the detection and treatment of these conditions is often delayed, resulting in an increased risk of adverse outcomes that impact quality of life and strain healthcare systems.

In 2015, the First Nations Community Based Screening to Improve Kidney Health and Prevent Dialysis (FINISHED) program in Manitoba highlighted the efficacy of mobile point-of-care testing among adults and children in 11 rural and remote First Nations communities. Importantly, the program reported that a majority (87%) of CKD cases identified by albuminuria or a decreased estimated glomerular rate were early-stage and potentially treatable, representing an opportunity to prevent or delay kidney failure (4). As the lifetime health and economic burden of CKD is dependent on the severity of the disease, early detection and management represents a crucial opportunity to reduce this burden through risk factor modification including blood pressure control, diabetes management and the use of reno-protective medications, such as Renin-Angiotensin-Aldosterone System

(RAAS) and Sodium-glucose co-transporter-2 (SGLT2) inhibitors (5).

Modelled after FINISHED, Kidney Check is an Indigenous-led screen and treat program working to bring early detection and preventive kidney care to rural and remote Indigenous communities across Canada (Manitoba, Ontario, British Columbia, Alberta, Saskatchewan) [Table 1]. Using portable diagnostic equipment, specialized Kidney Check health teams screen participating adults and children ages 10 and up for CKD, diabetes, and hypertension. True to its name, point-of-care testing (POCT) is designed for use at the site of patient care, presenting an opportunity to expand preventive healthcare to regions with diminished access. Following screening, participants are triaged according to their individualized kidney failure risk prediction scores and are referred to additional resources accordingly. An affiliate of the patient-oriented Canadians Seeking Solutions and Innovations to Overcome Chronic Kidney Disease (Can-SOLVE CKD) research network, the programs design and implementation is guided by foundational research priorities set by patient partners. These and other collaborative partnerships between Kidney Check, Indigenous healthcare providers, adult and pediatric clinician specialists and engaged policy makers contribute to the programs sustainability and success.

Table 1 Kidney Check screening communities for British Columbia, Alberta and Manitoba

Province	Number of communities	Anticipated screening participants*
British Columbia	13	1011
Alberta	3	750
Manitoba	5	959

* Anticipated screening participants refers to the number of people in each community expected to attend the screening event.

CONTEXT: CANADIAN INDIGENOUS HEALTH CARE

Contemporary Indigenous health policies cover an array of federal programs, provincially provided services, and highly bureaucratized additions best characterized by jurisdictional ambiguity. For the majority of Canadians, health services are covered by the national health insurance plan under the Canadian Health Act, administered at the provincial and territorial level. Indigenous people are covered by provincial Medicare plans, but on-reserve, some health services fall under federal jurisdiction with many people receiving supplemental federal insurance. In some cases, this coverage is adequate, but in other situations the gaps and ambiguities created by a complex policy environment have created barriers to equitable healthcare services (6,7). This is particularly relevant for the provision of subspecialty services such as diabetes and CKD care, which often falls on the provincially funded health system. The result is often a patchwork of services which differ widely across regions (8).

Geographical isolation from mainstream health services further compounds barriers created by policy ambiguities. As of 2018, nearly half (49.3%) of First Nations people with registered Indian status live on more than 3100 reserves across Canada, most of which are in rural or remote locations (9). On reserve, health centers are mainly operated by nurses or community health workers whose limited scope of practice requires individuals to travel long distances to access advanced treatment facilities and specialized care. The impact of rural and remote dwelling location on CKD and diabetes prevalence has shown to be significant, with rates 2 to 4-fold higher compared to urban dwelling Indigenous people, respectively (2). With on-reserve populations continuing to grow, innovative models of

healthcare delivery are needed to address these barriers (10).

Over the past several decades, shifts toward pluralism and self-government have prompted policy changes aimed at transferring governance and allocation of Indigenous health services to communities and tribal councils. Today, approximately 89% of First Nations and Inuit communities manage their own community health programs on some level, either within their own community or via affiliation with tribal councils or various health authorities (8). In recognition of these communities' self-governance, Kidney Check has established standardized procedures for engaging with healthcare leadership on a local, provincial and federal level. In doing so the program aims to further collaborative relationships between engaged healthcare stakeholders while upholding culturally safe practices.

THE FINISHED PROGRAM

In 2015, the FINISHED program introduced a comprehensive screening, triage and treatment initiative in 11 rural and remote First Nations communities in Manitoba, Canada. Spanning 3-years, the programs' primary objective was to provide mobile, community-wide screening for CKD, diabetes, and hypertension followed by individualized risk-based counseling and treatment plans. Led by the Diabetes Integration Project and the Manitoba Renal Program, the project was designed in collaboration with Indigenous nurses and physicians, adult and pediatric clinician specialists and a communications expert (11). Overall, the program screened 1,700 individuals including 1,346 adults, achieving a 22.4% overall screening rate, calculated using the entire registered on-reserve population 18 years or older as the denominator (5,860). Out of 1,346 adults screened, 343 (25.5%) were found to have CKD as defined by a single measurement of elevated urine albumin-to-creatinine ratio (UACR)

or estimated glomerular filtration rate (eGFR), ($<60\text{mL}/\text{min}/1.73\text{m}^2$). Of the 343 adults with CKD, 216 (60.2%) had elevated hemoglobin A1c (HbA1c) levels ($\geq 6.5\%$) and 94 (27.4%) had elevated blood pressure (systolic blood pressure $\geq 140\text{ mm Hg}$ or diastolic blood pressure $\geq 90\text{ mm Hg}$) (4). Additionally, of 353 children screened, 15% had evidence of early kidney disease, 17.3% had prehypertension or hypertension and 3.8% were at risk for, or had, overt diabetes (12). Importantly, the program reported that patients screened in communities accessible only by air showed a higher prevalence of CKD than communities accessible by road. Furthermore, had the program only screened participants with known CKD risk factors, such as diabetes or hypertension, 97 (28.3%) of those who were found to have CKD would have been missed (4). Overall, 90% of identified CKD patients were seen by a nephrologist following the event. Of those at risk, 8.4% are regularly monitored by a nephrologist 18 months after screening, compared to 2.5% prior to screening.

Furthermore, cost-effectiveness analysis of this program showed screening was associated with an incremental cost-effectiveness ratio (ICER) of \$23,700 per quality adjusted life year (QALY). In a usual care scenario, total costs were \$12,790 and effectiveness was 12.9869 QALYs, where screening was associated with a cost of \$13,400 and effectiveness of 13.0124 QALYs (13).

KIDNEY CHECK, CANSOLVE CKD AND PATIENT PARTNERS

Kidney Check screening procedures

Established in 2018, Kidney Check is a national iteration of the FINISHED program. Led by a project leadership team, advisory committee, community partners and patient partners, the program provides high quality, cost-effective POCT to Indigenous communities across Canada. Communities are selected in collaboration with

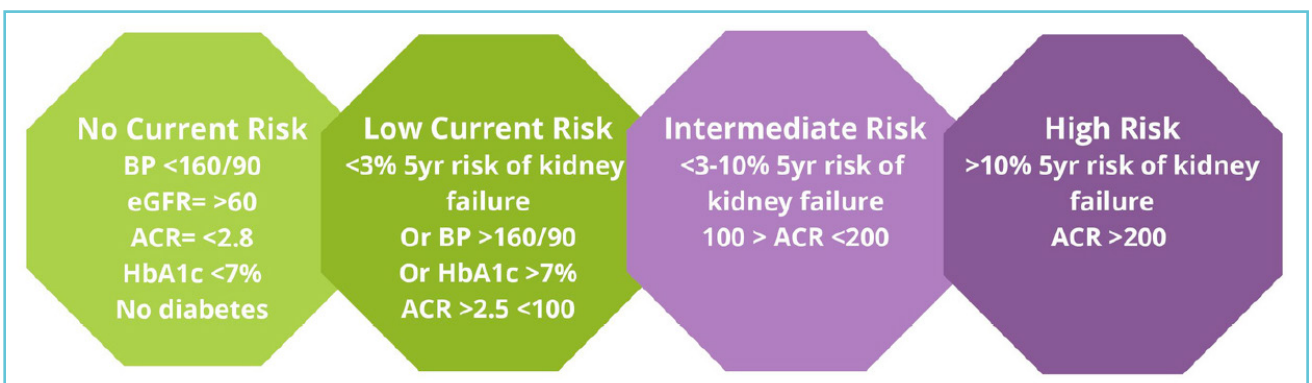
patient partners at the discretion of the provincial teams. Various community characteristics including population size, accessibility to urban hubs of care, travel accessibility and consideration of recent kidney screening programs are all taken into consideration [Table 2]. In most cases, screening teams consist of two registered nurses and a healthcare aid. Screening takes place at a variety of different locations depending on the community. Methods of the screening process have been described in detail previously (14). In brief, finger prick droplet blood samples are collected and analyzed for blood chemistry on an i-STAT Alinity analyzer (Abbott Point of Care Inc., Princeton, NJ). An additional blood sample is used to analyze for HbA1c and a urine sample is provided to determine uACR on a DCA Vantage analyzer (Siemens, Erlangen, Germany). Blood pressure is averaged using 6 measurements taken over 6 minutes according to best practices outlined by the Canadian Hypertension Education Program (CHEP). Patients clinical values are inputted into a secure, custom iPad application built for Kidney Check that automatically calculates their eGFR. These values are further utilized to provide participants with their 2 and 5-year risk of developing kidney failure as calculated by the Kidney Failure Risk Equation (KFRE). Validated in more than 700,000 adults across 30 countries, the KFRE predicts risk of requiring dialysis or kidney transplant for individuals whose eGFR $<60\text{ml}/\text{min}/1.73\text{m}^2$ (15). Pediatric (<18 years) patients are triaged using a separate algorithm developed in collaboration with pediatric nephrologists and endocrinologists (11).

Immediately following screening, every participant is offered risk-based counseling and additional resources accordingly [Figure 1]. These discussions follow scripts developed in collaboration with Indigenous patient partners that outline the patient's current risk and what steps need to be taken to preserve kidney health. A critical component of these discussions is upholding

Community	Urban/ Rural	Distance from nearest service centre	Travel accessibility	Accessibility to follow-up care	Means of transportation
1.	Rural	10 km	Not convenient	Not accessible	Airplane/ boat
2.	Urban	10 km	Not convenient	Somewhat accessible	Car/ ferry
3.	Rural	1 hour drive	Not convenient	Not accessible	Car/ airplane
4.	Rural	1 hour drive	Not convenient	Not accessible	Car
5.	Rural/ Remote	More than 1 hour drive	Somewhat convenient	Accessible	Car/ ferry
6.	Rural/ Semi-Remote	1 hour drive	Convenient	Somewhat accessible	Car
7.	Remote	More than 1 hour drive	Not convenient	Somewhat accessible	Airplane/ ferry
8.	Mix	Mix	Mix	Mix	Car/ ferry
9.	Urban	10 km	Somewhat convenient	Somewhat accessible	Car/ ferry

* **Accessibility/non accessible** is defined as the travel costs associated with getting to the community, the distance to the community and how difficult it is to access the community via air, car or boat.

Figure 1 Kidney Check Risk Prediction Counseling is based on the below risk parameters



the principles of shared decision making and the traditional values and medicines unique to each community. Treatment plans are discussed with input from Elders and traditional healers in order to incorporate traditional medicines and diets. If patients have a primary care provider their results and treatment plan are provided to them. All individuals determined to be at intermediate or high risk of kidney failure are immediately referred to a multidisciplinary CKD clinic where they are followed by a specialized team and undergo a long-term treatment plan.

QUALITY ASSURANCE PROGRAM

Kidney Check relies on a comprehensive quality management program to ensure patient results can be confidently reported for use in clinical decision making. This program covers pre-analytical quality and staff competency, POCT equipment quality control, and external proficiency testing. Overseen by Shared Health Diagnostic Services, quality management procedures are based on the Accreditation Canada Qmentum Guidelines on Point-of-Care testing (16). To perform screening procedures, all POCT device operators must complete initial training and pass competency assessments annually. Only staff whose training and competence has been established, recorded, and regularly updated are permitted to perform and supervise screening. Screening staff are responsible for the regular maintenance of POCT devices, including consumables and reagents, at their respective sites. Day-to-day quality control procedures include checking the performance of POCT devices against pre-determined criteria. Kidney Check utilizes two high-quality POCT devices, the i-STAT Alinity® (Abbott Point of Care Inc., Princeton, NJ, USA) and the DCA Vantage®. Both systems are designed with sophisticated internal quality control measures and additional quality control checks are run daily by device operators. In addition, the program subscribes to an external proficiency testing program through the College

of American Pathologists, CAP (<https://www.cap.org/laboratory-improvement/proficiency-testing>). External proficiency testing provides regular, independent assessments of POCT devices to ensure results meet quality standards. Challenge samples are sent to be analyzed twice each year, with three samples spanning different measurement ranges.

KEY PERFORMANCE INDICATORS

Kidney Check uses several key performance indicators to measure its performance. From a patient perspective, an Indigenous patient group meets regularly to provide qualitative feedback on the program and an Indigenous patient meets with the leadership team on a biweekly basis ensuring the patient voice is considered in all aspects of the program. A second KPI involves the concept of “personalized care”. This quantitative metric ensures that 100% of patients entering the program have a customized treatment plan activated according to their level of calculated risk. A third KPI considers “patient wellness” measuring the number of patients in each risk category which can be scored in real time. In terms of clinician confidence, metrics were evaluated in the form of qualitative interviews by an independent body collecting feedback from clinical stakeholders participating in the program finding near universal agreement that the early detection and treatment of CKD in this format was helpful. Other KPI's have addressed health system administration and cost effectiveness. Importantly, a well-developed cost effectiveness model was published in a reputable nephrology journal based on this program finding this yielded excellent value for money for healthcare payers.

CONCLUSION

CKD, hypertension and diabetes are potent risk factors for multiple comorbidities such as kidney

failure and cardiovascular disease that greatly impact mortality.

Canadian Indigenous populations are disproportionately affected by these conditions, with prevalence rates reaching epidemic levels in some communities. This is of particular concern in rural and remote communities, who face significant health inequities that prevent them from receiving optimal care. In 2015, the FINISHED screening initiative proved the efficacy of POCT for these chronic conditions in rural and remote Indigenous communities.

The Kidney Check program represents a national iteration of this program. Fostering collaborative partnerships between patients, clinicians, communities and policy makers, Kidney Check aims to help bridge these gaps in health equity.



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Is COVID-19 impacting prostate cancer screening? A survey of prostate-specific antigen test requests during a local outbreak

Anna Ferrari¹, Fabian Sanchis-Gomar², Camilla Mattiuzzi³,
Brandon M. Henry⁴, Giuseppe Lippi^{1,5}

¹ Service of Laboratory Medicine, University Hospital of Verona, Verona, Italy

² Department of Physiology, Faculty of Medicine, University of Valencia, Spain

³ Service of Clinical Governance, Provincial Agency for Social and Sanitary Services, Trento, Italy

⁴ Cardiac Intensive Care Unit, The Heart Institute, Cincinnati Children's Hospital Medical Center, Ohio, USA

⁵ Section of Clinical Biochemistry, University of Verona, Verona, Italy

ARTICLE INFO

Corresponding author:

Prof. Giuseppe Lippi
Section of Clinical Biochemistry
University Hospital of Verona
Piazzale L.A. Scuro, 10
37134 Verona
Italy
Phone: 0039-045-8122970
Fax: 0039-045-8124308
E-mail: giuseppe.lippi@univr.it

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coronavirus disease 2019, COVID-19,
SARS-CoV-2, prostate cancer; screening

ABSTRACT

Background

Although the ongoing pandemic of coronavirus disease 2019 (COVID-19) is directly contributing to negatively affect global health and fitness, the restrictive measures applied for containing the outbreaks are also impacting detection and management of many diseases, including cancers. This study aimed to establish if and how the COVID-19 outbreak may have impacted the practice of routine prostate cancer screening in Verona, Italy.

Methods

We searched the laboratory information system of the Service of Laboratory Medicine of the University Hospitals of Verona to identify all test requests for total prostate-specific antigen (PSA) and vitamin D (Vit D);

i.e., the locally most requested immunochemical test) for outpatients during the last five years (December 10, 2016, to December 10, 2020). The weekly requests for these tests placed between February 25 and December 9, 2020, were compared to those placed during the same period of previous four years (i.e., 2016-2019).

Results

The volume of test requests for both Vit D and PSA did not differ in 2020 compared to previous four years. However, a dramatic decline was observed during the local lockdown period (between March 10 and May 17, 2020), with median decrease of 76% for Vit D and 62% for total PSA, respectively. This reduction was compensated by 13% increase for Vit D and 43% increase for total PSA in post-lockdown period.

Conclusion

These results show that the lockdown period established during the first peak of the COVID-19 outbreak in Italy's Verona province was associated with a dramatic decrease in routine prostate cancer screenings.



INTRODUCTION

Evidence now clearly attests that the ongoing coronavirus disease 2019 (COVID-19) pandemic is not only directly causing unprecedented morbidity and mortality around the world, but its continuous and virtually unstoppable spread is also influencing detection and management of many other acute and chronic diseases [1,2]. The potential consequences to global health is multifaceted, as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection exacerbates pre-existing diseases such as cancer, diabetes, cardiovascular disease, etc., leading to increased morbidity and mortality in such infected patients. Moreover, the continuous restrictions

are consistently limiting access to primary and secondary care, thus potentially causing diagnostic delays, underdiagnosis and undertreatment of non-COVID-19-related illnesses [3]. Many warning signals have been raised on observed decreases in care for routine pathologies during the pandemic, for example, hospitalizations for acute myocardial infarction were considerably decreased during the first wave of the outbreak [4-7].

Similar evidence has been provided with respect for general [8], emergency [9] and trauma surgery utilization [10], the diagnosis and therapeutic management of diabetes [11] and cancer [12], along with many other severe or life-threatening conditions [13], with pediatric care being no exception [14]. The widespread public avoidance of hospitals and delay in seeking routine medical care during the pandemic is likely translating into a large burden of underdiagnosis, with missed opportunities to provide timely and appropriate treatments, consequently leading to increased out-of-hospital chronic disability and mortality.

Prostate cancer is the third most frequently diagnosed malignant disease worldwide, the second in the male sex, and is responsible for 350,000 deaths every year [15]. Although debate continues as to the benefit of prostate cancer screening on all-cause mortality [16], prostate-specific antigen (PSA) testing has now been endorsed by the vast majority of international guidelines as an inexpensive, low-invasive, and relatively accurate means of detection for purpose of prostate cancer screening [17]. Moreover, it has been recently found that routine PSA testing would improve the detection of any type of prostate cancer, especially the localized forms. As such, it has been emphasized that a decrease in PSA screening would cause a substantial reduction in prostate cancer detection, with non-negligible increase in prostate cancer-specific mortality [18].

Therefore, the aim of this study was to analyze the volume of PSA test requests placed to a local service of laboratory medicine, compared to those of vitamin D (Vit D; i.e., the most requested immunochemical test in local laboratories), to establish if and how the ongoing COVID-19 outbreak may have impacted the local practice of routine prostate cancer screening in the province of Verona, Italy.

MATERIALS AND METHODS

The Service of Laboratory Medicine of the University Hospitals of Verona encompasses two separate medical laboratories, one in the Policlinic (~600-bed facility) and the other in the General Hospital (~1200-bed facility), located at the opposite sides of the town of Verona (Southbound and Northbound, respectively). These two hospitals serve an area of 3096 km², with a population of nearly 922,000 inhabitants, and provide both routine and urgent testing, averaging a total of ~6 million tests in 2019 (60.8% of which in the Policlinic, 46.0% for outpatients). Routine and urgent laboratory testing for inpatients and outpatients was preserved throughout the COVID-19-related lockdown period within the Verona province (i.e., between March 10 and May 17, 2020), as access to routine laboratory testing was exempted from national, regional, and provincial restrictions.

An electronic search was carried out in the local laboratory information system (LIS; Concerto, Dedalus Italia, Firenze, Italy) database to identify all test requests placed in both laboratories for total PSA and Vit D in outpatients during the last five years (i.e., from December 10, 2016, to December 10, 2020). The number of new daily diagnoses of SARS-CoV-2 infection in Italy and Verona's province was retrieved from the official website of the Italian National Institute of Health (Istituto Superiore di Sanità; ISS). Both PSA (assayed with Roche Elecsys, Roche

Diagnostics, Rotkreuz, Switzerland) and Vit D (measured with Liaison XL, DiaSorin, Saluggia, Italy) tests were freely available for request, and the local guidelines regulating their prescription remained unchanged throughout the study period, as well as the analytical platforms. The weekly volume of total PSA and Vit D outpatient tests during the different periods was reported as median with interquartile range (IQR). The significance of differences and correlations were assessed with Mann-Whitney U and Spearman's tests, respectively. The variation in the number of weekly test requests placed to the local laboratories for both Vit D and total PSA in 2020 compared to the same weeks of the previous four years was expressed as a ratio (i.e., [weekly test requests in 2020] / [mean weekly test requests between 2016-2019]). Statistical analysis was performed using Analyse-it (Analyse-it Software Ltd, Leeds, UK) and MedCalc (MedCalc Software Ltd, Ostend, Belgium). The study was conducted in accordance with the Declaration of Helsinki, under the terms of relevant local legislation. The entire work was based on anonymized searches in the local LIS as part of a systematic laboratory workflow analysis. Therefore, no informed consent or ethics committee approval was necessary.

RESULTS

The cumulative number of weekly diagnoses of SARS-CoV-2 infections in Italy and the Verona province since the beginning of the local outbreak (i.e., February 25, 2020) is shown in Figure 1. Two distinct "waves" can be seen, interspersed by the summer months of the year. A significant correlation was found between the number of weekly COVID-19 diagnoses in Italy and those specifically recorded in the Verona province ($r=0.95$; 95% CI, 0.93-0.96; $p<0.001$).

The cumulative number of weekly test requests for Vit D and total PSA, as recorded between

February 25 and December 10, 2020, is summarized in Table 1. Although the volume of test requests placed for both Vit D and total PSA throughout this period did not differ in 2020 compared to the mean number recorded during the same period of the previous four years, a dramatic decline could be observed during the lockdown period in the province of Verona, with median decrease of 76% (IQR, -84% to -40%) for Vit D and 62% (IQR, -79% to -41%) for total PSA respectively. An opposite trend could be observed

when test requests for both Vit D and total PSA were analyzed during periods of 2020 without lockdown restrictions as compared to the mean number recorded during the same weeks of the previous four years. More specifically, the test requests exhibited a median increase of 13% (IQR, 5% to 29%) for Vit D and 43% (IQR, 24% to 54%) for total PSA. These same trends can also be seen in the variation ratio between test requests placed in 2020 and the previous four years (Figure 2).

Figure 1 Cumulative number of weekly diagnoses of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections in Italy and Verona's province since the beginning of the local outbreak (i.e., since February 25, 2020)

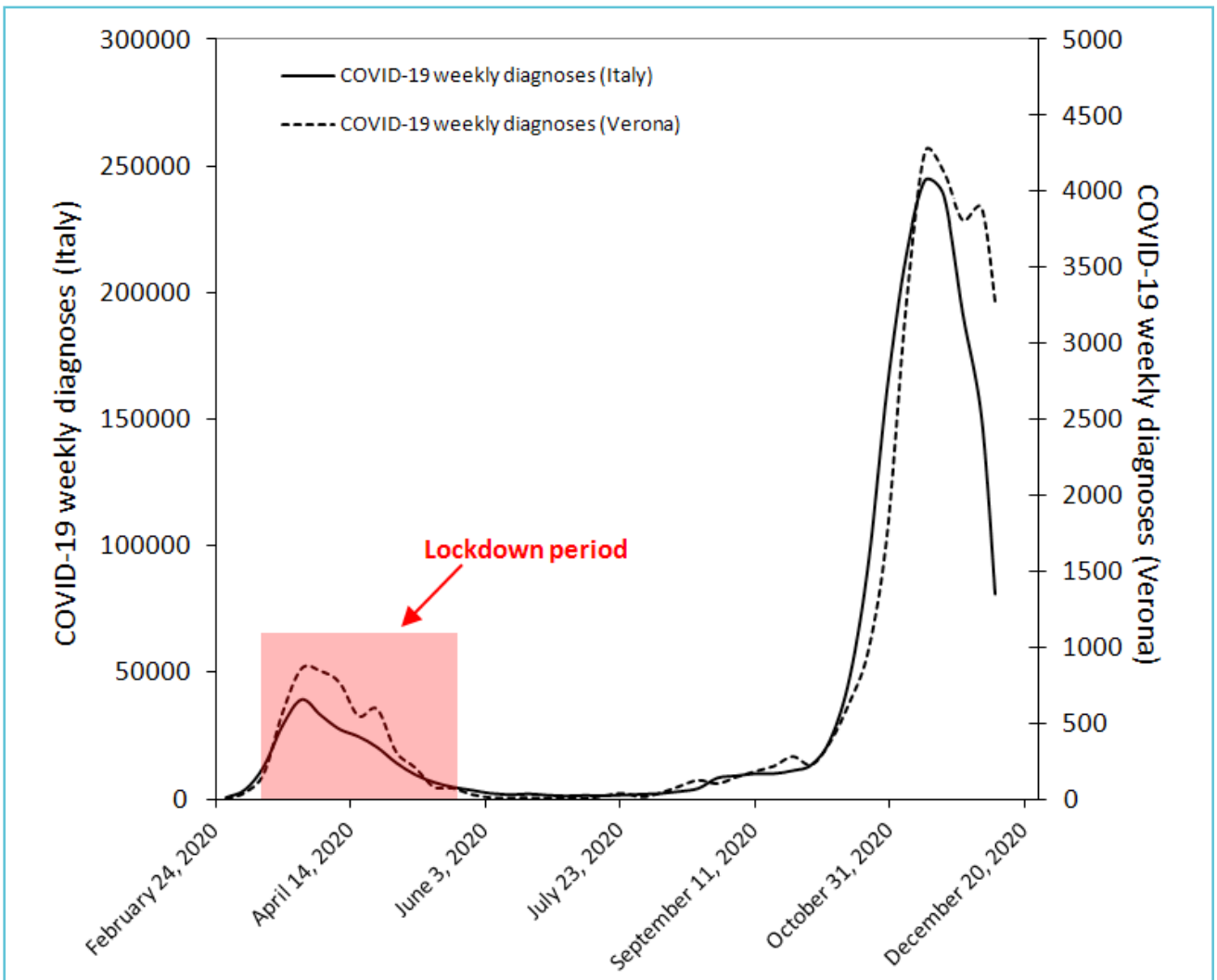


Table 1 Weekly number of Vitamin D (Vit D) and total prostate-specific antigen (PSA) requests placed to the local laboratories between February 25 and December 9, 2020, compared to the mean number of requests placed during the same week of the previous four years (i.e., 2016-2019)

Analyte	Test requests in 2020	Mean test requests in 2016-2019	p
Vit D			
Total period	278 (196-319)	268 (232-285)	0.192
Lockdown period*	66 (48-126)	283 (271-288)	<0.001
No lockdown period	295 (267-322)	256 (228-280)	<0.001
Total PSA			
Total period	171 (126-196)	138 (117-151)	0.052
Lockdown period*	52 (29-76)	146 (129-147)	<0.001
No lockdown period	181 (165-201)	135 (116-151)	<0.001

Results are shown as median with interquartile range (IQR).

* Lockdown period was between March 10 and May 17, 2020.

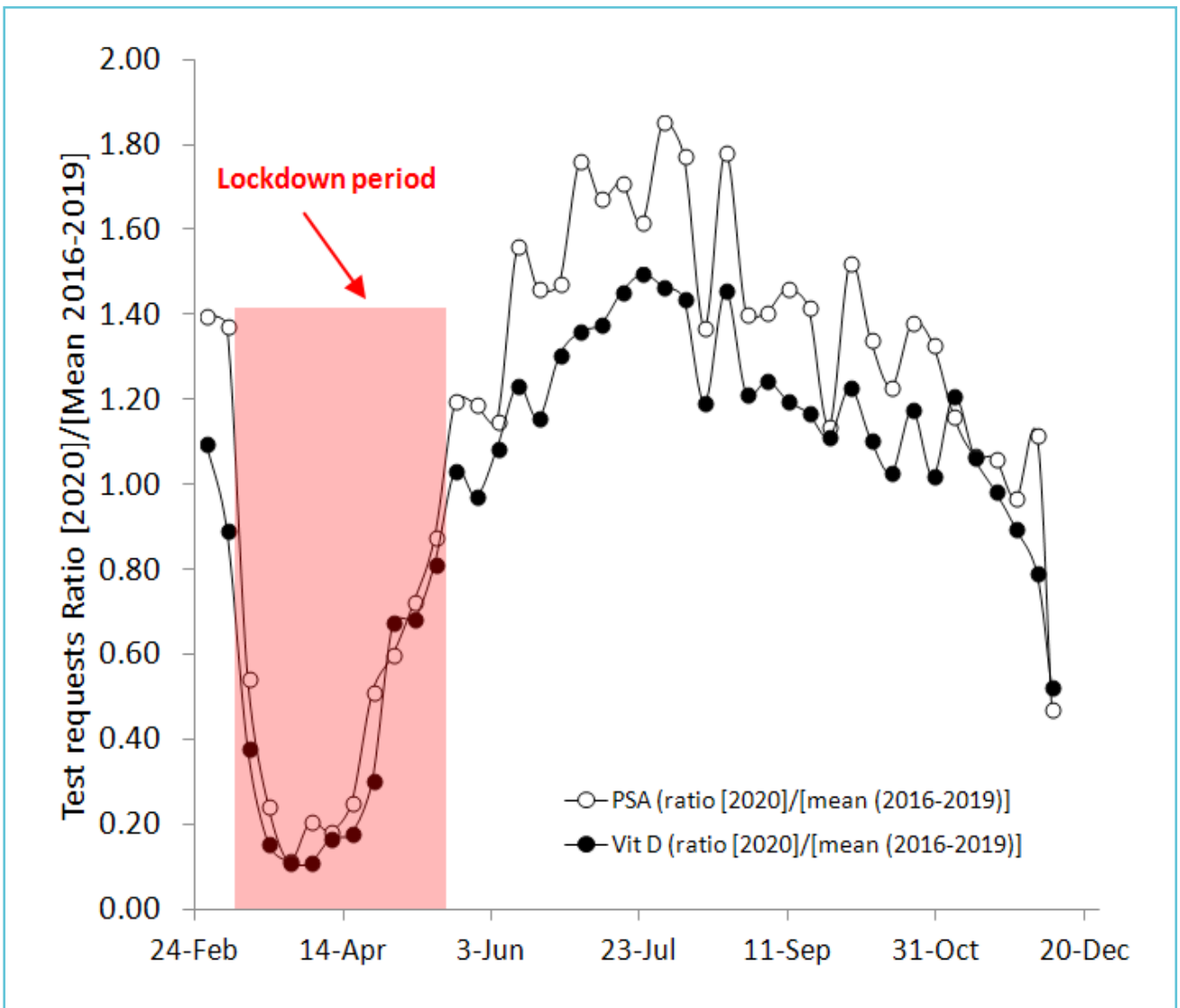
A significant correlation was found between the variation in test requests placed from February 25, 2020, to December 10, 2020, compared to the same period of the previous four years, for Vit D versus total PSA, ($r = 0.94$; 95% CI, 0.90-0.97; $p < 0.001$).

DISCUSSION

The results of our analysis of Vit D and total PSA test requests placed for outpatients in a Northern Italian town since the beginning of the COVID-19 outbreak shows that the lockdown resulted in a dramatic decrease in the number of total PSA and Vit D tests performed, despite the fact that local restrictions did not include a ban on access to routine diagnostic testing.

The reduction in test requests for both assays, as high as 76% for Vit D and 62% for total PSA, were likely due to identical causes (i.e., fear of being infected by leaving home, derangement of public transportation, lacking or inefficient communication that routine laboratory testing was still allowed and available), as a virtually perfect correlation could be found between the number of missing Vit D and total PSA analyses. These findings are congruent with those reported by De Vincentiis et al. [19], who reported that the number of histological prostate cancer diagnoses was decreased by 75% in 2020 compared to the average number recorded in the previous two years at a secondary care hospital network in central Italy. It can thus be proffered that the establishment of a generalized lockdown,

Figure 2 Variation in the number of weekly test requests for Vitamin D (Vit D) and total prostate-specific antigen (PSA) between February 25 and December 9 in 2020 compared to the mean number of weekly requests placed in the previous four years (i.e., 2016-2019). The values are expressed as a ratio, calculated as: [weekly test requests in 2020] / [mean weekly test requests between 2016-2019]



without restrictions on access to routine care, may still have dramatic consequences on cancer screening policies, with PSA representing a paradigmatic example. While the increased volume of testing recorded in the post-lockdown period may have filled the gap observed during the lockdown period in terms of total number of

annual tests (Figure 2 and Table 1), this will not void the delay that may have occurred in diagnosing some prostate cancers, whose prognosis is negatively influenced by inaccurate or delayed detection [20].

Although the putative benefits may vary largely among the different types of malignant diseases,

there is now clear, unquestionable evidence that a timely diagnosis may improve cancer survival and enhance patient quality of life. In a systematic review, Neal et al. concluded that a delayed diagnosis might negatively impact the outcomes of colorectal, breast, testicular, head and neck, pancreatic, bladder, and prostate cancers [21]. With respect specifically to prostate cancer, O'Brien reported that surgical delay may be associated with poorer prostatectomy outcomes, including a significantly adverse progression of disease, even in patients with low-risk prostate cancer criteria [22]. In a more recent study, Banerji et al. revealed that a reduction in the number of PSA tests was associated with increased likelihood of diagnosing higher clinical stage disease, potentially leading to many avoidable cancer deaths [23]. Almost identical findings were reported by Qu et al., who showed that diagnostic delay of 1 month or longer was associated with higher clinical stage and biopsy grade [24]. In keeping with these findings, Tørring and colleagues elucidated the existence of a significant association between a longer diagnostic interval and enhanced prostate cancer mortality [25]. On the contrary, a recent study failed to show negative survival outcomes when radical prostatectomy was delayed up to 6 months in patients with clinically localized, high-risk prostate adenocarcinoma [26]. However, Sun and colleagues highlighted that a treatment delay of around three months between diagnosis and prostatectomy may require more extensive periprostatic tissue ablation, thus impairing erectile function and postoperative continence [27]. Last but not least, missing or delaying active surveillance, with PSA testing considered a central part of prostate cancer follow-up, may also have dramatic consequences on disease progression or relapse, as supported by a recent meta-analysis by Enikeev et al. [28]. In conclusion, the lockdown period imposed during the first wave of the COVID-19 outbreak in the Verona province of Italy was associated

with a dramatic decrease in total PSA test requests (and Vit D) requisition from the local laboratories. Since evidence exists that shorter time to diagnosis is associated with more favorable outcome for prostate cancer, as well as for many other malignancies, the restrictive measures applied for containing SARS-CoV-2 spread in the community should be accompanied by improved communication and clear warnings by both public health authorities and medical care givers that essential cancer screenings should not be abandoned or delayed. Notably, extensive resource re-allocation is constantly demanded during this ongoing COVID-19 pandemic outbreak. Rationalization in healthcare utilization is of paramount importance, and may become a definite reason for unavoidable collateral consequences. COVID-19 may also have dramatic implications on routine laboratory testing, and our observed decrease in Vit D test requests may not only reflect underutilization, but perhaps also a more rationalized use of routine laboratory services.

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Monitoring of diabetic patients with poor glycemic control. Are international recommendations met?

José Antonio Delgado¹, Josep Miquel Bauça^{1,2}

¹ Department of Laboratory Medicine, Hospital Universitari Son Espases, Palma, Spain

² Institut d'Investigació Sanitària de les Illes Balears, Spain

ARTICLE INFO

Corresponding author:

Jose Antonio Delgado
Department of Laboratory Medicine
Hospital Universitari Son Espases
Ctra. de Valldemossa, 79, J+1
07010 Palma
Balearic Islands
Spain
Phone: +34 871205876
E-mail: jose.delgado@ssib.es

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hyperglycemia, follow-up, diabetes mellitus, biomarker, HbA1c, glycated hemoglobin

ABSTRACT

Background-aim

Diabetes mellitus is one of the most prevalent diseases worldwide. According to the ADA 2020 guidelines, individuals with unstable glycemic control should be monitored every three months by measuring glycosylated hemoglobin (HbA1c). The aim of this study was to evaluate the demand adequacy for HbA1c in the monitoring of patients with diabetes mellitus with a highly unstable glycemic control.

Methods

Retrospective observational study (2016-2019). All HbA1c tests from individuals ≥ 18 years requested by hospital physicians were considered.

Highly unstable glycemic control was defined as $HbA1c \geq 10.0\%$, and their monitoring was classified as: *optimal*, *out of recommendations* (if > 3 months) and *lack of monitoring* if no further HbA1c measurement was performed by the laboratory.

For individuals classified as *lack of monitoring*, medical records were reviewed and further reclassified as: [1] due to patient's responsibility, [2] attributable to the requesting physician, [3] monitored by POCT, [4] unfeasibility of monitoring or [5] referral outside our area for follow-up.

Results

During the assessed period, 1,156 patients had an HbA1c value $\geq 10.0\%$. 67.5% of them were monitored either in the clinical laboratory or as POCT (33.7% optimal monitoring), whereas 21.0% patients were not monitored due to preventable situations.

Conclusion

Lack of monitoring due to physician's reasons or patient's responsibility highlights the urgent need for an improvement.



INTRODUCTION

Diabetes mellitus is a chronic and progressive disease which affects about 422 million people worldwide and may lead to serious damage to cardiovascular, nervous and renal systems, among others.¹ The measurement of glycated hemoglobin (HbA1c), in combination with fasting glucose, is the recommended strategy for the monitoring of diabetic individuals.² A value of HbA1c $< 6.5\%$ is related with a good glycemic control, while less strict objectives (HbA1c $< 7.0\%$ or HbA1c $< 8.0\%$) may be acceptable for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications or long-standing diabetes. In such individuals, the glycemic goal might be difficult to achieve despite diabetes self-management education, and effective doses of multiple glucose-lowering agents. Hence, goals are not designed to be applied rigidly but to be used as a broad construct to guide clinical decision-making.

According to the American Diabetes Association guidelines (ADA) in 2020, individuals with a diagnosis of diabetes mellitus and unstable glycemic control (HbA1c $> 7.0\%$) or with a change in their treatments, should get tested every three months either in clinical laboratories or by means of point-of-care testing devices (POCT).³ Other biomarkers have also recently been included in some protocols for specific cases,⁴ especially where HbA1c is not suitable or interferences are present, such as in individuals with anemia, altered erythrocyte indices or certain hemoglobin variants.⁵

These recommendations are of special relevance for patients with an even higher concentration of HbA1c, such as those above 10.0%. The aim of this study was to evaluate the demand adequacy for HbA1c in the monitoring of patients with diabetes mellitus with a highly unstable glycemic control in a hospital setting.

METHODS

This is a retrospective observational study performed in the Hospital Universitari Son Espases (Mallorca, Spain), a tertiary hospital, between 2016–2019. We considered all HbA1c tests from individuals aged ≥ 18 years requested by hospital physicians (general practitioners from primary healthcare offices were excluded). Data were obtained from the laboratory information system (LIS) GestLab (Indra, Spain). HbA1c was measured on the HPLC HA-8180V platform (Menarini, ArkrayAdams, USA) using a reversed-phase cation exchange chromatographic method. Results were presented according to the Diabetes Control and Complications Trial (NGSP/DCCT).⁶ Individuals with a diagnosis of hemoglobinopathy or the detection of a peak of hemoglobin variants in the chromatogram were also excluded.

Highly unstable glycemic control was defined as HbA1c $\geq 10.0\%$. According to the ADA 2020 guideline, the monitoring of individuals with a HbA1c $\geq 10.0\%$ result was classified as: optimal

monitoring if HbA1c was retested ≤ 3 months, out-of-recommendations monitoring if retested > 3 months and lack of monitoring if no further HbA1c measurement was performed by the laboratory in the assessed period.

For the individuals classified as lack of monitoring, after obtaining the approval by the Ethics Board of our institution [Research Ethics Committee of the Balearic Islands (CEI-IB)], medical records were reviewed and further reclassified as [1] no monitoring due to patient's responsibility (they do not attend the next medical appointment for follow-up), [2] no monitoring attributable to the requesting physician (no referral to specialist or general practitioner for follow-up and no retest requested), [3] POCT (HbA1c monitoring was performed, for instance at the doctor's office, but not in the clinical laboratory), [4] unfeasibility of monitoring (exitus, no medical record in the hospital information system (HIS) or patient has moved to another region/country) or [5] referral to specialist at another hospital or general practitioner for follow-up. The clinical information was obtained from the HIS Millennium (Cerner, USA).

All methods were carried out in accordance with relevant guidelines and regulations.

Means and standard deviations were calculated for each group. The Student's t-test was used for statistical analyses and significance was set at 0.05. The Excel 2010 (Microsoft Inc., USA) software was used for all calculations.

RESULTS

During the assessed period, a total of 101,145 HbA1c results were considered (98,868 patients), of which, 1,703 (1,156 patients) had a value $\geq 10.0\%$. Values above 12% represented 31% of the total number of individuals with HbA1c $\geq 10.0\%$, indicating an extremely poor glycemic control.

Among them, 249 individuals presented an optimal monitoring, 494 individuals had a monitoring out of the ADA 2020 recommendations, and 413 individuals were not monitored at all, according to the records in the LIS (Figure 1).

Nevertheless, LIS data, together with medical record review, showed that the number of monitored individuals either in the clinical laboratory or as POCT was 780 (67.5% of individuals with HbA1c $\geq 10.0\%$), whereas 243 (21.0%) patients were not monitored due to preventable situations (Table 1). All individuals with HbA1c $\geq 10.0\%$ had a previous diagnosis of diabetes mellitus and were under treatment, so the finding of high values was not unexpected.

When considering the three categories of follow-up (optimal monitoring, lack of monitoring and out-of-recommendations monitoring), no statistical differences were seen in HbA1c concentrations, nor in the age or sex of individuals.

DISCUSSION

In this study, the monitoring of individuals with a poor glycemic control (HbA1c $\geq 10.0\%$) was evaluated, and the causes for the lack of a proper monitoring were registered.

During the four years assessed, laboratory requests (by hospital physicians) with a high HbA1c $\geq 10.0\%$ represent about 1.7% of HbA1c requests. International guidelines on diabetes care,⁷ recommend a close follow-up for individuals with poor glycemic control in order to consider possible changes in the therapeutic strategies and tackle comorbidities. Even though a high percentage of such individuals were monitored in our area, 32.5% of them did not show any retest of HbA1c, either in the LIS or as POCT.

Despite POCT instruments are usually not connected to the LIS, proper quality assurance programs warrant the transferability of the results obtained thereof. Some general practitioners

Figure 1 Flow diagram for the inclusion/exclusion of individuals in the study

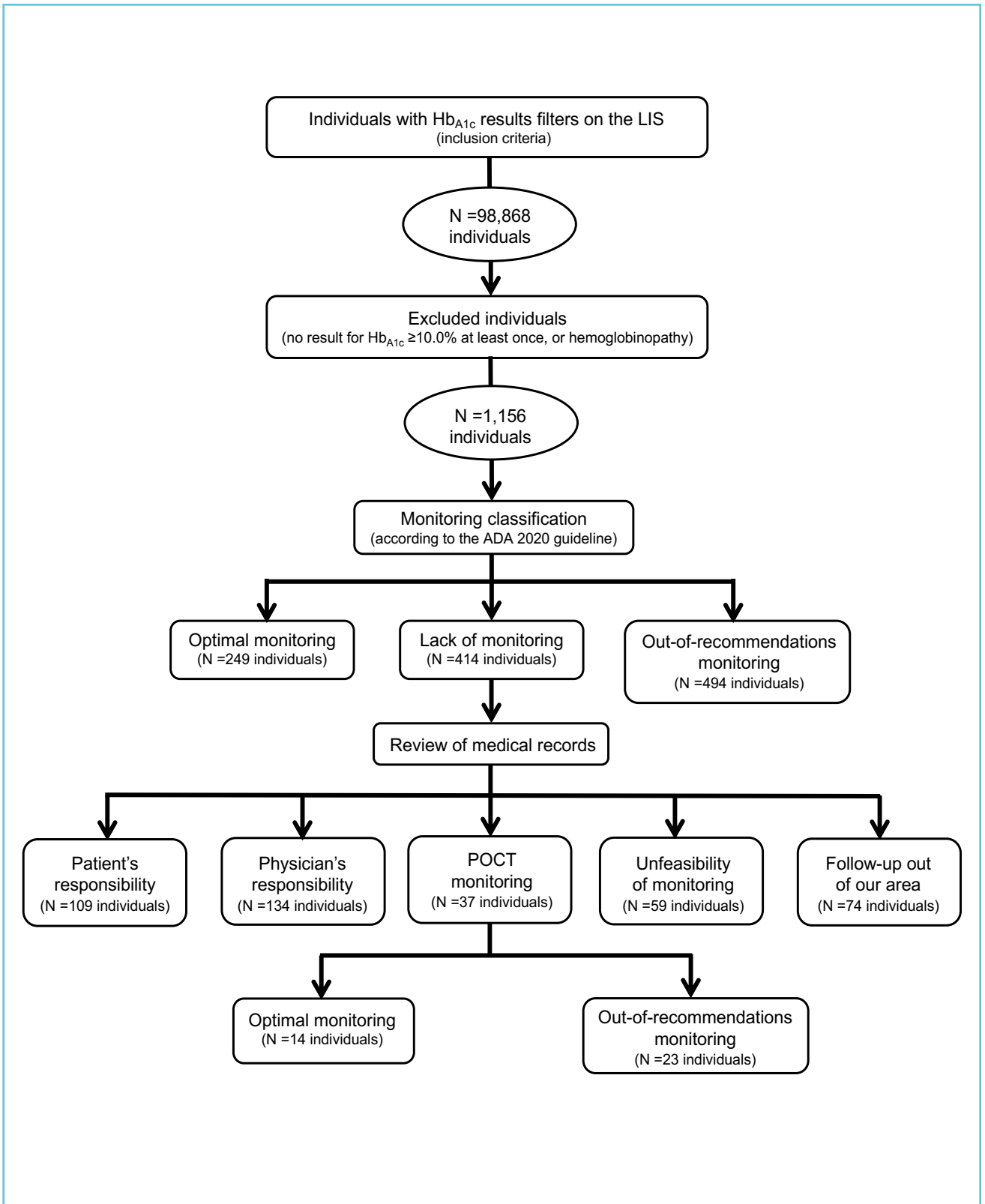


Table 1 Type of monitoring for individuals with HbA1c $\geq 10.0\%$. Results are presented as mean (standard deviation)

HbA1c $\geq 10.0\%$ n = 1,156	Monitoring classification					
	Optimal	Out-of-recommendations	Lack of monitoring			
			Patient's responsibility	Physician's responsibility	Unfeasibility of follow-up*	Follow-up out of our area
HbA1c, %	11.5 (1.4)	11.2 (1.2)	11.5 (1.4)	11.3 (1.2)	11.4 (1.2)	11.7 (1.3)
Retesting interval, days	48 (26)	281 (205)	-	-	-	-
Age, years	59 (19)	60 (19)	55 (17)	63 (17)	67 (25)	58 (20)
n, %	263, 22.8%	517, 44.7%	109, 9.4%	134, 11.6%	59, 5.1%	74, 6.4%

* Due to: exitus, no medical record in the hospital information system or patient has moved to another region/country.

and endocrinologists have portable devices at their offices for a quick HbA1c test, which is used in selected patients. Therefore, in our study, individuals with a retest performed on POCT systems were considered as monitored.

A lack of monitoring due to physician's reasons or due to patient's responsibility has been reported in 21.0% of cases, which highlights the need for an improvement; as such individuals may develop serious micro and macroangiopathic comorbid situations.

To the best of our knowledge, this is one of the few studies assessing the monitoring of individuals with a poor glycemic control. Most reports on HbA1c uses for monitoring focus on the pre-analytical issues related with an improper retesting interval, thus recommending a minimum of 2–3 months for a retest.⁸ Automatic rules in LIS prevent the need of performing excessive retests for the same individual. Even though no study was found on whether international

recommendations are followed in terms of maximum retesting intervals, nevertheless, Salinas and colleagues⁹ have recently described a deficient number of HbA1c measurements in Spanish laboratories in comparison with the incidence of diabetes in the country. Their finding is emphasized with our observations.

In our study, we found a non-negligible percentage of individuals with very poor glycemic control had not been properly monitored. In this sense, clinical laboratory professionals should take a proactive attitude by alerting endocrinologists and other medical specialists to monitor them, for example by including flags in their LIS if a retest is not performed within a certain period of time. In addition, the inclusion of POCT systems has shown to improve the monitoring of these individuals.¹⁰

This study has some limitations, mainly related to its retrospective nature and the trust in the records from the laboratory and hospital

information systems. Besides, a lack of follow-up for an individual during the assessed period does not imply that they were not extensively studied before or after the described dates. Likewise, no information is available on the adequacy of monitoring after referral to other hospitals or primary care. Pregnancy was not considered as a variable in our study, although the success of follow-up for gestational diabetes mellitus might be different from the general population. In addition, given no differences in age, sex or HbA1c values which could explain the variability in the monitoring, there might be uncontrolled variables in this study which should have been considered, thus representing potential improvements for future projects.

Further studies on the long-term clinical impact of a lack of monitoring will enable to assess possible hyperglycemia-related micro and macroangiopathic diseases, as well as comorbid situations and mortality.

In summary, the monitoring of diabetic individuals by means of HbA1c measurement is pivotal, in order to optimize their treatment and prevent complications and is crucial especially for those with a poor glycemic control. The lack of a proper monitoring for these patients might lead to damage both for the patient's safety and for the healthcare system.



ADDITIONAL INFORMATION

Ethics approval and consent to participate

The study was approved by the Ethics Board of our institution.

Consent for publication

Consent to submit has been received explicitly from all co-authors, as well as from the responsible authorities. Authors whose names appear on the submission have contributed sufficiently to

the scientific work and therefore share collective responsibility and accountability for the results.

Data availability

This is a retrospective observational study performed at Hospital Universitari Son Espases (Palma de Mallorca, Spain). Analytical data were obtained from the laboratory information system GestLab (Indra, Spain), and the clinical information was extracted from the hospital information system Millennium (Cerner Corporation, USA).

Conflicts of interest

All authors declare no conflicts of interest.

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Authors' contributions

All authors contributed to the experimental design and approved the final version of the manuscript.

Study conception and design

JAD, JMB; acquisition of data: JAD; analysis and interpretation of data: JAD; drafting of manuscript: JAD, JMB; critical revision: JAD, JMB.



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Multicenter survey of physicians' perception of interpretative commenting and reflective testing in Nigeria

Lucius Chidiebere Imoh¹, Chinelo Pamela Onyenekwu²,
Kenneth Ogar Inaku³, Alexander Oghielu Abu⁴, Chibuzo David Tagbo⁵,
Idris Yahaya Mohammed⁶, Modupe Akinrele Kuti⁷

¹ Department of Chemical Pathology, University of Jos and Jos University Teaching Hospital, Plateau State, Nigeria

² Department of Chemical Pathology, Ben Carson Snr School of Medicine, Babcock University and Babcock University Teaching Hospital, Ogun State, Nigeria

³ Department of Chemical Pathology, University of Calabar, Calabar, Nigeria

⁴ Department of Chemical Pathology, Federal Medical Centre, Benue State, Nigeria

⁵ Department of Chemical Pathology, University of Port Harcourt Teaching Hospital, Rivers State, Nigeria

⁶ Department of Chemical Pathology & Immunology, College of Health Sciences Bayero University & Aminu Kano Teaching Hospital, Kano State, Nigeria

⁷ Department of Chemical Pathology, College of Medicine, University of Ibadan, Ibadan, Nigeria

ARTICLE INFO

Corresponding author:

Lucius Chidiebere Imoh
Department of Chemical Pathology
University of Jos
Jos University Teaching Hospital
Jos, Plateau State
Nigeria
Phone: +2348035085697
E-mail: imohc@unijos.edu.ng
drluciusimoh@gmail.com

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ABSTRACT

Background

Interpretative commenting (IC) and reflective testing have recently generated interest because of their potential for adding value to Clinical laboratory testing. Physicians' perception to this post-testing service in Nigeria is unknown. This study examined the practices and physician's disposition regarding IC and reflective testing.

Methods

This cross-sectional study was conducted among 232 doctors working in public and private hospitals across eight purposively selected states in Nigeria. Doctors

who have worked and/or currently working in a health facility within their state of residence and who consented to participating in this survey were given a structured questionnaire to fill and return.

Results

Paper-based reporting (213; 91.8%) was the most commonly practiced reporting method. One hundred and thirty-three (57.4%) doctors responded that interpretative comments were added to laboratory reports. "Free-handed text" (85/133; 63.9%) was the most commonly practiced form of IC; 184/232 (79.3%) and 166/232 (71.6%) doctors respectively considered comments on "potential implication of results" and "suggestions on further investigation" as the most "helpful" aspect of IC. Also, 192/232 (82.7%) doctors strongly agreed/agreed that IC influences patient's management. Only 125 (53.7%) doctors responded that they welcomed reflective testing. Concerns about cost implications (68/107; 63.6%) and delays in release of result (48/107; 44.9%) were among reasons for not supporting reflective testing.

Conclusion

Nigerian doctors generally have a positive disposition towards addition of interpretative comments but less so concerning reflective testing. However, challenges such as lack of LIS, EQA schemes for IC and gaps in physicians' education should be addressed to improve this aspect of laboratory services in Nigeria.



INTRODUCTION

The principal business of clinical laboratory is to provide data in form of test results that are essential for patient care. The crucial role that laboratory data play in patient management have been previously highlighted [1–3]. Apart from

factors related to the generation of laboratory results, the interpretation and application of these results in patients' care may affect clinical outcome [2,3]. The utility of results generated from the clinical laboratory can be enhanced by addition of interpretative comments to guide the end users in applying the test report to patients' care.

Physicians are trained in the rudiments of interpreting laboratory results in accordance with provisional diagnosis made from history and physical examination. However, the need for added comments and interpretations by laboratorians in reporting of laboratory result has become more evident with the increasing spectrum and complexity of tests in addition to increasing number of platforms and technologies for testing [2,4]. Specialist laboratory professionals possess more comprehensive knowledge of the principles, procedures and limitations of the tests and this places them in a good position to add useful comments to laboratory test.

Clinical practice also presents common scenarios where laboratory test results may be inconclusive and may warrant additional testing before arriving at appropriate diagnosis. In such cases, physicians and other end users may benefit from reflective testing. Reflective testing is a procedure in which the laboratory specialist adds additional tests and/or comments to an original request following inspection and reflection on the results [5,6].

Interpretative commenting (IC) and reflective testing have recently generated interest because of their potential for adding value to the testing services that laboratories were traditionally known to provide [7,8]. Indeed, the relative contributions of these post-testing services in improving patients' outcomes has been reported [1,2].

Despite these, the practice of IC and reflective testing may be perceived in different lights among physicians [9]. The cooperation of the requesting physicians is crucial in the successful implementation of interpretative commenting and reflective testing in clinical laboratories. The careful examination of factors that may affect this practice including physicians' perceptions and concerns is therefore important. Available studies regarding this subject have been predominantly in Western countries with much more advanced laboratory technology with well-established post-analytical services. This may not be practicable in resource-poor settings given that provision of IC vary from one country to another, and between laboratories in the same country [2]. There are unfortunately few studies in Nigeria on the subject of laboratory management that focuses on post laboratory testing phase. Additionally, data regarding the practices and utility of interpretative comments and reflective testing in the context of patients' management in Nigeria are scarce. Equally, the perception of physicians to this post laboratory testing service has not been well explored in this setting. This study is therefore aimed at examining the practices and physicians' perception regarding IC and reflective testing.

METHODS

This cross-sectional study was conducted over a six months' period among Doctors working in public and private hospitals across eight purposively selected states, four each from Southern and Northern Nigeria including: Anambra, Cross River, Ogun, Rivers, Benue, Nassarawa, Plateau, and Abuja, the Federal Capital Territory. Doctors who had worked or were currently working in a health facility within their state of residence and who consented to participating in this survey were given a structured questionnaire to fill and return.

The questionnaires were administered during daily departmental seminar presentations as well as to doctors who were on duty during the period of the study. The questionnaire explored information regarding demographics, cadre of doctor, speciality and level of experience. We specifically sought for information regarding the practice, perception and acceptance of interpretative commenting and reflective testing for clinical chemistry tests in the respondents' hospital. The questions on interpretative comment addressed: the format of interpretative commenting practiced, providers of interpretative comment, laboratory tests covered by interpretative comment, information contained in the interpretative comment, perception of practice and usefulness of reflective testing and interpretative comment for clinical chemistry tests. The respondents were encouraged to select all options that applied to a particular question and to include other responses wherever necessary. The self-administered questionnaire was pre-tested using response from seven physicians and laboratory specialists who are knowledgeable about the subject. Areas in the questionnaire that could be potentially misinterpreted were identified, modified or removed from the questions included in the study. Care was taken to avoid loosely used laboratory terms that may not be easily understood by physicians or provide a definition of such terms if their use could not be avoided.

Ethical considerations

Ethical approval was obtained from the Health Research and Ethics Committee of the Jos University Teaching Hospital (reference no. JUTH/DCS/ADM/127/XXV/152) in compliance with the ethical principles for medical research involving human subjects, in accordance with the Declaration of Helsinki. Informed consent was obtained from the respondents and confidentiality was ensured.

Statistical analysis

The data collected were compiled in Microsoft Excel® version 2.0 and exported to Statistical Package for Social Sciences (SPSS® Incorporated Chicago Version 18.0) software for analysis. Descriptive statistics were presented as counts, percentages, frequency tables, and charts. Inferential statistics to test associations was conducted using chi-square or Fisher's exact test where appropriate. P-value < 0.05 was regarded as significant.

RESULTS

A total of 232 doctors were surveyed across eight states in the primary, secondary and tertiary health centers distributed equally in the North and South of Nigeria. Majority of the respondents practiced in tertiary healthcare setting, 183 (78.9%) and in Public hospitals 204 (87.9%). Forty-five (19.4%) of the respondents were Intern doctors, 27 (11.6%) and 81 (35%) respectively were Specialists (Consultants) and Specialist in-training (Registrars) from specialties such as Family medicine (21), Internal Medicine (16), Obstetrics and Gynaecology (18), Paediatrics (19), Surgery (14) among others (20), see Table 1.

Doctors responses on the practice regarding interpretative commenting

Reporting format (n=232)

Paper-based reporting (213; 91.8%) was the most practiced reporting method, while 19 (8.2%) and 2 (0.8) doctors indicated that Laboratory Information System and other methods (e.g. telephone, text messages) respectively was practiced in their health facility.

Provision of interpretative comment on laboratory report (n=232)

One hundred and thirty-three (57.4%) doctors responded that interpretative comments were

added to laboratory reports; whereas 88 (37.9%) reported that interpretative comments were not added to laboratory report in their hospital and 11 (4.7%) did not give any response.

Format of interpretative comments (n=133) *

Among doctors who indicated that their Hospital laboratories provided Interpretative Comments, "Free-handed text" (85/133; 63.9%) was the most commonly practiced form of IC, this was followed by "flagging" of "abnormal" results (29/133: 21.8%) and "canned/pre-coded" comments (13/133: 9.8%), see Table 2.

Provider of interpretative comment (n=133) *

The providers of IC as identified by the responding doctors include, Lab Scientist/Technologist (41/133: 30.8%), Pathologist in-training (25/133: 18.8%), Pathologist (65/133; 48.9%) and 8.3% (11/133) gave no response.

* Respondents selected all that apply hence more than one response per respondents may be allowed as applicably in practice.

Aspects of interpretative comment considered helpful

Regarding the aspect of IC considered helpful to the doctors, 184/232 (79.3%) considered comments on potential implication of results helpful, 166/232 (71.6%) doctors selected "suggestions on further investigation", 116/232 (50%) doctors appreciated comments on "suggested interventions" while 110/232 (47%) and 102 (44%) doctors selected comments on "pre-analytical factors" and "analytical factors" respectively, see Figure 1.

Perceptions on interpretative commenting

Furthermore, 192/232 (82.7%) doctors "strongly agreed/agreed" that IC will indeed influence patient's management, 143/232 (61.3%) said it will help to prevent misdiagnosis; 91/232 (39.2%)

Table 1 General characteristics of respondents

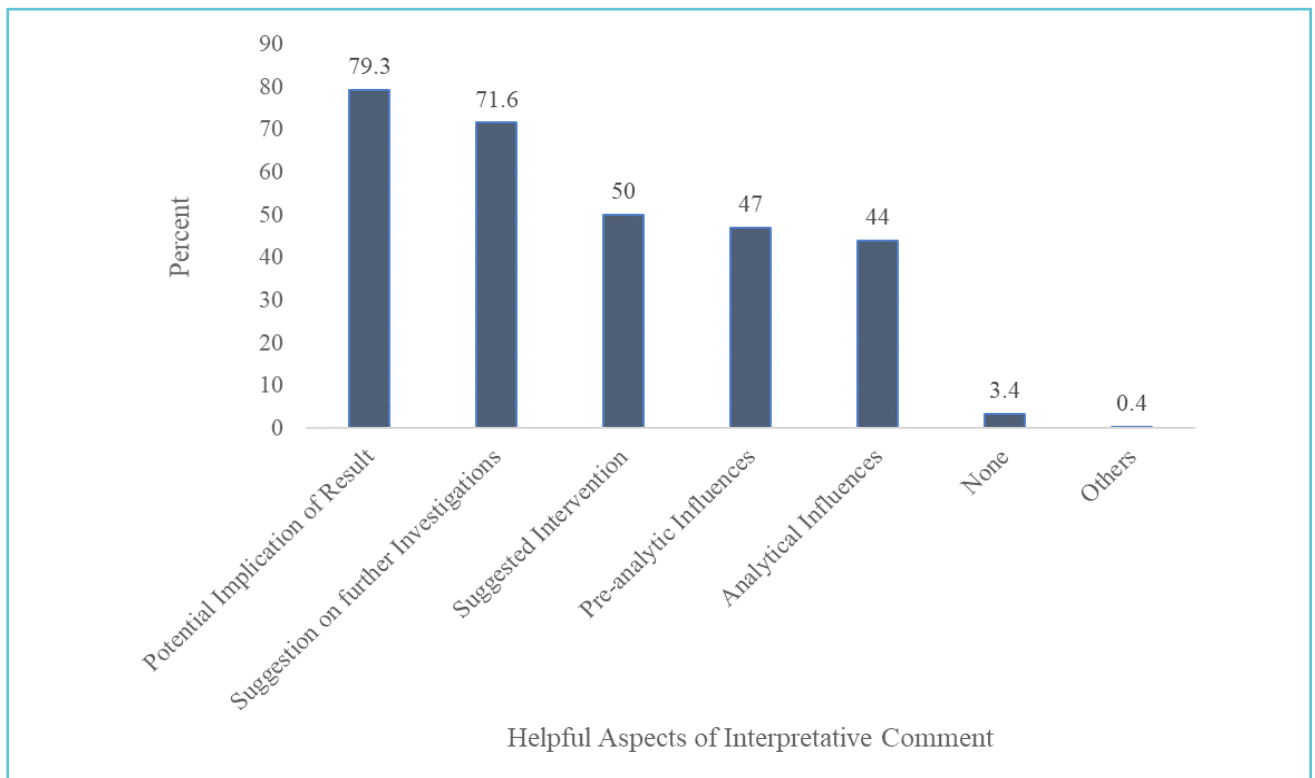
Variable	Frequency	Percent
Hospital category		
Faith-Based Mission	15	6.5
Government/Public	204	87.9
Private	13	5.6
Region		
North	116	50
South	116	50
Level of hospital		
Primary	6	2.6
Secondary	43	18.5
Tertiary	183	78.9
Cadre of doctor		
Intern Doctors	45	19.4
Non-specialist Medical Officers	68	29.3
Specialist in-training (Registrars)	81	35.0
Specialists (Consultant)	27	11.6
Others	11	4.7
Available pathology specialty*		
Chemical Pathology	111	47.8
Hematology	123	53.0
Microbiology	113	54.7
Histopathology	121	67.7

* Respondents selected all that apply hence more than one response per respondents may be allowed as applicably in practice.

Table 2 Doctors perceptions on interpretative commenting

Variable	Strongly agree	Agree	Indifferent	Disagree	Strongly disagree
Influences Patients' Management	103 (44.4)	89 (38.3)	24 (13.8)	2 (0.9)	6 (2.6)
Cause Delay in releasing lab results	18 (7.8)	63 (27.1)	62 (26.7)	71 (30.6)	18 (7.8)
Reduces time to diagnosis	20 (8.6)	71 (30.6)	57 (24.6)	58 (25)	26 (11.2)
Reduces number of needless tests that would be performed	21 (9)	67 (28.9)	60 (25.9)	59 (25.4)	25 (10.8)
Prevents misdiagnosis	50 (21.6)	93 (40.1)	56 (24.1)	26 (11.2)	7 (3)
Concerned about the competency of the staff adding comments on results	85 (36.6)	58 (25)	51 (22)	31 (13.4)	7 (3)

Figure 1 Physicians' response on aspects of interpretative comment they consider helpful



and 88/232 (37.9%) considered IC reduces time to diagnosis and number of needless tests that would be performed. However, 81/232 (34.9%) believed that IC causes delays in releasing laboratory results while 143/232 (61.3%) doctors are concerned about the competency of the staff that provide the interpretative comments, see Table 2.

Perception of usefulness of interpretative comments

The doctors who had used or currently used listed biochemical tests were asked which tests they considered IC to be "very useful"/ "useful". All tests listed had more than 80% of doctors indicating that IC was useful in interpreting the tests.

The greatest approval was for tests such as Thyroid function tests, fertility hormones and endocrine tests, tumour markers, Electrolytes including Na, K, Cl, Mg, PO₄²⁻ and Mg, Lipid profile, Therapeutic Drug Monitoring (TDM), Liver function tests, Blood gases and HbA1c with more than 90% of doctors indicating the usefulness of IC.

Perception on reflective testing

Only 125 (53.7%) doctors responded that they welcomed reflective testing by the testing laboratory. Fifty-three (22.8%) doctors did not agree to reflective testing while 54 (23.3%) were unsure. The reasons given for not supporting reflective testing include: Concerns about cost implications (68/107;63.6%), Concerns about delays in release of result (48/107; 44.9%) and "No added value to test report' (43/107; 43.0%).

Factors associated with provision of interpretative comment and support for reflective testing

Regarding factors associated with provision of IC, IC was more likely to be provided in Tertiary health facilities (P<0.001) and availability of specialists in Chemical pathology, Hematology, Microbiology and Histopathology was significantly associated with provision of IC (p < 0.05). Support for reflective testing was not associated with the type of Health facility, level of care of the facilities, practice of IC or availability of specialists in Chemical pathology, Hematology, Microbiology and Histopathology, p >0.05, see Table 3.

Table 3 Factors associated with provision of Interpretative comments and acceptance of reflective testing

Variable	Provide interpretative comment		X ²	P-value	Welcome reflective testing		X ²	P-value
	Yes (%)	No (%)			Yes (%)	No (%)		
Hospital category								
Faith-Based Mission	5 (35.7)	9 (64.3)	4.05	0.132	9 (60)	6 (40)	0.539	0.764
Government/Public	119 (61.3)	75 (38.7)			110 (53.9)	94 (46.1)		
Private	9 (69.2)	4 (30.8)			6 (46.2)	7 (53.8)		

Level of hospital								
Primary	2 (33.3)	4 (66.7)	13.2	0.001	3 (50)	3 (50)	0.043	0.979
Secondary	16 (38.1)	26 (61.9)			23 (53.5)	20 (46.5)		
Tertiary	115 (66.5)	58 (33.5)			99 (54.1)	84 (45.9)		
LIS								
Yes	12 (70.6)	5 (29.4)	0.832	0.362	11 (57.9)	8 (42.1)	0.134	0.714
No	121 (59.3)	83 (40.7)			114 (53.5)	99 (46.5)		
Paper-based								
Yes	124 (60.5)	81 (39.5)	0.111	0.731	115 (54)	98 (46)	0.013	0.909
No	9 (56.3)	7 (43.8)			10 (52.6)	9 (47.4)		
Available specialists								
Chemical Pathology								
Yes	79 (70.5)	33 (29.5)	10.16	0.001	64 (54.7)	53 (45.3)	0.064	0.800
No	54 (49.5)	55 (50.5)			61 (53)	54 (47)		
Hematology								
Yes	99 (69.2)	44 (30.8)	13.85	<0.001	81 (54.7)	67 (45.3)	0.119	0.730
No	34 (43.6)	44 (56.4)			44 (52.4)	40 (47.6)		
Microbiology								
Yes	85 (68.5)	39 (31.5)	8.25	0.004	69 (54.3)	58 (45.7)	0.023	0.879
No	48 (49.5)	49 (50.5)			56 (53.3)	49 (46.7)		
Histopathology								
Yes	96 (64.9)	52 (35.1)	4.1	0.043	89 (56.7)	68 (43.3)	1.54	0.214
No	37 (50.7)	36 (49.3)			36 (48)	39 (52)		

DISCUSSION

Post analytic activities such as Interpretative commenting and Reflective testing are essential to adding value in laboratory medicine practice [7,8], and their impact on patients' treatment outcomes is increasingly under focus especially in Europe, Asia and America [2,10]. Our findings show that unlike these regions, post-analytic service in clinical laboratories in resource-poor settings like Nigeria is mainly driven by paper-based reporting systems which is bedeviled by several problems (such as missing data or request forms and improperly filled data) that hamper the goal of translating laboratory test results into clinical outcome. The most appropriate interpretation of a test will often be provided when the results are correlated with the clinical context of the patient. Unavailable or inaccurately provided relevant clinical information may therefore hinder or mislead the provision of comments [5]. Zemlin et al, reported that incorrectly completed request forms for thyroid function tests limited pathologists' ability to provide meaningful advice to clinicians leading to potentially serious medical errors [11].

Adding interpretative comments to routine test results even in settings aided by automation and laboratory information system (LIS) is daunting given the sheer volume of testing and the expectation on turnaround time [5,12,13]. This task becomes almost unrealistic in high workload laboratories practicing paper-based reporting. Although it could be argued that IC need not be provided for all test categories, nearly half of the doctors surveyed did not receive IC in reports provided by their hospital laboratories. Interpretative Comments were more likely to be provided in tertiary health facilities especially where specialists in pathology disciplines are available. In addition to the infrastructural deficit, it is clear that availability of specialists in the pathology disciplines is a crucial factor

if IC would be practiced satisfactorily in clinical laboratories across Nigeria. With only about 500 pathologists to serve nearly 200 million people, the number of pathologists in Nigeria is grossly inadequate [14]. This is in keeping with the submission of Laposata who suggested that availability of sufficient specialists in the clinical laboratory constitute the "largest barrier" to more widespread implementation of interpretative comment programs [15]. Kappelmayer et al, proposed that in order to maximize the available manpower, expert laboratorian's attention would be most needed for interpretative comments in specialized testing and subspecialties such as several flow cytometric analyses, genetic and molecular diagnostics and autoantibody testing [16]. Other tests that would nearly always require interpretative comments include: coagulation disorders, hemoglobin and anemia evaluations, serum protein analysis, immunophenotyping analysis, endocrinology, toxicology and new tests or complex panel tests [17].

According to our survey, IC is mainly provided by pathologist, pathologist-in-training and in almost one-third of the cases, they can be obtained from laboratory scientist and technologist. This variation probably reflects the availability of appropriate manpower in different tiers of health facilities. Pathologists and pathologist-in-training for instance are more likely to be available in teaching hospitals and tertiary health facilities.

"Free-handed text" was the most commonly practiced form of IC in this study. Use of canned comments was not very common. This is not surprising as these forms of IC would often require robust IT infrastructure which are not readily available in most of the hospitals surveyed. Canned comments are often "standardized" on the basis of agreed criteria or rules in many cases generated by the LIS softwares [5].

Unlike canned comments, free handed text provides flexible opportunity for laboratories to attend to patient-specific issues that may impact the lab result. Patient-specific interpretation requires extensive cross-referencing to other information contained in the patients' record such as previous test results, other related tests, and clinical history [12].

This information will be difficult to access in most Nigerian health facilities in the absence of functional electronic based information system. Free handed text IC typically contains one or more distinct ideas such as suggesting a probable diagnosis; suggesting which diagnoses can be excluded; and suggesting additional investigations [18]. Other aspects of IC include potential pre- and post-analytical variables that affect the test, variables relating to performance characteristics of the test e.g. reference intervals, decision limits, limit of detection, error estimates etc. Nonetheless, free handed text IC is often non-standardized and therefore run the risk of inclusion of inappropriate and sometimes misleading comments [4,15].

The most useful aspect of IC according to 80% of doctors was comments relating to the potential implications of the results. This was followed by suggestions on further investigations to consider. This finding agrees with earlier studies that showed that physicians increasingly welcomed IC which provided advice on what to do next [2,3]. The usefulness of adding an interpretative comment depends on the knowledge of the recipient of the test result [5]. It had been suggested that test reports being returned to requesters who specialize in the condition being investigated are less likely to require comments other than those related to the pre-analytical and analytical phase [5]. In this study however, more than half of the doctors did not consider comments relating to pre-analytical and analytical factors that could impact on the test result helpful. A possible explanation could be that a

substantial number of physicians do not appreciate the impact that numerous factors in the pre-analytic and analytic phase of testing could have on the test result. With increasingly lesser exposure to diagnostic medicine in most medical schools, the physician's knowledge gap on these aspects of testing is widening [8].

It has been reported that many physicians acknowledge the clinical value of the interpretative services and perceive that the interpretations improved clinical care by saving them time, helping prevent misdiagnoses, and shortening the time to diagnosis [2,9,19,20]. A similar perception towards IC was observed in this study. The majority of doctors in this survey judged that IC influences patient's management and helped to prevent misdiagnosis. Regarding specific biochemical tests, more than 80% of doctors acknowledged that interpretative comments were useful for all biochemical tests they were asked about.

On the other hand, some negative perceptions towards IC were reported by some doctors in this study. About one third of the doctors believed that IC causes delays in releasing laboratory results. This may not be unrelated to long turnaround time for routine test which is already a concern for clinical laboratories especially in resource-poor settings [21]. Notably, more than sixty percent of the doctors expressed concern regarding the competencies of the staff that provide the interpretative comments. This concern has been echoed by several experts in this subject [3,4,8]. It is therefore critical that input in the form of interpretative comments and reflective testing is provided by competent laboratory staff. Generally, desirable qualities of such laboratory personnel would include; requisite medical experience and knowledge of the pathophysiology and clinical correlates, understanding of the analytical processes involved in generating the results, and knowledge of performance characteristics

of the test methodology [3,4,15]. Interpretation also requires recognition of potential pre- and post-analytical variables as well as astute communication skills [18].

In order to better develop the skill for IC, adequate training for those who provide IC has been advocated [5,8]. In addition, there is need for regular assessment for providers of IC to ensure best practices in the provision of this post-testing interpretative service [5]. Experts have suggested that this can be done in the form of educative External Quality Assessment (EQA) programme for IC and several ways of effectively achieving this have been proposed [4,22]. Nevertheless, there is yet no consensus on the modality of this EQA schemes although efforts are ongoing in this regard [8,23,24]. National laboratory societies have been called upon to facilitate these schemes [10]. To our knowledge there are no streamlined EQA schemes for IC in Nigeria although efforts have been made through individual pathology disciplines in collaboration with foreign partners to provide some form of educative IC assessment programmes for their members. Also, pathologists and other laboratory professional groups take advantage of social medial platforms to provide informal educative assessment on IC although these forms of assessment lack some key tenants of formal EQA schemes and their effectiveness have not been ascertained. The need for formal structured EQA programmes in Nigeria and sub-Saharan Africa is thus glaring and could benefit from support from more advanced countries with well-established IC EQA schemes.

In this study we found that about half of the responding doctors do not welcome reflective testing. This is at variance with reports from other climes where reflective testing has been considered a useful way of improving patients' outcome by different general practitioners or other clinicians [8,25]. In the present study

support for reflective testing was not associated with the type of health facility, level of care of the facilities, practice of IC or availability of specialists. Doctors who did not approve of reflective testing were mainly concerned about the added cost that this may place on their patients. Besides the financial implications of adding tests, the doctors were also concerned that adding further tests would lead to overall delays in the reporting of the result of the requested tests. Furthermore, some doctors were not convinced that adding further tests will add value to the reports. Although there has been debates as to whether reflective testing positively influence patient management, studies have shown that reflective testing as well as narrative interpretation of results may aid to reduce medical error [26,27].

Reflective testing may assist the requesting clinician to help exclude a diagnosis, expedite a diagnosis that is fairly obvious, or obtain a diagnosis when the original set of results is equivocal [6]. It had previously been reported that adding magnesium results suggestive of hypokalemia with $K^+ \leq 2.5$ mmol/L increased the incidence of the diagnosis of hypomagnesaemia [27]. Despite these advantages, the practicality of reflective testing will be limited if appropriate data is not available to the laboratory specialists. Furthermore, there is no consensus regarding when reflective testing is indicated, for which tests, and for what type of results. Also there are no quality indicators (QIs) or performance criteria that have been set for added testing [8,10,28].

LIMITATIONS AND CONCLUSIONS

This study had some limitations. The study was conducted among physicians at different level of experience and specialties which is likely to influence their perceptions on adding comments on tests results as well as reflective

testing although inferential statistics did not show this to be so. A probability-based sampling would have been better representative although majority of the health facilities in this study serviced cosmopolitan cities. Also, this study did assess the types of reflective test or comments frequently conveyed to the clinicians. Furthermore, this study did not cover interpretative service by telephone. The extent of this form of consultation that may have been included in the response provided by the physicians is unknown. Despite these limitations, this study has provided rare data about the provision of post-analytical services in the form of interpretative comments and reflective testing in a resource-poor setting. It is obvious that physicians in Nigeria have a positive disposition towards addition of interpretative comments, though less so for reflective testing. This study has also highlighted challenges such as lack of LIS across health facilities, lack of EQA schemes for IC as well as gaps in physicians' education that should be addressed to improve this aspect of clinical laboratory services in Nigeria.



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Availability of data and materials

All relevant data supporting the conclusion are within the paper. The datasets used for this

manuscript are available from the corresponding author on reasonable request.

Authors' contributions

Authors Contribution: LCI served as the lead investigator; LCI, CPO, KOI, AOA and CDT, contributed to study conception/design and data acquisition, LCI, CPO, KOI, AOA, CDT, IYM and MAK contributed to data analysis and interpretation, and writing of article; LCI, CPO, KOI, AOA, CDT, IYM and MAK contributed to editing, reviewing and final approval of article. All authors read and approved the final version of the manuscript.

Conflicts of interest

The authors declared that there is no competing interest.

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E-gene RT-PCR crossing point value and other biochemical parameters as useful markers of death risk in COVID-19 patients

Alba Bellés-Bellés^{1,2}, María Bernal³, Javier Gómez-Arbonés⁴,
Albert Bernet^{1,2}, Silvia Picó³, Jessica Bueno¹, Carlos Chávez³,
Mercè García-González^{1,2}, Mercè Ibarz^{2,3}

¹ Sección de Microbiología, Hospital Universitari Arnau de Vilanova, Lleida, Spain

² Universitat de Lleida (UdL), Spain

³ Servicio de Análisis Clínicos, Hospital Universitari Arnau de Vilanova, Lleida, Spain

⁴ Institut de Recerca Biomèdica (IRB) Lleida, Departament de Medicina, Universitat de Lleida, Spain

ARTICLE INFO

Corresponding author:

Alba Bellés Bellés, PhD
Sección de Microbiología
Hospital Universitari Arnau de Vilanova
Avda. Rovira Roure 80
25198, Lleida
Spain
Phone: +34 973 70 53 30
E-mail: abelles.lleida.ics@gencat.cat

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ABSTRACT

The identification of laboratory markers which predict the outcome of COVID-19 patients is a great concern. Real-time reverse transcriptase–polymerase chain reaction (RT-PCR) has been used to confirm the clinical diagnosis. The aim of this study is to evaluate laboratory parameters of COVID-19 patients as well as to evaluate the RT-PCR crossing point (Cp) value and correlate blood test abnormalities and the Cp value with patients survival. Two hundred thirty patients with positive RT-PCR of SARS-CoV-2 were included in the study. Molecular diagnosis of SARS-CoV-2 was performed by RT-PCR (LightMix, TibMolbiol, Germany). Clinical information, biochemical parameters and Cp values were collected in an anonymized database and variables were analyzed with SPSS v25.0 (IBM Corporation, Armonk, NY, USA). No-survivors were significantly older (>65 years old) than survivors

($p=0.007$). A higher prevalence of cardiovascular comorbidities in patients who died than in those who survived was found ($p=0.002$). Statistically significant differences were obtained comparing RT-PCR Cp values for the E-gene of patients who died and those who survived, being lower (≤ 28) those of patients who died ($p=0.004$). No-survivors had significantly higher levels of CRP (>100) ($p=0.007$). E-gene Cp values ≤ 28 , which correlate with a high number of copies of SARS-CoV-2, as well as several demographical and biochemical parameters (Age above 65 years old, CRP levels >100 mg/L or cardiovascular comorbidities) could be useful markers of death risk in these patients.



INTRODUCTION

During the month of December 2019, several cases of pneumonia of unknown etiology were reported in Wuhan (Hubei, China). A novel member of the Coronaviridae family was identified as the causing agent being the seventh member of this family to infect humans (1-3). The novel virus and the disease were named SARS-CoV-2 and COVID-19, respectively. Human to human contacts and respiratory droplets are the main transmission mechanisms of the virus. The outbreak of COVID-19 was declared a Public Health Emergency of International Concern on 30 January 2020 and has put the health authorities on high alert across the world. Until February 11, 2021 the number of SARS-CoV-2 cases has globally reached one hundred six million, and more than two million three hundred thousand people have died (<https://www.who.int/>, visited February 11, 2021). Specifically in Spain more than three million of SARS-CoV-2 cases have been declared until now, with the Spanish communities of Madrid and Catalonia the most deaths due to COVID-19 (<https://www.mscbs.gob.es>, visited February 11, 2021).

Clinical features of patients with COVID-19 have been recently described. The most frequent reported symptoms are fever, cough, myalgia or fatigue, and sputum production, headache, haemoptysis, and diarrhoea are less common symptoms. In addition, more than the 60% of patients had lymphopenia and cytokine storm could be related with disease severity (2). The SARS-CoV-2 can also cause severe respiratory illness and other serious complications leading to intensive care unit (ICU) admission and high mortality. Therefore, early diagnosis and treatment of critical cases is decisive (4). Real-time reverse transcriptase–polymerase chain reaction (RT-PCR) of nasopharyngeal swabs has been used to confirm the clinical diagnosis (5). The International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) recently published several biochemical and haematological parameters for monitoring COVID-19 patients (<https://www.ifcc.org>). Nonetheless, there is urgent requirement for identification of laboratory biomarkers for progression towards severe and lethal forms of COVID-19 (6, 7).

Therefore, the aim of this study is to assess biochemical and haematological characteristics in the first blood test of patients with positive RT-PCR of SARS-CoV-2 as well as to evaluate the RT-PCR crossing point (Cp) value and correlate blood test abnormalities and the Cp value with patients survival.

1. MATERIALS AND METHODS

Study subjects and data collection

Two hundred and thirty patients with positive RT-PCR of SARS-CoV-2 admitted to the Hospital Universitari Arnau de Vilanova (Lleida, Spain) between March 18, 2020 and April 3, 2020 were included in the study. Clinical information, including biochemical and haematological parameters, from the 230 patients were collected at the earliest time points possible

upon laboratory-confirmed diagnosis of SARS-CoV-2. Permission to conduct the study was approved by the “Hospital Universitari Arnau de Vilanova de Lleida Ethics Committee”.

Clinical and laboratory data

All electronic medical records were checked and demographic data (sex and age), requesting service, comorbidities of patients (cardiovascular disease, immunodeficiency or respiratory disease) and outcomes were included in an anonymized database.

Molecular diagnosis of SARS-CoV-2 was performed in all patients by real time RT-PCR (LightMix, TibMolbiol, Germany) with the Light-Cycler 480 real-time PCR system (Roche, Basel, Switzerland) in nasopharyngeal swabs. Nucleic acid extraction was performed with the automated system Qiasymphony with DSP Virus/Pathogen kit (Qiagen, Hilden, Germany), 60 μ L eluate was obtained from 200 μ L of the original sample.

RT-PCR crossing point (Cp) is defined as the point at which the fluorescence rises above the background fluorescence (8). The Cp value correlates with the number of copies of the target organism in an exponential and inversely proportional relationship (9). Cp values for the E-gene of SARS-Cov-2 were collected in the database.

All patients had a blood test performed at the earliest time possible upon laboratory-confirmed infection of SARS-CoV-2 which included a complete blood count, serum biochemical test and coagulation profile. Measurements of ferritin, C-reactive protein (CRP), D-dimers (DD), lactate dehydrogenase (LDH), leucocytes and lymphocytes counts were included in the database due to the alteration of these parameters has been previously described as risk factors for severe disease and mortality (7, 10, 11).

Statistical analysis

The anonymized databases were captured and analyzed with SPSS v25.0 (IBM Corporation, Armonk, NY, USA). Categorical variables were described using absolute and relative frequencies. When dealing with continuous variables, mean and standard deviation (SD) were reported. Variables were analyzed using the χ^2 -test, and t-Student test or One-Way ANOVA when appropriate. Survival analysis was done by Kaplan-Meier procedure and Log-rank test and, in order to decide which of the variables related to survival are independent risk factors of increased mortality, we applied a Cox's proportional hazards model. The selected p value for considering differences as statistically significant in all analyses was $p < 0.05$.

2. RESULTS

Clinical data

Two hundred and thirty patients (71 females 159 males) with positive RT-PCR of SARS-CoV-2 were included in the study. The clinical characteristics of the patients are shown in Table 1. The average age of patients was 63.9 years old. The percentage of deaths was 11.3 % (26/230) and the mean age of patients who died was 75.3 years old. Patients who died were older than those who survived ($p=0.007$) (Table 1).

Thirty eight patients (38/230; 16.5%) required admission in the ICU setting. A 63.5 % of the patients (146/230) had at least one comorbidity: 137 patients (59.6%) presented cardiovascular comorbidities, 28 (12.2%) were obese patients, 18 (7.8%) presented respiratory comorbidities (asthma, COPD, bronchiectasis, etc) and 7 patients (3.5%) were immunosuppressed. A higher prevalence of cardiovascular comorbidities in patients who died than in those who survived was the only significant difference found ($p=0.002$).

Table 1 Clinical characteristics, E-gene Ct value, and biochemical parameters of the COVID-19 patients

Characteristics of patients	Number of patients (%)	Discharged (n=204)	Deceased (n=26)	p value risk**
Gender				
Nº males	159 (69.13)	141 (69.11)	18 (69.23)	p=0.994 RR=1.004
Nº females	71 (30.87)	63 (30.88)	8 (30.77)	
Age*				
<=65 years	122 (53.04)	115 (56.37)	7 (26.92)	p=0.007 RR=0.326
>65 years	108 (46.96)	89 (43.63)	19 (73.08)	
Cardiovascular disease*	Yes	137 (59.57)	114 (55.88)	p=0.002 RR=5.204
	No	93 (40.43)	90 (44.12)	
Respiratory disease	Yes	18 (78.26)	17 (8.33)	p=0.432 RR=0.471
	No	212 (92.17)	187 (91.67)	
Immunodeficiency/ Oncologic patients	Yes	7 (3.04)	5 (2.45)	p=0.145 RR=2.654
	No	223 (96.95)	199 (97.54)	
Obesity	Yes	28 (12.17)	24 (11.76)	p=0.567 RR=1.312
	No	202 (87.83)	180 (88.24)	
Clinical laboratory data				
E-gene RT-PCR Ct value *				
<=28	98 (42.61)	80 (39.22)	18 (69.23)	p=0.004 RR=3.031
>28	132 (27.39)	124 (60.78)	8 (30.77)	
Serum ferritin (ng/mL)				
<=400	43 (18.70)	40 (19.61)	3 (11.54)	p=0.953 RR=0.567
>400	187 (81.30)	164 (80.39)	23 (88.46)	
Serum CRP (mg/L)*				
<=100	112 (50.22)	106 (53.53)	6 (24.00)	p=0.007 RR=0.313
>100	111 (49.78)	92 (46.46)	19 (76.00)	
Serum D-dimers (ng/mL)				
<=243 ng/mL	40 (24.24)	39 (25.82)	1 (7.14)	p=0.131 RR=0.240
>243 ng/mL	125 (75.76)	112 (74.17)	13 (92.86)	

Serum LDH (U/L)				
<=378	21 (10.29)	19 (10.27)	2 (10.53)	<i>p</i> =0.841
>378	183 (89.71)	166 (89.73)	17 (89.47)	RR=1.025
Leucocytes count (x10⁹/L)*				
<=4.8	44 (19.38)	39 (19.31)	5 (20.00)	<i>p</i> =0.045
4.8-10.8	168 (74.01)	152 (75.25)	16 (64.00)	RR=1.193
>10.8	15 (6.61)	11 (5.45)	4 (16.00)	RR=0.426
Lymphocytes count (x10⁹/L)				
<0.9	85 (37.45)	72 (35.64)	13 (52.00)	<i>p</i> =0.157
0.9-5.20	142 (62.55)	130 (62.55)	12 (48.00)	RR=1.810

*Statistically significant differences.

** RR first line category vs other (for example RR males vs females: $RR=(18/159)/(8/71)=1.004$).

Crossing point values

The RT-PCR Cp values for the E-gene of the 230 samples were collected and analysed. Cp values ranged from 17.4 to 40. Ninety eight patients (42.6%) showed Cp values below 28 suggesting high levels of virus in these samples. Statistically significant differences were obtained comparing RT-PCR Cp values for the E-gene of patients who died and those who survived (Table 1), being lower (≤ 28) the Cp values of patients who died ($p=0.004$).

Laboratory findings

Laboratory data obtained in the first blood test of patients is shown in Table 1. Measurements of CRP, serum ferritin, DD, LDH, leucocytes and lymphocytes counts were collected. Due to the retrospective study design, not all laboratory tests were done in all patients. Consequently their role might be underestimated.

CRP levels were obtained in 223 patients. All these patients but five (97.75%) had levels of CRP above the reference range (0-6mg/L) in the first analytic, with a median value of 128.74 mg/L. Compared with patients who survived, those who died had significantly higher levels of CRP (>100) than those who did not die ($p=0.007$) (Figure 1). Leucocytes count was performed to

227 patients. Patients who died showed higher levels of leucocytes ($>10.8 \times 10^9/L$) in the first analytic than those who survived ($p=0.045$).

DD, LDH and serum ferritin were elevated in most cases (Table 1) but no significant differences were found between patients who died and those who survived.

Two risk groups were established scoring several risk factors (1 point each one): laboratory abnormalities (1 point each parameter with values outside the reference rang), age above 65 years, cardiovascular comorbidities and ICU admission. A significant association was found between mortality and patients with more than 5 points in this risk score ($p=0.008$).

In survival the multivariate analysis, using the Cox proportional-hazards model, the E-gene Cp value ≤ 28 ($p=0.044$), CRP levels >100 mg/L ($p=0.026$) and presence of cardiovascular disease ($p=0.018$) remained as independent significant predictors for survival with an adjusted Hazard Ratio of 0.419, 2.855 and 4.303 respectively.

3. DISCUSSION

The identification of laboratory markers which predict the outcome of COVID-19 patients is

a great concern. These predictors are needed for guiding the managed care of COVID-19 patients. To the best of our knowledge, this is the first study in Spain of laboratory markers in the earliest clinical analysis performed upon 230 patients with laboratory-confirmed infection of SARS-CoV-2 which may help identify patients at enhanced risk of dying.

The results of this study show the main differences in clinical and laboratory characteristics between positive SARS-CoV-2 RT-PCR survival patients and those who died. We observed in accordance with the results of a recent Italian study and with a meta-analysis performed including exclusively Asian population data (6, 7) that several laboratory tests as well as certain clinical and demographical characteristics exhibit significant differences in COVID-19 patients who died compared with survival patients.

The lethality rate in our study was 11.3 %, lower than the percentage reported in other studies performed in the United States (19%) and in an area of the north of Spain (13%) (12, 13). On the other hand, the lethality rate observed in Spain as of May 1, 2020 was 8% (14), so our data provide a higher rate than what was observed.

Patients who died were significantly older (> 65 years old), as previously described (12, 15, 16), presented cardiovascular comorbidities and showed CRP levels in the clinical analysis above 100 mg/L. Bonetti et al. reported higher CRP levels in patients who died than in those who did not die (7) and Du et al. described a major risk of mortality in patients suffering from cardiovascular disease (16).

Patients who died presented significantly lower Cp values ($C_p < 28$; $p=0.004$), which correlate with a high number of copies of SARS-CoV-2.

In contrast with other studies reporting higher levels of serum ferritin, LDH, DD in severe cases of COVID-19 (4, 7, 17) no differences were found in these parameters in the earliest clinical

analysis between patients who died and those who survived, nevertheless the number of participants in those studies was very low.

In conclusion, this is the first report in Spain of abnormalities in clinical laboratory data predicting fatal outcome among positive SARS-CoV-2 RT-PCR patients. Our findings suggest that low E-gene Cp values (≤ 28) as well as several demographical and biochemical parameters (Age above 65 years old, CRP levels >100 mg/L or cardiovascular comorbidities) could be useful markers of death risk in these patients.



Conflicts of interest

The authors declare that there is no conflict of interests.

Authors' contributions

AB and MB have contributed equally.

All authors participated in data interpretation and in writing the manuscript. All authors took responsibility for the decision to submit for publication.



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Diabetic euglycemic ketoacidosis induced by oral antidiabetics type SGLT2i

Guillermo Velasco de Cos¹, María Isabel Sánchez-Molina Acosta²,
María Matilde Toval Fernández¹

¹ Hospital Universitario Marqués de Valdecilla, Santander, Spain

² Hospital Comarcal de Laredo, Spain

ARTICLE INFO

Corresponding author:

Guillermo Velasco de Cos
Servicio de Análisis Clínicos Hospital
Universitario Marqués de Valdecilla
Santander
Spain
E-mail: guillermovelascocodcos@gmail.com

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ABSTRACT

Euglycemic diabetic ketoacidosis (euglycemic DKA) is a serious complication of diabetes, which can occur in some patients treated with oral antidiabetics called sodium-glucose co-transporter 2 inhibitors (SGLT2i). This group of drugs works by increasing renal excretion of sodium and glucose, thereby lowering blood glucose levels.

Euglycemic DKA is characterized by having blood glucose levels in the normal range, usually below 200 mg/dL (11 mmol/L), which complicates early diagnosis.

We present the case of a 67-year-old patient with type 2 diabetes mellitus, treated with metformin and empagliflozin, who was admitted to the Intensive Care Unit in a coma with severe ketoacidotic decompensation.

INTRODUCTION

Classic diabetic ketoacidosis (DKA) is one of the most serious complications of diabetes. It is accompanied by hyperglycemia, metabolic acidosis, and increased ketone bodies in the blood and urine [1][2]. In a subgroup of patients, blood glucose is in the normal range or at the high limit, with values below 200 mg/dL (11 mmol/L), associated with an elevated metabolic anion gap and positive ketones. This clinical manifestation is defined as euglycemic diabetic ketoacidosis (euglycemic DKA). [3]

Conditions that can cause euglycemic DKA are: prolonged fasting, dehydration, excessive alcohol consumption, salicylate overdose, lactic acidosis, reduced insulin doses, viral or bacterial infections, tricyclic antidepressant overdose, renal tubular acidosis, starvation, glycogen storage disorders, and SGLT2i treatment. [4]

The glyphlozin family (SGLT2i), is a group of oral hypoglycemic drugs, which are used in the treatment of type 2 diabetes. Included in this group are dapagliflozin, canagliflozin and empagliflozin. These drugs were authorized in 2012 by the FDA and the EMA and are recommended as second-line therapy associated with insulin and other oral antidiabetics, such as metformin, as they improve glycemic control [5].

CLINICAL CASE

A 67-year-old male was found unconsciously in his home by his son with a drooping corner of the mouth to the right side. His son referred hyporexia of several days.

On arrival of emergency services, the patient was still unconscious: Glasgow Coma Scale (ECG) 4/15, blood pressure (BP) 197/136 mmHg, heart rate (HR) 127 l.p.m., O₂ saturation 97%. Orotracheal intubation was performed after sedation of the patient. Serotherapy was initiated followed by noradrenaline perfusion for arterial hypotension.

He was transferred to the referral hospital and admitted to the Intensive Care Unit (ICU).

It should be noted that his past medical history showed remarkable high blood pressure, diabetes mellitus type 2 (DMT2) and dyslipidemia along with chronic obstructive pulmonary disease (COPD), transient ischemic attacks (TIAs) with cardioembolic profile, former heavy drinker, no Q Killip I NSTEMI (non-ST-segment elevation myocardial infarction) and depressive syndrome. Up to the moment of hospital admission, the patient was receiving treatment with several drugs, which were disulfiram, bronchodilators, lansoprazole, paroxetine, metformin and empagliflozin, lorazepam, rosuvastatin, amlodipine and olmesartan/amlodipine.

In the ICU the patient presented poor general condition with a decreased level of consciousness (ECG 3/15), hypotensive, tachycardia and tachypnea, asthenic habit, distal coldness, and dryness of mucous membranes.

Biochemistry tests were requested highlighting: glucose 191 mg/dL (10.6 mmol/L), urea 83 mg/dL (13.82 mmol/L), creatinine 1.54 mg/dL (0.14 mmol/L) (glomerular filtrate CKD-EPI 46 mL/min/1.73m²), ultrasensitive troponin I 533 ng/L, phosphorus 7.6 mg/dL (2.45 mmol/L), magnesium 1.1 mg/dL (0.45 mmol/L), serum osmolarity 327 mOsm/Kg and osmol gap 43, remaining tests were normal. The hemogram showed 15.4 × 10⁹/L leukocytes, hemoglobin 13.1 g/dL (8.13 mmol/L) and 187000 platelets, with coagulation of no clinical significance. In Elemental and sediment stood out: glucose (4+) and ketone bodies (4+).

The gasometry displayed severe metabolic acidosis with a pH of 6.92, bicarbonate of 7.7 mmol/L, pCO₂ of 41 mmHg, pO₂ 119 mmHg and an excess of bases of -24.8 mmol/L (ABLflex 800 Radiometer®).

The patient was monitored and a right central venous catheter was placed. Due to hypotension

and poor distal perfusion, noradrenaline and intense fluid therapy were continued, associating bicarbonate for severe metabolic acidosis, together with calcium and magnesium (Table 1: Timeline laboratory tests).

After reaching a certain hemodynamic stability, a cranial *computerized axial tomography (CAT)* was requested, in which bilateral and symmetrical hypodensity of both lenticular nuclei with expansive effect was detected due to volume increase, suggesting toxic/metabolic etiology.

With the suspicion of coma of possible toxic/metabolic origin, a complementary study was carried out. Toxics in urine were negative. In the cooximetry the patient presented: carboxy-hemoglobin 0.7% and methemoglobin 1.6%, ruling out poisoning by toxins and CO.

Given the symptoms of metabolic acidosis with elevated anion gap (osmol gap 43 on admission), normal lactate (1.8 mmol/L), and the patient's history, alcohol poisoning was suspected. Nephrologists decided to administer hemodialysis. After the first session the patient maintained a Glasgow of 3/15, correct renal function, good diuresis rhythm and persistence of acidosis. Sample for ethanol and methanol determinations was sent to the laboratory, being within the reference range (day of admission and the following day), which rules out alcohol intoxication.

The patient needed insulin perfusion in dextran on the 3rd day of admission to the ICU, which corrected acidosis (negative ketone bodies in urine), but the patient's poor neurological response ECG: 3/15.

Once the ingestion of toxins (drugs of abuse, ethanol, methanol, salicylates, CO...) had been ruled out, the symptoms could correspond to euglycemic ketoacidosis due to empagliflozin. For its diagnosis, levels of β -hydroxybutyrate were determined in serum with a result of 103.7 mg/dL (9.96 mmol/L) (reference value <3.1 mg/dL ó < 0.3 mmol/L), improving ketoacidosis with

the administration of insulin and the suspension of antidiabetic treatment from the beginning. No neurological changes at any time on the Glasgow scale.

Finally, the poor evolution and prognosis of the patient's baseline situation led to exitus on the 8th day of admission to the ICU.

DISCUSSION

Euglycemic DKA is a rare entity, which occurs with blood glucose levels below 200 mg/dL (11 mmol/L). There are several possible etiologies, with the recent use of SGLT2i being one of the triggering mechanisms. [6]

These drugs inhibit the reabsorption of sodium and glucose in the proximal and distal renal tubules, with increased glycosuria and natriuresis, thus decreasing the concentration of plasma glucose [7]. The amount of glucose eliminated by the kidney through this mechanism depends on the concentration of glucose in the blood and the glomerular filtration rate.

In addition to their hypoglycemic effect, SGLT2i have other beneficial effects such as weight and blood pressure reduction, and may help prevent heart disease due to plasma volume depletion.

Glycosuria and hypoglycemia caused by SGLT2i reduce insulin secretion in pancreatic β cells and promote glucagon production. These changes in insulin and glucagon promote lipolysis and thus the production of free fatty acids, which are metabolized to ketone bodies (acetoacetate and β -hydroxybutyrate) in the liver by β -oxidation. [8], [9], [10]

Euglycemic DKA in patients being treated with SGLT2i, poses a challenge to the physician because of the few or non-specific symptoms: nausea, vomiting, abdominal pain, anorexia, polydipsia, dyspnea, confusion, normal blood glucose values, and ketoacidosis. [6] The diagnosis of this entity is sometimes late, delaying the patient's

Table 1 Timeline of laboratory tests

	Basal	1 day	2 day	3 day	4 day	5 day	6 day	7 day	8 day	Reference ranges
Markers of severe metabolic acidosis										
pH	6.92	7.3	7.38	7.33	7.34	7.29	7.40	7.44	7.46	7.35 - 7.45
Bicarbonate mmol/L	7.9	9.3	12.7	15.3	21.9	21.3	25.5	24.9	26.6	21 - 26
Base excess mmol/L	-24.8	-16	-19	-9	-3.2	-3.6	0.7	0.7	3.1	-2.5 - 2.5
Lactate mmol/L	1.8	2.8	0.6	0.7	0.6	0.6	0.7	1.4	0.6	0.5 - 2
Clinical Chemical										
Glucose mg/dL (mmol/L)	191 (10.6)	128 (7.10)	116 (6.44)	237 (13.15)	195 (10.82)	208 (11.54)	191 (10.60)	161 (8.94)	171 (9.49)	74 - 109 (4.1 - 6.1)
Urea mg/dL (mmol/L)	83 (13.82)	70 (11.65)	44 (7.32)	79 (13.14)	94 (15.64)	85 (14.15)	74 (12.31)	74 (12.31)	72 (11.98)	19 - 49 (3.16 - 8.16)
Creatinine mg/dL (mmol/L)	1.54 (0.14)	1.20 (0.11)	0.85 (0.08)	0.90 (0.08)	1.04 (0.09)	.76 (0.07)	0.68 (0.06)	0.73 (0.07)	0.70 (0.06)	0.72 - 1.18 (0.063 - 0.10)
Calcium mg/dL (mmol/L)	7 (1.77)	7.6 (1.89)	8.3 (2.07)	9.0 (2.25)	8.6 (2.12)	8.3 (2.07)	8.4 (2.10)	8.1 (2.02)	7.7 (1.92)	8.4 - 10.4 (2.1 - 2.6)
Magnesium mg/dL (mmol/L)	1.1 (0.45)	1.7 (0.70)	1.4 (0.58)	1.7 (0.70)	1.6 (0.66)	1.4 (0.58)	1.3 (0.53)	1.4 (0.58)	1.7 (0.70)	1.6 - 2.5 (0.7 - 1.03)
Phosphorus mg/dL (mmol/L)	7.6 (2.45)	4.4 (1.42)	3.9 (1.26)	1.8 (0.58)	2.1 (0.68)		2.6 (0.84)	2.8 (0.90)	3.1 (1.00)	2.4 - 5.1 (0.8 - 1.65)
Urine analysis										
Glucose	4+			4+						-
Ketone bodies	4 +			±						-

treatment, most of the time due to exclusion. [4] The temporary cessation of SGLT2i, hydration, frequent carbohydrate intake and administration of insulin boluses, together with the administration of bicarbonate, allows the control of ketoacidosis in 12 hours, although most severe cases necessitate several days of care in the ICU. [5], [8].

In the case described, due to the patient's poor condition and personal history, a diagnosis of toxic/metabolic coma (toxins, CO, salicylates, methanol) was made. Once this diagnosis was dismissed, the possibility of treatment with SGLT2i (empagliflozin) was assessed as the cause of the severe ketoacidosis that he presented (very high osmol gap), confirming the new diagnosis with the result of β -hydroxybutyrate in serum days after his admission. The outcome of this case is a result of the severe decompensation he presented upon arrival at the hospital, his diagnosis by exclusion and delay in treatment.

Euglycemic DKA due to SGLT2i is extremely uncommon, with an estimated incidence of 2 out of every 10,000 patients treated with these drugs. It can sometimes go unnoticed, making it an under-diagnosed entity. Euglycemic DKA is more common in patients treated with dapagliflozin than with empagliflozin. [9]

Patients treated with SGLT2i are recommended to make follow-up appointments with their physician, to be aware of possible complications, and to periodically have ketone bodies in blood or urine (test strips) measured (it is important to note that when these levels are high, the patient should report to the emergency department). [11]

LEARNING POINTS

- Euglycemic DKA is a rare and dangerous adverse effect of SGLT2i type drugs.
- The use of SGLT2i is indicated only in type 2 diabetics; its use in insulin-dependent diabetics multiplies the risk of euglycemic DKA.

- The determination of a pH lower than 7.2 together with glycemia lower than 200 mg/dL (11 mmol/L) and ketonuria are the main biochemical indicators of euglycemic DKA.
- In patients treated with SGLT2i, the determination of ketonuria is recommended as a screening procedure.



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