Klin. Biochem. Metab., 27 (48), 2019, No. 1, p. 16–18.

Cystatin C – Implementation in clinical laboratory practice

Šálek T.[1,2,3], Friedecký B.[1], Budina M.[1]

[1]SEKK, spol. s.r.o., Za Pasáží 1609, 530 02 Pardubice
[2]Department of Clinical Biochemistry and Pharmacology, Tomas Bata Hospital in Zlín a. s., Havlíčkovo nábřeží 600, 762 75 Zlín, Czech Republic
[3]Medical Faculty of the University of Ostrava, Department of Biomedical Sciences, Syllabova 19, 703 00 Ostrava – Zábřeh

SUMMARY
Objectives: Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend reporting the cystatin C concentration result together with estimated glomerular filtration rate (eGFRcys). The extent to which the recommendation is implemented to practice is not known. The aim of this study is to determine the implementation extent and to show how laboratories that have not yet implemented the measure can be guided to adopting it to their routines.
Design: Cross – sectional study.
Settings: SEKK, spol. s.r.o., Za Pasáží 1609, 530 02 Pardubice.
Material and methods: Evaluation of cystatin C post-analytical phase was performed by an online electronic questionnaire which was added to routine cystatin C External Quality Assessment (EQA) scheme. A total of 70 participants (59 from the Czech Republic and 11 from Slovakia) were given the questionnaire. They reported traceability of their method calibration to international standard ERM DA471/IFCC, and equations for eGFRcys. Answers were analysed.
Results: In the end, 63 participants responded to the questionnaire. Traceability of calibration to ERM DA471/IFCC was declared by 53 responders. A total of 53 laboratories stated reporting eGFR in all adult patients and 4 participants stated reporting eGFR only on direct request. Six laboratories did not report eGFR. The Chronic Kidney Disease Epidemiology Collaboration (CKD - EPI) equation was used by 57 laboratories. Of them, 22 laboratories also used combined equation with creatinine and three laboratories also calculated Caucasian, Asian, Pediatric and Adult (CAPA) equation.
Conclusion: Majority of laboratories follow the KDIGO guidelines. Further education on calibration traceability and eGFR accompanying all cystatin C concentration results is still needed.
Keywords: Cystatin C, Glomerular filtration, Estimated glomerular filtration rate, Post-analytical phase, External Quality Assessment.

SOUHRN
Šálek T., Friedecký B., Budina M.: Cystatin C – Implementace do laboratorní a klinické praxe
Cíl: Doporučení Kidney Disease Improving Global Outcomes (KDIGO) doporučuje vydávat výsledek koncentrace cystatinu C společně s odhadovanou glomerulární filtrací (eGFRcys). Míra implementace tohoto doporučení v praxi není známa. Cílem této studie je stanovit míru této implementace a laboratořím, které tak ještě neučinily, poskytnout návod k jejímu zavedení.
Typ studie: průřezová.
Název a sídlo pracoviště: SEKK, spol. s.r.o., Za Pasáží 1609, 530 02 Pardubice.
Materiál a metody: Hodnocení implementace doporučení bylo provedeno pomocí internetového elektronického dotazníku, který byl přidán k cyklu externího hodnocení kvality (EQA). 70 účastníkům (59 z České republiky a 11 ze Slovenska). Účastníci odpovídali, jestli má jejich metoda návaznost kalibrace na mezinárodní referenční materiál ERM DA471/IFCC a jestli počítají eGFRcys. Odpovědi byly analyzovány.
Výsledky: Na dotazník odpovědělo 63 účastníků. Návaznost kalibrace měření k mezinárodnímu referenčnímu materiálu ERM DA471/IFCC uvedlo 53 odpovědí. Celkem 53 laboratoří uvedlo vydávání eGFR u všech dospělých pacientů a čtyři vydávají eGFR jen na vyžádání. Šest laboratoří nepočítá eGFR. The Chronic Kidney Disease Epidemiology Collaboration (CKD - EPI) rovnice byla užívána 57 laboratořemi. Z nich 22 počítá také kombinovanou rovnici s kreatininem a tři laboratoře počítají také Caucasian, Asian, Pediatric and Adult (CAPA) rovnici.
Závěr: Většina laboratoří dodržuje KDIGO doporučení. Nicméně další edukace ohledně návaznosti měření a výpočtu eGFR s každým výsledkem je stále potřebná.
Klíčová slova: Cystatin C, Glomerulární filtrace, Odhadovaná glomerulární filtrace, Post-analytická fáze, Externí hodnocení kvality.

Introduction

EQA is a key tool for improvement of analytical performance characteristics of laboratory tests. Total testing process (TTP) includes pre-analytical, analytical, and post-analytical phases. A problem in any of these phases can compromise patient care. Medical laboratories are responsible for all three phases. That is why EQA organisations created schemes also for pre-analytical and post-analytical phases [1].

Glomerular filtration rate (GFR) is a key parameter for the diagnosis of chronic kidney disease (CKD) and for dosing of drugs excreted by kidneys. Cystatin C is an alternative marker of GFR in patients who lost their

muscle mass and creatinine is not suitable. KDIGO guidelines recommend eGFRcys or gold standard method in situations where creatinine is an unreliable method for estimation of GFR. Each result of serum concentration of cystatin C should be accompanied by eGFRcys [2]. Cystatin C is also included as the recommended marker of GFR in Czech Republic national guidelines for the diagnosis of CKD [3]. Cystatin C is a stronger predictor of the risk of death and cardiovascular events in elderly persons than creatinine [4]. Cystatin C serum levels are also associated with non GFR factors such as C – reactive protein, white blood cell count, lower serum albumin, diabetes. All these factors should be considered when the GFR is estimated from serum levels of cystatin C in patients at high cardiometabolic risk [5].

Traceability of measurement to international reference material is the most important step to lower method bias, which leads to comparable results at different places and time. Standardisation of cystatin C measurement has been completed by traceability of calibration to international reference material ERM DA471/IFCC [6].

Standardisation of laboratory tests and mainly its implementation to routine laboratory practice are of key importance for patient safety [7]. Patient safety requires standardization of all phases of TTP [8]. EQA of post-analytical phase also has an important educational role for participants.

Patient safety is the reason why it was decided to perform the questionnaire study of implementation of standardized cystatin C measurement and its eGFR reporting.

Materials and methods

Subjects

A total of 70 laboratories (59 from the Czech Republic and 11 from Slovakia) participated in the April 2018 cycle of cystatin C EQA. Participation of medical laboratories in EQA is mandatory in the Czech Republic and Slovakia. The control samples for cystatin C scheme are distributed two times per year.

Methods

Laboratories were given online electronic questionnaires with three questions (see Table 1) about cystatin C measurement and post-analytical phase.

Results

A total of 70 laboratories were eligible for the online electronic questionnaire during cystatin C EQA in April 2018. Of them, 63 participants responded. Traceability of calibration to ERM DA471/IFCC was declared by 53 responders.

A total of 53 laboratories reported eGFR in all adult patients and 4 participants report eGFR only on direct request. Six laboratories did not report eGFR.

CKD - EPI equation was used by 57 laboratories. A total of 22 laboratories also used combined CKD – EPI equation with creatinine and the laboratories also calculated CAPA equation.

All participants received educational commentaries with intention to improve the current situation. Commentaries are in Table 2.

Discussion

We analysed EQA results of cystatin C post-analytical phase. We found that 10 out of 63 laboratories did not know if their method was traceable to available international standard ERM DA471/IFCC and 10 out of 63 participants did not report eGFRcys together with cystatin C concentration result. It means that there is still opportunity to improve the situation.

EQA is a very important tool for assessment of all phases of a laboratory test [9]. It is consistent with our approach to assess not only the analytical phase.

Questionnaire is proposed as effective method for examination of post-analytical phase [10]. We have also adopted this practice.

Traceability of measurement is key to analytical method standardisation and common reference intervals [11]. It is consistent with our first comment which

Table 1: The text of the questions in the online questionnaire.

Question Number	Question Text
1	Is calibration of your method traceable to international standard ERM DA471/IFCC?
2	Do you report eGFRcys together with cystatin C concentration?
3	Which equation do you use for eGFRcys in adult patients?

Table 2: The text of the educational comments to questions in the questionnaire.

Educational comment to question 1	Each laboratory's cystatin C method should be traceable to ERM DA471/IFCC standard.
Educational comment to question 2	Calculation of eGFRcys should accompany cystatin C concentration results.
Educational comment to question 3	CKD – EPI and CAPA equations are recommended for adult patients.

recommends performing cystatin C measurement with calibrator traceable to international standard ERM DA471/IFCC.

EQA has an important educational role, which may improve quality of TTP [12]. We also added educational comments to our survey results.

Harmonisation in laboratory medicine also includes reporting laboratory test results [13]. It is in accordance with our post-analytical EQA scheme that promotes reporting eGFR together with cystatin C concentration result.

The limitation of this study is a relatively small number of participants.

Conclusion

EQA was historically developed to improve analytical performance characteristics of laboratory tests. Nowadays extra-analytical phase schemes have been added to EQA to ensure quality of TTP and patient safety.

References

1. **Krleza, J. L., Dorotic, A., Grzunov, A.** External quality assessment of medical laboratories in Croatia: preliminary evaluation of post-analytical laboratory testing. *Biochem Med* (Zagreb) 2017, 27(1), p.144–52.
2. **Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group.** KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease: Chapter 1: Definition and classification of CKD. *Kidney Int Suppl* 2013, 3(1), p. 1–150.
3. **Zima, T., Racek, J., Tesař, V., Viklicky, O., Teplan, V., Schuck, O., Janda, J., Friedecky, B., Kubiček, Z., Kratochvila, J., Rajdl, D., Šalek, T., Kalousova, M., Granatova, J.** Doporučení k diagnostice chronického onemocnění ledvin (odhad glomerulární filtrace a vyšetřování proteinurie) České nefrologické společnosti ČLS JEP a České společnosti klinické biochemie ČLS JEP. *Klin. Biochem Metab* 2014, 22 (43), 3, p. 138-152.
4. **Shlipak, M. G., Sarnak, M. J., Katz, R., Fried, L. F., Seliger, S. L., Newman, A. B.,et al.** Cystatin C and the risk of death and cardiovascular events among elderly persons. *New England Journal of Medicine* 2005, 352.20: 2049-2060.
5. **Stevens, L. A., Schmid, C. H., Greene, T., Li, L., Beck, G. J., Joffe, M. M., Levey, A. S.** Factors other than glomerular filtration rate affect serum cystatin C levels. *Kidney international* 2009, 75(6), p. 652-660.
6. **Grubb, A., Blirup-Jensen, S., Lindström, V., Schmidt, C., Althaus, H., Zegers, I. et al.** First certified reference material for cystatin C in human serum ERM-DA471/IFCC. *Clin Chem Lab Med* 2010, 48(11), p.1619–21.
7. **Bargnoux, A-S., Piéroni, L., Cristol., J-P., Kuster, N., Delanaye, P., Carlier, M-C., et al.** Multicenter Evaluation of Cystatin C Measurement after Assay Standardization. *Clin Chem* 2017, 63(4), p.833–41.
8. **Friedecký, B.** Quality in clinical laboratory and patient safety. *Klin Biochem Metab* 2010,18(39), p. 136–43.
9. **Badrick, T., Gay, S., McCaughey, E. J., Georgiou, A.** External Quality Assessment beyond the analytical phase: an Australian perspective. *Biochem Med* (Zagreb) 2017, 27(1), p. 73–80.
10. **Krleza, J. L., Celap, I., Tanaskovic, J. V.** External Quality Assessment in Croatia: problems, challenges, and specific circumstances. *Biochem Med* (Zagreb) 2017, 27(1), p. 86–92.
11. **Tate, J. R., Koerbin, G., Adeli, K.** Opinion Paper: Deriving Harmonised Reference Intervals – Global Activities. *EJIFCC* 2016, 27(1), p. 48–65.
12. **Parham, D. M., Coleman, D., Kodikara, S., Moss, S., Ellis, IO., Al-sam, S. et al.** The NHS breast screening programme (pathology) EQA: experience in recent years relating to issues involved in individual performance appraisal. *J Clin Pathol* 2006, 59(2), p. 130–7.
13. **Šálek, T., Franeková, J., Jabor, A., Friedecký, B.** Postanalytická fáze a interpretace laboratorního testu (post-postanalytická faze). *Klin Biochem Metab* 2016, 24(45), p. 82–87.

Střet zájmů: Autoři prohlašují že nejsou ve střetu zájmů

Do redakce došlo 20. 8. 2018

Adresa pro korespondenci:
MUDr. Tomáš Šálek, Ph.D.
Krajská nemocnice T. Bati, a. s.
Havlíčkovo nábřeží 600, 762 75 Zlín
email: tsalek@seznam.cz