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Clinical Usefulness of Calculated Parameters for the Diagnosis of Renal, Liver and Acid Base Disorders

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ABSTRACT

Calculated indices are now emerging as clinically useful tools for the preliminary diagnosis of a variety of disorders/diseases. Such indices are derived from a measured analyte or set of analytes and they will then be used as tools to monitor/evaluate the preliminary clinical condition associated with a particular organ such as liver, kidney or respiratory related problems. Among such calculated parameters, eGFR and FENa for renal,liver enzyme ratios, FIB-4 and APRI for liver and anion gap for acid base disorders have been extensively used. This review article highlights the recent research findings in the use of such calculated parameters for clinical use, and its merits and demerits in providing awareness to clinicians about its significance and use in clinical practice.

Introduction

In Laboratory diagnosis, both qualitative and quantitative test results are being used for treatment and prognostic monitoring. Of all the sections of clinical laboratory services, clinical biochemistry help clinicians by providing mostly quantitative results either in the form of individual test result or profile tests for organ related disorders. Some test results could be used to calculate factors/ratios, the so called calculated parameters which may in turn help preliminary diagnosis of certain diseases or disorders. Such calculated parameters are mostly used as supporting information for the diagnosis of renal, liver and acid base disorders. This review article summarises the recent findings in the use of calculated parameters for the diagnosis of the above diseases/disorders.

Renal Diseases

Surveillance of Glomerular Filtration Rate (GFR) is crucial in the management of kidney transplant recipients with special emphasis on Serum Creatinine (SrCr) calibration assay. The performance of all equations was not uniform throughout the whole range of GFR, with some deterioration at the extremes of GFR levels. In addition, good performance of the Modification of Diet in Renal Disease (MDRD) equation was seen in subjects taking Calcineuria Inhibitor (CNI). The overall performance of the MDRD equation was superior to the Nankivell and Cockcroft Gault (CG) formulae in renal transplant recipients including subjects treated with CNI.[(1)] The (MDRD) variability, but not classic CG variability or corrected CG variability, showed a positive correlation with the GFR rate. In patients with Chronic Kidney Diseases(CKD) in stage 5, the variability of the different estimated equations were similar. With advanced CKD, the classic CG equation is more accurate than the MDRD equation.[(2)]

Both the MDRD and CG equation over estimated the strength of the association of GFR with measured SrCr. MDRD equation in out patients with moderate to advanced kidney disease as well as in those with diabetic nephropathy suggest that its use is problematic in healthy individuals. It is important to emphasizes the complexity of laboratory calibration of SrCr measurements, a determining factor when estimating GFR in both healthy individuals and CKD patients with preserved GFR.[(3)]

MDRD Study equation provides reasonably accurate GFR estimates in patients with CKD with a measured GFR of less than 90 mL/min/1.73 m^2. By using the reexpressed MDRD Study equation with the standardized SrCr assay, clinical laboratories can report more accurate GFR estimates.[(4)] The current Creatinine Clearance (Cr-Cl) equations and even the original CG formula did not accurately predict the measured Cr-Cl. Normalization for body surface area in the original CG formula demonstrated more accuracy to estimate Cr-Cl, particularly in patients with diminished renal function and is recommended to physicians who wish to use the Cr-Cl formula in their practice until more credible formulae are developed.[(5)]

The CG formula and the MDRD equation are commonly used to estimate GFR, but their validity based on extreme body weight is questionable. Because the eGFR by the CG is proportional to body weight, it is not suited for obese diabetic patients. Although it is less easy to calculate, the MDRD is not affected by weight, and its use would avoid delay in referral to nephrologists.[(6)] The National Kidney Foundation recommends stratification of renal failure into moderate with GFR = 30-60 mL/min/1.73 m^2, severe (15-30) or terminal (<15) using the CG or the MDRD equations. [(7)] In elderly patients, GFR estimates using MDRD and CG formulae differ widely and identify different numbers of individuals with CKD. Prospective comparative studies are needed to validate these formulae and their different thresholds to better detect elderly patients at higher risk of bleeding when treated with Low molecular weight Heparin (LMWH).[(8)]

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MDRD formula gives a higher eGFR compared to CG formulae by about 10 to 30 mL/min/1.73 m^2. Only Cr-Cl measured by the CG formula is a predictor of mortality in the very old population. In the octogenarian, none of these two formulas is ideal. However, based on the results of studies targeted to this elderly population, the best solution seems to be the use of the CG formula expecting new methods of evaluation of renal function.[9] In elderly, GFR should only be estimated using the MDRD formula, since the CG formula systematically underestimates GFR, and it tends to decrease with age, but it should be 60 mL/min/1,73 m^2 or higher in all subjects who do not suffer from CKD, regardless of age.[10] Overall, evidence supports the use of the 4 variables (age, sex, black race &creatinine) in MDRD formula as an improved estimate of GFR in people with moderate/advanced CKD. Neither formula performs well in people with normal and mildly reduced kidney function. However, there remain significant problems with this approach and areas where further research is required. In particular, the widespread adoption of eGFR reporting has refocused attention on the limitations of SrCr based measurement and highlighted clinical situations in which the formulae are inadequate.[11]

In clinical practice, GFR is often estimated by the MDRD or CG formulae. No data are available, however, on the performance of these formulae in Arab individuals.CG formula was found to be the most appropriate for calculation of GFR in Arab individuals. It is possible to reduce the bias and improve precision in Arab individuals with normal renal function by multiplying the result obtained by CG formula by 1.0446.[12] Analysis of ability to correctly predict the patient's GFR below or above 60/ml/min/1.73 m^2 showed a higher prediction for the cystatin C (CysC) formula than the MDRD formula (91.6 versus 84.1%, $p < 0.0005$) and a higher prediction trend than the CG formula (91.6 versus 88.3%, $p = 0.078$), suggesting that CysC based equation is a reliable marker of GFR with a very high diagnostic accuracy and ability to predict patients with CKD and GFR under 60/ml/min/1.73 m^2.[13] Analysis of the ability to correctly predict GFR below and above 45 mL/min/1.73 m^2 showed a high prediction for all formulae, CysC based formula, as just is a reliable marker of GFR in the elderly and comparable to other formulae, including the Chronic Kidney Disease – Epidemiology Collaboration (CKD-EPI) formula.[14]

CysC and the newer creatinine formule CKD-EPI were proposed to calculate eGFR.[15] The CKD-EPI equation appears to perform better than the MDRD equation. CysC has been widely evaluated as a better marker for GFR and seems to be more sensitive than creatinine based formulae.[16] According to Kidney Disease Improving Global Outcomes (KDIGO) recommendations, many indications remain for GFR measurements using a clearance method. In that context, it should be recalled that radiolabeled-tracer serum or urinary clearance methods, are safe, simple, accurate and reproducible.[17] The MDRD equation derives from a multiple regression used to analyze the relation of GFR measurements by a radioisotope technique over SrCr after data linearization by logarithm transformation and with control for the 4 variables. The equation has not been validated for GFR >60 mL/min / 1.73 m^2 because the study did not include healthy persons. The two equations often give conflicting estimates of GFR. Nephrologists have to understand the rationale of the two equations for the correct interpretation of these discrepancies.[18]

The CG formula over estimated Cr-Cl by 14% to 35%, gave a negative correlation with the difference between the predicted GFR by CG and measured GFR and overestimating GFR by<13 ml/min/1.73 m^2. The over estimation of GFR by the MDRD equation was not associated with urinary creatinine excretion. However, both CG and the MDRD predictions showed a positive, but weak, correlation with body fat. The MDRD equations were more accurate in predicting the group mean GFR in patients with End Stage Renal Disease (ESRD) than the CG formula. However, the predicted GFR using either formula was related to the basal GFR and percentage body fat.[19] There is substantial prevalence of significantly abnormal renal function among patients identified by laboratories as having normal-range creatinine, and calculated estimates of GFR as in routine laboratory reporting may help to facilitate the early identification of patients with renal impairment.[20]

In patients with oliguria, measurement of Fractional Excretion of Sodium (FE_{Na}) is helpful in distinguishing prerenal from intrinsic renal causes of Acute Kidney Injury (AKI). A value less than 1% of FENa indicates a prerenal cause of AKI, whereas a value greater than 2 % indicates an intrinsic renal cause. In patients on diuretic therapy, however, a FE_{Na} higher than 1 % may be caused by natriuresis induced by the diuretic, and is a less reliable measure of a prerenal state. In such cases, fractional excretion of urea may be helpful, with values less than 35 % indicating a prerenal cause. FE_{Na} values less than 1 % are not specific for prerenal causes of AKI because these values can occur in other conditions, such as contrast nephropathy, rhabdomyolysis, acute glomerulonephritis, and urinary tract obstruction.

In Acute Renal Failure (ARF), tubular function is intact and the decrease in filtration is associated with enhanced tubular sodium reabsorption, and when creatinine accumulates in the blood as a result of a fall in GFR with intact tubular function, a decrease below 1% was observed with a previously undamaged kidney. A paradoxically high FE_{Na} despite the presence of prerenal azotemia occurs during diuretic treatment, including mannitol, within the preceding 24 h in the presence of glucosuria or excretion of an alkaline urine, which decreases tubular sodium reabsorption. Also, renal vasoconstriction in patients with advanced chronic renal failure may not be associated with a FE_{Na} below 1% because of chronic adaptation to an increased single-nephron GFR. A reduced effective circulating volume also stimulates antidiuretic hormone (ADH) release. ADH results in increased distal water and urea reabsorption, and it was found that a low FE_{urea} (<35%) is more sensitive and specific than FE_{Na} in differentiating between prerenal and renal causes of ARF, especially when diuretics have been administered.[21] Evaluation of renal function by estimation of the GFR is very important for the diagnosis and treatment of patients with CKD. The CG and MDRD formulae are the most commonly used estimations. The CG and MDRD formulae had some limitations for proper GFR estimation and K/DOQI-CKD classification by GFR levels alone.[22]

Liver Diseases

Patients with nonalcoholic fatty liver disease (NAFLD) and advanced liver fibrosis are at the highest risk for progressing to End Stage Liver Disease (ELD). Age, hyperglycemia, body mass index (BMI), platelet count, albumin, and Aspartate transferase / Alanine transferease (AST/ALT) ratio were independent indicators of advanced liver fibrosis. A scoring system with these 6 variables had an

Area Under the Receiver Operating Characteristic Curve (AUROC) of 0.88 and 0.82 in the estimation and validation groups, respectively. By applying the low cutoff score (-1.455), advanced fibrosis could be excluded with high accuracy (negative predictive value of 93% and 88% in the estimation and validation groups, respectively). By applying the high cutoff score (0.676), the presence of advanced fibrosis could be diagnosed with high accuracy (positive predictive value of 90% and 82% in the estimation and validation groups, respectively). By applying this model, a liver biopsy would have been avoided in 75% of the patients, with correct prediction in 90%. A simple scoring system accurately separates patients with NAFLD with and without advanced fibrosis, rendering liver biopsy for identification of advanced fibrosis unnecessary in a substantial proportion of patients.[23]

To optimize the management of patients with Chronic Hepatitis C virus (HCV) infection, non invasive tests to determine the degree of hepatic fibrosis have been developed. A Fibrosis-4 index (FIB-4) higher than 3.25 had a positive predictive value to confirm the existence of a significant fibrosis (F3-F4) of 82.1% with a specificity of 98.2%. Using these ranges, 72.8% of the 847 liver biopsies were correctly classified. The FIB-4 index was strongly correlated to the Fibro test results for a score <1.45 or >3.25 (kappa = 0.561, P < 0.01). A FIB-4 value <1.45 or >3.25 (64.6% of the cases) was concordant with Fibro test results in 92.1% and 76%, respectively. For values outside 1.45-3.25, the FIB-4 index is a simple, accurate, and inexpensive method for assessing liver fibrosis and proved to be concordant with Fibro test results.[24]

The AST to Platelet Ratio Index (APRI) has been proposed as a noninvasive and readily available tool for the assessment of liver fibrosis in Chronic Hepatitis C (CHC). APRI can be a useful noninvasive alternative for the diagnosis of significant fibrosis and cirrhosis in CHC patients. APRI values of < or = 0.3 and < or = 0.5 rule out significant fibrosis and cirrhosis, and a value of > or = 1.5 rules in significant fibrosis. In patients with NAFLD, APRI values tend to increase with the degree of fibrosis, suggesting that it could be useful in this disease. APRI appears to be of no value in patients with Auto Immune Hepatitis (AIH).[25] Accurate evaluation of liver fibrosis in patients with NAFLD is important to identify patients who may develop complications. The AST/ALT ratio, BARD score, FIB-4 and NAFLD fibrosis scores had negative predictive values greater than 90% (93%, 95%, 95% and 92% respectively). Positive predictive values were modest. In order to exclude advanced fibrosis, liver biopsy could potentially be avoided in 69% with AST/ALT ratio, 62% with FIB-4, 52% with NAFLD fibrosis score and 38% with BMI and AST/ALT ratio. IB-4 and NAFLD fibrosis scores can reliably exclude advanced fibrosis in a high proportion of patients with NAFLD, allowing liver biopsy to be used in a more directed manner.[26] The FIB-4 index is superior to 7 other noninvasive markers of fibrosis in patients with NAFLD; however its performance characteristics highlight the need for even better noninvasive markers.[27]

Although most patients with severe acute hepatitis are conservatively cured, some progress to acute liver failure (ALF) with a high rate of mortality. Based on the evidence that over-activation of macrophages, followed by disturbance of the hepatic micro circulation, plays a key role in ALF and it is due to a rapid increase in the ALT-LDH index in conservative survivors but not in fatal patients. While the prognostic sensitivity and specificity of the ALT-LDH index was low on admission, at day 3 they were superior to the results of Model for End stage Liver disease (MELD).ALT-LDH index was useful to predict the prognosis of the patients with acute liver injury and should be helpful to begin preparation for Low throughtout soon after admission.[28]

Currently, a major clinical challenge is to distinguish between CLD caused by metabolic syndrome, NAFLD from that caused by long term or excessive alcohol consumption leading to Alcoholic Liver Diseases (ALD). The etiology of severe liver disease affects treatment options and priorities for liver transplantation and organ allocation. Adiponectin and Tumor Necrosis Factor (TNF)-α were significantly lower in NAFLD than in ALD without Cirrhosis (ALDNC) or ALD with Cirrhosis (ALDC) patients. Significantly higher serum concentrations of cell death markers, hyaluronic acid, adiponectin, and TNF-α were found in ALDC compared to ALDNC. Using machine learning techniques it was able to discern NAFLD and ALDNC (up to an AUROC of 0.9118±0.0056) or ALDC and ALDNC (up to an AURUC of 0.9846±0.0018), respectively. Machine learning techniques relying on ALT/AST ratio, adipokines and cytokines distinguish NAFLD and ALD. In addition, severity of ALD may be non-invasively diagnosed *via* serum cytokine concentrations .[29]

NAFLD is caused by abnormal accumulation of lipids within liver cells. Its prevalence is increasing in developed countries in association with obesity, and it represents a risk factor for non-alcoholic steatohepatitis (NASH), cirrhosis and HCC. Since NAFLD is usually asymptomatic at diagnosis, new non-invasive approaches are needed to determine the hepatic lipid content in terms of diagnosis, treatment and control of disease progression. The potential of Magnetic Resonance Imaging (MRI) was used to quantitate and monitor the hepatic triglyceride concentration in humans. Multi-Echo MRI is an accurate approach to determine the hepatic lipid concentration by using novel equation, representing an economic non-invasive method to diagnose and monitor NASH in humans.[30] Extreme elevations of this ratio, especially in association with AST levels greater than five times normal, should suggest NASH causes of hepatocellular necrosis in alcoholic patients.[31]

Acid Base Disorders

The urine osmolality is used to assess ADH action and the osmolality of the renal medulla and to determine the etiology of polyuria and/or hypernatremia. The urine osmolality can also be used to assess the ammonium concentration using the urine osmolalgap and to detect unusual urine osmoles.[32] A total of 14 equations have been previously described to estimate plasma osmolality, but none agree best with measured osmolality. The equation that provides the best fit between measured and calculated osmolality is 1.86(Na+K) + 1.15 (Glu/18) + (Urea/6) +14, followed by 2Na + 1.15 (Glu/18) + (Urea/6). The equation 1.8 6(Na+K) +1.15 (Glu/18) + (Urea/6) +14 is the most accurate. The widespread use of the equation 2(Na+K) + (Glu/18) + (Urea/6) is also acceptable.[33]

The equation, osmolality=1.86 (sodium + potassium) +glucose/18 + Urea/6 + 9, was found to predict only crudel plasma osmolality. The plasma sodium: osmolality ratio was 0.49. Water and electrolyte disorders are classified into 3 types based on the measurement of electrolytes and osmolality : (1) Hypertonic dehydration (true dehydration desiccation), osmolality greater than 300 mOsm/Kg, associated with water deprivation, some gastrointestinal emergencies and some types

of diarrhoea; (2) hypotonic dehydration (acute desalting water loss), osmolalities less than 260 mOsm/kg, associated with acute diarrhoea, particularly salmonellosis; (3) isotonic dehydration (normal electrolyte and osmolality levels), in horses losing electrolytes and water in almost equal proportions. The importance of these observations and their significance in rational clinical management has been extensively discussed.[34]

The serum anion gap, calculated from the electrolytes measured in the clinical laboratory, is defined as the sum of serum chloride and bicarbonate concentrations subtracted from the serum sodium concentration. This entity is used in the detection and analysis of acid-base disorders, assessment of quality control in the clinical laboratory, and detection of such disorders as multiple myeloma, bromide intoxication and lithium intoxication. The normal value may vary widely, reflecting both differences in the methods that are used to measure its constituents and substantial inter individual variability. Low values most commonly indicate laboratory error or hypoalbuminemia but can denote the presence of a paraproteinemia or intoxication with lithium, bromide, or iodide. Elevated values most commonly indicate metabolic acidosis but can reflect laboratory error, metabolic alkalosis, hyperphosphatemia, or paraproteinemia. Despite these caveats, calculation of the serum anion gap remains an inexpensive and effective tool that aids detection of various acid-base disorders, hematologic malignancies, and intoxications.[35] If one finds high incidence of increased anion gap (>24 mmol/L) or decreased anion gap (<2 mmol/L), one should check the quality control of electrolyte and whether the patients were hypoalbuminemia or hyperglobulinemia. An anion gap exceeding 24 mmol/L will suggest the presence of metabolic acidosis. It is very rare to find anion gap with the negative sign.[36]

Conclusion

This review article summarises the research work done during the last 15 years on the clinical usefulness of calculated parameters such as eGFR and FENa for renal, liver enzyme ratios, FIB-4 and APRI for liver diseases and Anion gap for the diagnosis of Acid base disorders. This article also highlights the use of various formulae for calculating eGFR, its correlation to Cr-Cl and creatinine and cystatin C based formulae to calculate GFR for the diagnosis of renal diseases. For liver related disorders, fibrosis indices were extensively discussed to classify liver diseases. The contents of this review article could certainly be useful to set standard guidelines for the use of calculated parameters for the diagnosis of renal, liver and acid base disorders.

Reference

1) Poggio ED, Wang X, Weinstein DM, Issa N, Dennis VW, Braun WE, Hall PM. Assessing glomerular filtration rate by estimation equations in kidney transplant recipients. Am J Transplant. 2006;6(1):100-8.

2) Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, Kusek JW, Van Lente F. Chronic Kidney Disease Epidemiology Collaboration. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med. 2006;145(4):247-54.

3) Poggio ED, Wang X, Greene T, Van Lente F, Hall PM. Performance of the modification of diet in renal disease and Cockcroft-Gault equations in the estimation of GFR in health and in chronic kidney disease. J Am SocNephrol. 2005;16(2):459-66.

4) Shoker A, Hossain MA, Koru-Sengul T, Raju DL, Cockcroft D. Performance of creatinine clearance equations on the original Cockcroft-Gault population. ClinNephrol. 2006;66(2):89-97.

5) Rigalleau V, Lasseur C, Perlemoine C, Barthe N, Raffaitin C, Chauveau P, Combe C, Gin H. Cockcroft-Gault formula is biased by body weight in diabetic patients with renal impairment. Metabolism. 2006;55(1):108-12.

6) Rigalleau V, Lasseur C, Perlemoine C, Barthe N, Raffaitin C, de La Faille R, Combe C, Gin H. A simplified Cockcroft-Gault formula to improve the prediction of the glomerular filtration rate in diabetic patients. Diabetes Metab. 2006;32(1):56-62.

7) Gouin-Thibault I, Pautas E, Mahé I, Descarpentries C, Nivet-Antoine V, Golmard JL, Siguret V. Is Modification of Diet in Renal Disease formula similar to Cockcroft-Gault formula to assess renal function in elderly hospitalized patients treated with low-molecular-weight heparin? J Gerontol A BiolSci Med Sci. 2007;62(11):1300-5.

8) Andro M, Estivin S, Comps E, Gentric A. Assessment of renal function in elderly after eighty years: Cockroft and Gault or Modification of diet in renal disease equation?.Rev Med Interne. 2011;32(11):698-702.

9) Froissart M, Rossert J. How to improve estimation of renal function in the elderly. Rev Prat. 2005;55(20):2223-9.

10) Lamb EJ, Tomson CR, Roderick PJ. Clinical Sciences Reviews Committee of the Association for Clinical Biochemistry. Estimating kidney function in adults using formulae. Ann ClinBiochem. 2005;42(5):321-45.

11) Al-Khader AA, Tamim H, Sulaiman MH, Jondeby MS, Taher S, Hejaili FF, Ghamdi G, Flaiw A, HakamiA.What is the most appropriate formula to use in estimating glomerular filtration rate in adult Arabs without kidney disease? Ren Fail. 2008;30(2):205-8.

12) Hojs R, Bevc S, Ekart R, Gorenjak M, Puklavec L. Serum cystatin C-based equation compared to serum creatinine-based equations for estimation of glomerular filtration rate in patients with chronic kidney disease. ClinNephrol. 2008;70(1):10-7.

13) Bevc S, Hojs R, Ekart R, Gorenjak M, Puklavec L. Simple cystatin C formula compared to sophisticated CKD-EPI formulas for estimation of glomerular filtration rate in the elderly. TherApher Dial. 2011;15(3):261-8

14) Bevc S, Hojs R, Ekart R, Gorenjak M, Puklavec L. Simple cystatin C formula compared to serum creatinine-based formulas for estimation of glomerular filtration rate in patients with mildly to moderately impaired kidney function. Kidney Blood Press Res. 2012;35(6):649-54.

15) Soares AA, Eyff TF, Campani RB, Ritter L, Camargo JL, Silveiro SP. Glomerular filtration rate measurement and prediction equations. ClinChem Lab Med. 2009;47(9):1023-32.

16) Prigent A. Monitoring renal function and limitations of renal function tests. SeminNucl Med. 2008 Jan;38(1):32-46.

17) Cirillo M. Rationale, pros and cons of GFR estimation: the Cockcroft-Gault and MDRD equations. zG ItalNefrol. 2009;26(3):310-7.

18) Kuan Y, Hossain M, Surman J, El Nahas AM, Haylor J.GFR prediction using the MDRD and Cockcroft and Gault equations in patients with end-stage renal disease. Nephrol Dial Transplant. 2005;20(11):2394-401.

19) Duncan L, Heathcote J, Djurdjev O, Levin A. Screening for renal disease using serum creatinine: who are we missing? Nephrol Dial Transplant. 2001;16(5):1042-6.

20) Carvounis CP, Nisar S, Guro-Razuman S. Significance of the fractional excretion of urea in the differential diagnosis of acute renal failure. *Kidney Int*62, 2002 :2223– 2229.
21) Rossini Botev, Jean-Pierre Mallié, CeciléCouchoud, Otto Raúl Jiménez-Agüero, José I Emparanza, Adolfo Beguiristain, Luis Bujanda, José M Alustiza, Elisabeth García, Elizabeth Hijona, Lander Gallego, Javier Sánchez-González, María J Perugorria, José I Asensio, Santiago Larburu, MaddiGarmendia,MikelLarzabal, María P Portillo, Leixuri Aguirre and Jesús M Banales**.**Novel equation to determine the hepatic triglyceride concentration in humans by MRI: diagnosis and monitoring of NAFLD in obese patients before and after bariatric surgery. *BMC Medicine*. 2014; 12:137.
22) Toniutto P, Fabris C, Bitetto D, Falleti E, Avellini C, Rossi E, Smirne C, Minisini R, PirisiM.Role of AST to platelet ratio index in the detection of liver fibrosis in patients with recurrent hepatitis C after liver transplantation. J GastroenterolHepatol. 2007;22(11):1904-8.
23) Siervo M, Bunn D, Prado CM, Hooper L. Accuracy of prediction equations for serum osmolarity in frail older people with and without diabetes. Am J ClinNutr. 2014;100(3):867-76.
24) Martín-Calderón JL, Bustos F, Tuesta-Reina LR, Varona JM, Caballero L, Solano F. Choice of the best equation for plasma osmolality calculation: Comparison of fourteen formulae. ClinBiochem. 2015;48(7-8):529-33.
25) Bonvehi C, Ardiaca M, Barrera S, Cuesta M, Montesinos A. Prevalence and types of hyponatraemia, its relationship with hyperglycaemia and mortality in ill pet rabbits. Vet Rec. 2014;174(22):554.
26) Kraut JA, Madias NE. Serum anion gap: its uses and limitations in clinical medicine. Clin J Am SocNephrol. 2007 ;2(1):162-74.
27) Lolekha PH, Vanavanan S, Lolekha S. Update on value of the anion gap in clinical diagnosis and laboratory evaluation. ClinChimActa. 2001;307(1-2):33-6.
28) Ren R, Jiang X, Zhang X, Guan Q, Yu C, Li Y, Gao L, Zhang H, Zhao J. Association between thyroid hormones and body fat in euthyroid subjects. ClinEndocrinol (Oxf). 2014;80(4):585-90.
29) Schück,Jean-Pierre Fauvel, Jack F.M. Wetzels, Nelson Lee, Natale G. De Santo, and Massimo Cirillo.Estimating Glomerular Filtration Rate: Cockcroft–Gault and Modification of Diet in Renal Disease Formulas Compared to Renal Inulin Clearance.Clin J Am SocNephrol. 2009; 4(5): 899–906.
30) Angulo P, Hui JM, Marchesini G, Bugianesi E, George J, Farrell GC, Enders F, Saksena S, Burt AD, Bida JP, Lindor K, Sanderson SO,Lenzi M, Adams LA, Kench J, Therneau TM, Day CP. The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD.
31) Vallet-Pichard A, Mallet V, Nalpas B, Verkarre V, Nalpas A, Dhalluin-Venier V, Fontaine H, Pol S. FIB-4: an inexpensive and accurate marker of fibrosis in HCV infection. comparison with liver biopsy and fibrotest. Hepatology. 2007;46(1):32-6.
32) Loaeza-del-Castillo A, Paz-Pineda F, Oviedo-Cárdenas E, Sánchez-Avila F, Vargas-Voráckova F. AST to platelet ratio index (APRI) for the noninvasive evaluation of liver fibrosis. Ann Hepatol. 2008;7(4):350-7.
33) McPherson S, Stewart SF, Henderson E, Burt AD, Day CP. Simple non-invasive fibrosis scoring systems can reliably exclude advanced fibrosis in patients with non-alcoholic fatty liver disease. Gut. 2010 ;59(9):1265-9.
34) Shah AG, Lydecker A, Murray K, Tetri BN, Contos MJ, Sanyal AJ. Comparison of noninvasive markers of fibrosis in patients with nonalcoholic fatty liver disease. ClinGastroenterolHepatol. 2009;7(10):1104-12.
35) Kazuhiro Kotoh, Munechika Enjoji, Masaki Kato, MotoyukiKohjima, Makoto Nakamuta and Ryoichi Takayanagi. A new parameter using serum lactate dehydrogenase and alanine aminotransferase level is useful for predicting the prognosis of patients at an early stage of acute liver injury: A retrospective study. Comparative Hepatology. 2008; 7:6.
36) Jan-Peter Sowa, ÖzgürAtmaca, AlisanKahraman, Martin Schlattjan, et al., Non-Invasive Separation of Alcoholic and Non-Alcoholic Liver Disease with Predictive Modeling. PLOS, July 2, 2014.